Delish Study: Diabetes Education to Lower Insulin, Sugars, and Hunger

AKA Optimizing lifestyle interventions with mindfulness-based strategies in type 2 diabetes

Co-Principal Investigators:

Frederick M. Hecht, MD, Professor, UCSF Osher Center for Integrative Medicine

Elissa Epel, PhD, Professor, UCSF Department of Psychiatry

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4. *Minor adverse effects*: With this diet, several minor side effects may occur and include constipation, headache, muscle cramps, diarrhea, general weakness, and rash. Most of these occur at

STUDY TEAM ROSTER

Frederick Hecht, MD	*Rick.hecht@ucsf.edu*	*415-353-9743*
Elissa Epel, PhD	*Elissa.epel@ucsf.edu*	*415-476-7648*
Sarah Kim, MD	*Sarah.Kim@ucsf.edu*	*415-206-4969*
Ashley Mason, PhD	*Ashley.mason@ucsf.edu*	*415-514-6820*
Laura Saslow, PhD	*saslowl@umich.edu*	*615-260-3220*
Patricia Moran, PhD	*Patricia.moran@ucsf.edu*	*415-353-9745*
Veronica Goldman, BA	*Veronica.goldman@ucsf.edu*	*415-353-7561*
Alison Hartman, BA	*Alison.hartman@ucsf.edu*	*(415) 476-7634*
Hiba Abousleiman, BA	*Hiba.Abousleiman@ucsf.edu*	*(415) 353-9723*

PRÉCIS

Study Title

Delish Study: Diabetes Education to Lower Insulin, Sugars, and Hunger

(AKA Optimizing lifestyle interventions with mindfulness-based strategies in type 2 diabetes)

Objectives

R61 Specific Aims: We will enroll 60 persons with T2DM who will attend an in-person group course providing education on a carbohydrate-restricted (CR) diet. We plan 3 waves of about 20 persons each with 12 weekly sessions. We will randomize participants to receive basic behavioral strategies and diet education alone (Ed) or this same material with added MBI components (Ed+MBI), using a 1:1 ratio (Ed: Ed+MBI). We will use ecological momentary assessment (EMA) methods (via smartphone) to capture changes in eating in response to food cravings or difficult emotions. We will assess dietary adherence using ketone measures and 24-hour dietary recall. We will address the following specific aims:

1. Determine if our EMA measures of behavioral mechanisms have high response rates (> 90%) and are ready for R33 use.
2. Determine if there is preliminary evidence that the MBI intervention impacts our hypothesized mechanisms of action and that the proposed mechanisms predict improved dietary adherence.
3. Assess feasibility and acceptability of two intensities of maintenance (monthly group meetings alone or supplemented by individualized attention) to ensure they are ready for R33 testing.

R33 Specific Aims: We will randomize 120 persons with diabetes in a 1:2 ratio to the Ed (n=40) vs. Ed+MBI (n=80) arms and follow them for 12 months. After the 12-week intervention, we will observe participant for 8 weeks and then re-randomize them using an adaptive intervention design to receive further observation, light maintenance training, or intensive maintenance training, depending on level of adherence achieved during the observation period. We will address the following specific aims:

1. Test whether our proposed behavioral mechanisms (decreased eating in response to cravings or difficult emotions) predict dietary adherence.
2. Test the hypothesis that the Ed+MBI arm will have better dietary adherence than the Ed arm.
3. Compare randomized arms in the adaptive maintenance intervention design to optimize maintenance phase dosing in future trials.
4. Obtain preliminary assessment of intervention effects on clinical outcomes

Design and Outcomes

This is a two-phase study. Both phases will use a randomized, controlled trial design. After pilot testing in the first phase, the second phase will include employing an adaptive intervention design in the post-treatment phase to test optimization of the maintenance intervention (i.e. assigning maintenance intensity/dose based on how a participant is doing).

Interventions and Duration

Participants will attend 12-weekly study intervention classes based on their random assignment: either Education alone (Ed) or Education+Mindfulness (Ed+MBI). Both groups will learn and follow a CR diet, and will participate in maintenance phase activities. If assigned to Ed+MBI, they will also learn and practice mindfulness-based skills.

Sample Size and Population

Target sample size: 180 total (60 participants in the first/R61 phase,120 in the second/R33 phase).

1. STUDY OBJECTIVES

Our overall hypothesis is that improved ability to manage food cravings and emotional eating is a key mechanism through which mindfulness-enhancements can improve dietary adherence.

In the initial R61 phase, we will look for preliminary evidence for several hypothesized pathways by which the MBI components will influence dietary adherence. These pathways and their associated measures are as follows:

1.1 Primary Objective

Primary mechanistic outcome(s): This study is aimed at testing behavioral mechanisms by which training in mindful eating may improve dietary adherence. Our primary hypothesized mechanism is reduction in **frequency of eating in response to cravings** as a result of enhanced ability to address food cravings with mindfulness training. Our key measure of this mechanism is frequency of eating in response to cravings using ecological momentary assessment (EMA).

1.2 Secondary Objectives

Secondary mechanistic outcomes: We have four additional mechanistic measures to assess our hypothesis that mindfulness training will enhance dietary adherence:

- Enhanced ability to reduce craving-related eating/decreased impulsivity as measured by the Relative Reinforcing Value of Food or Delayed Discounting task.
- Decreased stress-related eating as measured by the Palatable Eating Motives Scale (PEMS) subscale for stress-related eating as a coping mechanism.
- Decreased emotion related eating as measured by the Emotional Overeating Questionnaire.
- Improved resilience (resumption of dietary adherence) after dietary non-adherence occurs. Our key measure will be the time from a ketone measure of < 0.2 mmol/L to higher levels of > 0.2 mmol/L, indicating a return to nutritional ketosis after a period of consuming foods that depress ketosis.

Secondary clinical outcomes:

- Glycemic control, using HbA1c. We view improving HbA1c as the primary clinical outcome that we seek to improve in subsequent studies.
- Fasting glucose
- Homeostatic model assessment (HOMA) index of insulin resistance (computed from insulin and fasting glucose measures)
- Weight
- Adherence to diet measured by 24-hour diet recall and by ketone measures

In the R33 phase, we will test the hypothesis that the Ed+MBI arm will have better dietary adherence than the Ed arm. We hypothesize also that reducing maladaptive responses to stress will promote dietary adherence.

2. BACKGROUND AND RATIONALE

2.1 Background on Condition, Disease, or Other Primary Study Focus

Type 2 diabetes mellitus (T2DM) is a major public health issue. T2DM is the most costly chronic disease in the United States, with 10% of healthcare dollars spent on T2DM.[1] There are currently about 22 million persons in the United States and about 350 million people worldwide with T2DM.[1,2] Lifestyle modification is a key component of disease management, but achieving long-term adherence to diet recommendations is a central challenge. Diet and exercise can improve glycemic control in T2DM. Lowering glycosylated hemoglobin (HbA1c), a central measure of glycemic control in T2DM, reduces the risk of complications such as nephropathy and retinopathy.[3] The Look AHEAD study, based on the successful Diabetes Prevention Program intervention, is the largest trial of lifestyle interventions in T2DM to date. Participants in the intensive lifestyle intervention arm (relative to the control arm) in this trial lost 8 kg more weight and lowered HbA1c by 0.6% after one year.[4] However, these advantages diminished to a 1.6 kg weight and 0.05% HbA1c difference at the end of the trial (with a median of 9.6 years of follow-up).[5] These weaker long-term benefits highlight the importance of developing sustainable approaches to diet intervention in T2DM.

2.2 Study Rationale

Eating in response to food cravings, defined as intense urges or desires to eat specific foods,[6] emotional eating, and mindless eating pose challenges to adherence to diet recommendations, especially for people with diabetes.[7,8] Efforts to achieve a healthy food environment, including changes in the foods available in one's home and workplace, are an important step in adherence to a healthy diet for T2DM. However, foods that are inconsistent with a healthy diet in T2DM are everywhere. Of packaged foods sold in the United States, 74% have added sugars.[9] Seeing desirable food can trigger spontaneous simulations of eating it, including thinking about the pleasure of eating the food, and can

activate brain areas involved in taste and reward as if one were actually eating the food.[10,11] Thus the abundant food cues sets up people for frequent cravings and easy access to highly sweetened foods. Enhanced behavioral strategies that support long-term dietary adherence in T2DM are critically needed not only for management of diabetes but for pre-diabetes and obesity, each of which affect over one-third of adult Americans.[12,13]

Mindfulness skills have the potential to enhance dietary adherence. We address an area NCCIH identifies as a high priority for mind-body intervention research in RFA-AT-16-005: "behavior change to promote healthy behaviors such as healthy eating." Jon Kabat-Zinn developed the Mindfulness-Based Stress Reduction (MBSR) program and describes mindfulness as "paying attention on purpose, in the present moment, and nonjudgmentally, to the unfolding of experience moment to moment." One hypothesized mechanism by which mindfulness may increase long-term dietary adherence is by equipping individuals with the skills to acknowledge and experience food cravings and negative emotions without acting on them and by increasing resilience after temporary lapses in dietary adherence. Mindfulness approaches seek to strengthen abilities to become aware of, tolerate, and adaptively self-regulate uncomfortable sensations (e.g., food cravings) without maladaptive responding (e.g., craving-related eating).[14] Current neurobehavioral models of eating behavior are based on experimental data showing that obese persons respond to pictures of high-calorie foods with greater activation of brain regions hypothesized to mediate motivational effects of food cues.[15] This suggests that heightened sensitivity to palatable food cues may confer greater vulnerability to overeating. Other experimental data show that greater sensitivity to palatable food cues is associated with increased palatable food intake only in persons with lower inhibitory control.[16] These data suggest that strengthening inhibitory control may enhance dietary adherence, and may be especially useful for individuals who are more susceptible to palatable food cues. Mindful awareness of one's own experience, a core focus of mindfulness training, can reduce both impulsive responses to attractive food stimuli and the thoughts that they trigger in experimental situations.[17]

In our theoretical model, mindfulness training directed at eating behavior strengthens the ability to tolerate negative states (e.g., cravings for foods incompatible with one's dietary goals) without enacting maladaptive automatic behaviors (e.g., eating in response to craving), providing a potentially powerful tool for facilitating healthy eating behavior. Given the relations above, we focus on cravings as a primary mechanism for overeating. Our intervention choice, mindfulness, may have the unique ability to help people tolerate cravings and reduce compulsive eating, as our pilot data suggests.

Mindfulness training can also bolster adaptive stress management, and thereby holds the potential to reduce stress-eating, which is associated with poorer metabolic health. **.** People who report stress-eating may be more vulnerable to developing obesity and metabolic syndrome.[18] Mindfulness is associated with lower stress-eating in people with diabetes, cross-sectionally.[8] Our mindfulness-based intervention will include MBSR-based stress management components and Mindfulness Based Eating Awareness Training,[19] which, taken together, act on stress-eating behavior, as well as eating in response to any negative emotions (emotional eating). Improving stress management skills may also directly influence blood glucose levels in T2DM via improvements in maladaptive neuroendocrine responses, as stress hormone responses counteract insulin thereby increasing blood glucose levels..[20,21] Strengthening adaptive coping responses to stress may also facilitate health behavior such as adhering to medication, diet, and exercise regimens.[22,23]

There are important new challenges in optimizing mindfulness-based interventions for diet change. This proposal builds on our group's study of the effects of including mindfulness-based eating and stress management to achieve weight loss and improve metabolic parameters in persons with obesity, but without T2DM (SHINE). While we found evidence of benefits in weight, lipids, and fasting

glucose, we also found variability in participant outcomes by teacher that highlights the need to further optimize the intervention manual/approach.

Carbohydrate restricted (CR) diets can provide an important biomarker (ketone level) for dietary adherence and may improve glucose control in T2DM. Current recommendations from the ADA suggest that a variety of carbohydrate levels may be appropriate for persons with T2DM, including reduced carbohydrate diets.[24] We aim to restrict carbohydrates to approximately 10% of caloric intake, or about 50 g/day in this study for several reasons. This induces a low level of ketone production, which has been termed "nutritional ketosis." This provides an *important biomarker* for dietary adherence that we aim to utilize in this study (See Measures in the Approach section). Unlike diabetic ketoacidosis, nutritional ketosis is a stable metabolic state associated with potential health benefits in persons with T2DM. Several studies suggest that lowering carbohydrate intake to this range can improve glucose control, insulin resistance, plasma triglycerides, plasma C-reactive protein, and body weight. [25-31] For example, in a short-term study conducted in a metabolic ward, 10 overweight persons with T2DM consumed their usual diets for 7 days, followed by a CR diet (21 g/day carbohydrate) for 2 weeks. Participants' mean 24-hour plasma profiles of glucose levels normalized, mean HbA1c decreased from 7.3% to 6.8%, and insulin sensitivity improved by approximately 75% on the carbohydrate restricted diet.[32] Our group has compared a CR diet (< 50 grams/day carbohydrate) to a conventional calorie-restricted diet for T2DM and found a significantly greater improvement in mean HbA1c in those on the carbohydrate restricted diet group (see Preliminary data in Approach for further details).[31]

As in other diet interventions, adherence remains a key challenge. In our diabetes pilot study, we found that with limited long-term behavioral support, by 12-months the improvements in HbA1c had declined -0.2% (-0.8 to 0.4, p = .5; unpublished data). While we considered including different diets in the current study, our primary focus is on the role of mindfulness-based intervention components on dietary adherence. We thus choose to keep the diet consistent across groups, and believe a low carbohydrate diet is a good choice because it offers an effective biomarker of adherence, potential health benefits for persons with T2DM, and clear adherence challenges.

This study includes several key innovations.

1. Our theoretical mechanistic model is novel and highly specific, but with broad significance. Cravings and stress lead to overeating sweets and carbohydrate, which worsen glucose control in T2DM. Our mindfulness intervention is uniquely tailored to focus on regulation of both cravings and stress. This pathway is important in obesity and related disorders, and addiction, and thus has the potential for widespread impact of tailored mindfulness-based behavioral interventions.
2. We measure eating in response to cravings and stress using innovative ecological momentary assessment (EMA) methods. We have developed a novel EMA tool to measure these behaviors in vivo and have over 90% compliance in our pilot studies. EMA methods reduce well-known biases of retrospective reporting in traditional single-administration self-report measures of eating.[33]
    a. We use an innovative biomarker approach to assessing dietary adherence to carbohydrate restriction using blood ketone monitoring. While this measure has been previously used in studies of carbohydrate restricted (CR) diets to monitor adherence to CR (including a study by our group) within a study diet arm, to our knowledge, this study would be the first time ketone monitoring will be used as a biomarker to compare different approaches (i.e., mindfulness versus education only) to achieving dietary adherence.
    b. We use an adaptive intervention design to test optimization of the maintenance phase intervention. Our goal is long-term adherence to health behavior change.

Few mindfulness-based interventions (MBI) have examined long-term maintenance strategies, despite the potential importance. In optimizing a maintenance phase intervention, we believe that calibrating the intervention dose based on how participants are doing may be important. Adaptive intervention designs assign intervention intensity/dose based on how a participant is doing (note that despite similar names and certain parallels. Adaptive intervention designs are a different entity from adaptive clinical trials: In adaptive interventions, therapy is individualized based on decision rules, whereas in adaptive clinical trials, the overall trial protocol is modified in response to accruing trial data.[34] We draw on Sequential Multiple Assignment Randomized Trial (SMART) design methods to test adaptive intervention strategies in the maintenance period.[35]. To our knowledge, adaptive intervention designs have not been tested before in published research on MBI interventions. Testing such approaches to MBI maintenance provides an innovative approach that is well-suited to our particular intervention and will provide an important model for future MBI research

3. STUDY DESIGN

This is a two-phase study. Both phases will use a randomized, controlled trial design. After pilot testing in the first phase, the second phase will include employing an adaptive intervention design in the post-treatment phase to test optimization of the maintenance intervention (i.e. assigning maintenance intensity/dose based on how a participant is doing).

We will use ecological momentary assessment (EMA) methods to measure eating in response to difficult emotions and/or food cravings. In the R61 phase, we will ensure this measure is appropriate for further testing and assess the impact of the MBI components on our hypothesized behavioral mechanisms in N=60 community-dwelling adults with T2DM. We plan 3 waves of 20 persons each with 12 weekly sessions followed by 3 monthly maintenance sessions, to be held at UCSF Osher Center for Integrative medicine. All participants will attend an in-person group course providing education on basic behavioral strategies for diet and physical activity. Participants will be randomized (1:1 ratio) to receive this education alone (Ed) or this same material with added MBI components (Ed+MBI). We will also pilot test two levels of intensity of maintenance phase intervention (monthly group meetings alone or supplemented by individualized attention) to prepare them for R33 testing. Assessments will be done at 0, 3 and 6 months. Study participation lasts approximately 8 months per participant. The R61 phase of the study is 2 years total.

We plan an R33 phase trial in which 120 persons with T2DM will be randomized (using a 1:2 ratio) to Ed or Ed+MBI conditions and followed for 12 months, including a 9-month maintenance phase. We will test the robustness of the effect of MBI components on our proposed behavioral mechanisms, and on dietary adherence, as well as preliminary effect sizes on weight and glycemic control. We will use an innovative adaptive intervention design to optimize maintenance phase intensity, which we believe may be key to augment the MBI effects. For this phase, assessments will be conducted at 0, 3, 6 and 12 months, with study participation lasting approximately 14 months per participant, and the entire r33 phase lasting 3 years.

In both phases, randomization will be done using blocked randomization to ensure approximately equal group sizes, with randomly selected block sizes and will be stratified by BMI (below and above

25, i.e. normal vs. overweight/obese). Neither participants nor study personnel will be blinded to treatment arm.

Primary mechanistic outcome(s): Our primary hypothesized mechanism is reduction in **frequency of eating in response to cravings** as a result of enhanced ability to address food cravings with mindfulness training. Our key measure of this mechanism is frequency of eating in response to cravings using ecological momentary assessment (EMA).

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

Participants must meet all of the inclusion criteria to participate in this study:

1. History of T2DM mellitus. If taking insulin, screening labs will include C-Peptide to rule out T1DM. The study intervention is not designed for people with Type 1 diabetes who make no insulin.
2. HbA1c > 6.5% and < 12.0% at screening. The lower limit confirms the diabetes diagnosis. Persons with a HbA1c > than 12% typically need immediate attention to the medical regimen, and we aim to have this done before entering the trial to better separate the effects of improved medical regimens from the diet intervention. Potential participants with a HbA1c > 12% can be enrolled once glucose control is improved.
3. Experience food-related cravings most days of the week and eat in response to these cravings regularly. A key hypothesis is that our mindfulness approach will reduce cravings and craving-related eating, and this is primary mechanistic outcome. Thus we need to recruit participants who experience this.
4. Aged 18 years old and older. We are not enrolling younger children as they may need an intervention that is better tailored to children.
5. Able to engage in light physical activity. We will be recommending physical activity as part of the intervention.
6. Willing and able to participate in the interventions. Must be interested in following a carbohydrate- restricted diet, willing to learn about mindful eating and behavioral strategies for following prescribed diets, have sufficient control over their food intake so that they can follow either diet, and otherwise be able and willing to participate in the intervention. Intervention content must be practiced to evaluate whether it is effective.
7. Have smartphone and are willing to use it on a regular basis for data collection (e.g. craving EMA assessment).
8. Ability to speak English. Groups will be conducted in English, and we do not have the capacity, given the resources available in this proposal, to translate all course material and conduct groups into another language. We enrolled Hispanic participants into the pilot study who were fluent in English, and expect to do this in the proposed study.

4.2 Exclusion Criteria

Candidates meeting any of the exclusion criteria at baseline will be excluded from study participation:

1. Unable to provide informed consent.
2. A substance abuse, mental health, or medical condition that, in the opinion of investigators, will make it difficult for the potential participant to participate in the intervention or that may need immediate changes in medical management that will affect study outcome measures. Such conditions may include cancer, liver failure, renal failure, untreated hypo or hyperthyroidism,

or history of serious bulimia. The study will be conducted in a group setting, and persons with significant substance abuse or mental health conditions that interfere with social functioning in a group setting may be disruptive. Other medical or mental health conditions that need immediate changes in management, such as thyroid disorders, need to be addressed before starting the intervention so that more reliable baseline measurements can be made prior to beginning the intervention. Some other serious medical conditions that may alter key study outcomes or require other important diet modifications, including untreated hypothyroidism, renal failure, cirrhosis, and conditions requiring oral or parenteral glucocorticoid treatment.

3. Pregnant or planning to get pregnant in the next 6 months, breastfeeding or less than 6 months post-partum. The intervention is not designed for the particular diet considerations during pregnancy and breast-feeding.
4. Current use of weight loss medications, such as Alli or amphetamine-based drugs that may affect weight. These treatments may make it difficult to discern the effects of the intervention on outcomes such as weight.
5. Planned weight-loss (bariatric) surgery or bariatric surgery within the past 18 months. Bariatric surgery is likely to change study outcome measures, making it difficult to distinguish the effects of the intervention program.
6. Currently enrolled in a weight loss program, such as Weight Watchers or a self-help group such as Overeaters Anonymous, or have unalterable plans to enroll in one of these programs in the next year. These plans may contaminate study intervention outcomes and provide participants with mixed messages about their diet.
7. Vegan or vegetarian. The carbohydrate-restricted intervention diet is more challenging for vegan or vegetarian participants and needs particular tailoring that is difficult to address in adequate detail in a group setting.
8. Unwilling to do home ketone monitoring.

4.3 Study Enrollment Procedures

Identifying and recruiting candidates for the trial entails advertising the study to potentially-eligible participants who will then contact the study for screening and enrollment steps. We will perform outreach based on methods from our previous research. These approaches will be tailored to each of the three main venues at which we plan to recruit: (1) San Francisco General Hospital (SFGH)/SF Health Network: The study team has extensive experience working with the SFGH population. Recruitment in this venue will capitalize on an existing infrastructure for diabetes education. In addition, outreach will be performed at the Diabetes clinic and the General Internal Medicine clinic. (2) UCSF Clinics: We will identify potentially eligible participants through the CTSI recruitment services unit, which reviews electronic medical records and sends patient letters. We have successfully used this service in prior studies. (3) General outreach: This includes outreach through online ads and in local newspapers, posting flyers in public locations, and outreach to community clinicians. Our team has successfully applied these methods in a variety of studies.

Potential participants will make initial contact either by completing the web-based, Qualtrics-powered eligibility screening survey or by calling the study line. Before completing the online study screener, participants will be asked to review the study website as well as the full-study consent (available on the website). They will then complete an online consent to be screened for study eligibility.

Any participants who are screened eligible from the Qualtrics screening survey will complete a phone screen to determine initial eligibility. During this call, staff will confirm basic eligibility criteria. The study procedures, including what is involved in participating in the study, as well as the assessment

visits will be described to potential participants. The goal is to ensure they understand the commitment involved in study participation. Those who do not meet primary eligibility criteria will be told that they are not eligible to participate. Those who meet initial criteria and express continued interest in participating will complete craving EMA screening and assessment. Those who successfully complete the above steps will come in for an in-person screening and consent visit.

Study enrollment, including reasons for ineligibility at any point along the steps to enrollment or for non-participation of eligible candidates, will be tracked within our study Salesforce database.

Randomization to intervention group and maintenance phase track will be done via the Salesforce database. The randomization table will be programmed by a database manager, who is not otherwise involved in enrollment or other participant procedures. Randomization will be done via the Project Director, Dr. Moran, who will not have access to the randomization table. When a participant ID number is entered into the database by study staff, a group assignment is revealed. This provides a computerized group assignment that cannot be altered by study staff and the group assigned is immediately recorded in the study database. Randomization will be done approximately 2 weeks prior to the start of classes in order to minimize post-randomization drop-out due to life circumstances that might affect participant ability to attend classes (e.g. such as job loss/change, family emergency, etc).

5. STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

All participants will attend 12-weekly study intervention classes based on their random assignment: either Education alone (Ed) or Education+Mindfulness (Ed+MBI). Study groups will be held at the UCSF Osher Center for Integrative Medicine. Both groups will learn and follow a carbohydrate-restricted (CR) diet for T2DM, and will participate in maintenance phase activities. If assigned to Ed+MBI, they will also learn and practice mindfulness-based skills.

Maintenance phase: In the R61 phase, we will pilot test two levels of intensity of maintenance phase intervention (monthly group meetings alone or supplemented by individualized attention) to prepare them for R33 testing.

5.2 Handling of Study Interventions

Intervention content for the Ed program: All participants will receive instruction in the CR diet and basic behavioral strategies in a weekly, in-person, group sessions meeting for 1 to 1.25 hours for 12 weeks. A nutritionist or health professional with experience implementing CR diets with people with T2DM will train participants in how to follow the study diet, utilizing our study manual and curriculum materials developed by the team based on prior studies. The study diet has approximately 10% of kcal coming from carbohydrate, typically 50 grams/day or fewer, not including fiber. Participants will be encouraged to eat a normal amount of protein, typically about 80-100 grams/day (about 20-25% of calories), and the rest of their calories from fat. Foods that are encouraged include green leafy and other non-starchy vegetables, nuts, seeds, oils (especially olive oil), fish, poultry, tofu, and avocados. Other foods consistent with the diet include berries (in modest amounts), meats, eggs, and cheese. Key foods to minimize include any sugar-sweetened foods or beverages, bread, pasta, potatoes, highly processed packaged foods, and other starchy foods. We have developed extensive

materials to educate participants in practical and nutritionally sound approaches to a carbohydrate restricted diet.

Cognitive and behavioral components**:** All participants will receive core behavioral intervention components derived from the Diabetes Prevention Program (DPP),[36] which include goal-setting and self-monitoring of weight, diet, and physical activity..

Intervention content for the Mindfulness program: In addition to the diet components, participants randomized to the Ed+MBI group will receive MBI components using the Eat Right Now (ERN) platform. This will consist of two integrated components: 1) use of the ERN app at home, during the week, to learn and practice mindfulness skills for food-cravings and eating, and 2) in-person group-based discussions of how the mindful eating practices are going, trouble-shooting obstacles/pain points, and doing group exercises and reflecting on them. The Eat Right Now program provides brief videos of 2 to 6 minutes in length on mindfulness and mindful eating topics. Participants can watch the video segments for the week at the beginning of in-person sessions each week. The video segments can also be viewed on a smartphone or tablet at home in a self-paced manner. In person sessions will be led by an experienced mindfulness instructor with training in mindful eating and familiarity with a CR diet for T2DM, and will focus on discussion of how the mindful eating practices are going, trouble-shooting obstacles/pain points, and doing group exercises and reflecting on them. The Eat Right Now app also includes the audio tracks of meditation exercises are core components of our mindful eating program (e.g. body scan, mindful eating practices) that participants can access at any time – which will allow them to cultivate their mindfulness practice in the context of their daily lives. Twelve one-hour sessions addressing mindful eating will be conducted weekly for 12-weeks (monthly during maintenance), before each diet session. The key content of the mindful eating intervention components focuses on: helping people improve their relationship with food and control food cravings, using mindful eating approaches including: paying attention, noticing habit loops, understanding brain science and food/sugar addiction, disrupting emotional and stress eating, cultivating acceptance and curiosity, learning lovingkindness, detaching from thoughts, using healthy restraint, and maintaining motivation.

5.3 Concomitant Interventions

5.3.1 Allowed Interventions

Participants are allowed to continue on medications prescribed by their physicians, except for those outlined in the exclusion criteria: oral or parenteral glucocorticoid treatment; weight loss medications or supplements such as Alli or amphetamine-based drugs that are believed to effect on weight.

5.3.2 Required Interventions

There are no required supplements or medications for this study.

5.3.3 Prohibited Interventions

As per the eligibility criteria, people utilizing the following interventions will be excluded from the study: current use of weight loss medications or supplements, such as Alli or amphetamine-based drugs that are believed to effect on weight; current enrollment in a weight loss program, such as Weight Watchers or a self-help group such as Overeaters Anonymous, or unalterable plans to enroll in one of these programs in the next year; history of or planned weight loss surgery.

5.4 Adherence Assessment

Our primary measure of adherence to study regimen is attendance at weekly class sessions, defined as 2/3 of the weekly study intervention sessions attended (i.e. 8/12).

6. STUDY PROCEDURES

6.1 Schedule of Evaluations

Assessment	Screening/ Consent Visit	Baseline Assessments	Randomization	Intervention Period	3 Month Follow-Up	Randomization to maintenance phase	6 Month Follow-Up
Informed Consent	x						
Health History	x						
Demographics and Background Information	x						
Inclusion/Exclusion Criteria	x						
Craving EMA Assessment	x	x		x	x		x
Blood Draw/Labs	x	x			x		x
Online questionnaires/self-report Measures		x			x		x
24-hour diet recall		x			x		x
Cognitive Measures	x				x		x
Weight		x			x		x
Enrollment/Randomization			x				
Diet and/or Mindfulness Education				x			
Ketone monitoring for Dietary Adherence				x	x		x
Home glucose monitoring for safety				x			
Randomization to maintenance phase						x	

6.2 Description of Evaluations

6.2.1 Screening Evaluation

Consenting Procedure

At the first visit, study staff will provide participants a copy of Experimental Subjects Bill of Rights, then review the consent form with the participant. A single consent form will be used; it describes both the screening and the study procedures. If they are interested, participants will have the consent form and HIPAA form read aloud to them and will have unlimited time to review it on their own carefully. The study staff will verbally outline the important points of the consent form, including that the study is voluntary and they can drop out at any time, that participation or lack thereof of will not affect their medical care, and that all information is kept confidential. The main requirements and inconveniences involved in the study will also be described. They will be informed about physical risks involved. Interested participants will then sign the consent form, the staff person will co-sign it, and a photocopy will be given to the participants to keep if desired.

Written informed consent with the participant will be done by either the Project Director, study coordinator, and/or research assistant. All staff involved in consenting will have completed human subjects CITI training. Documentation of signed consent will be completed in the study Salesforce database.

Screening

Online screener: Interested potential participants will visit the study website, which will consist of the IRB-approved study flier, with link to consent form and online screener. After completing online consent to be screened, they will complete a questionnaire to screen for initial eligibility of the following:

- T2DM, HBa1c within range, experience food cravings and craving-related eating, willing and able to participate in the interventions (including diet and mindfulness components, schedule allows for class attendance and study visits), able/willing to use own smartphone for study procedures; excluded substance abuse, mental health, medical conditions, or medications; 18 years or older, able to engage in light physical activity, English-speaking, pregnancy-related exclusions; weight-loss medications, programs, or surgery exclusions; vegan or vegetarian; unwilling to do home monitoring.

Phone screen: Study staff will review completed online screeners and call those who appear to be potentially eligible to confirm and further assess eligibility and discuss questions a participant may have.

Craving EMA: Those who pass the phone screen will be asked to complete the craving EMA screening and assessment. This step provides confirmation of food-craving and craving-related eating criterion. If this step is completed more than 4 weeks before the class start date, it will be repeated for baseline assessment prior to randomization.

In-person screening and consent visit: Those who successfully complete the above steps will come in for an in- person consent and screening visit. After completing written consent, they will complete additional screening and provide baseline data as follows:

- Demographics and background information
- Health history and medications to finalize screening for excluded substance abuse, mental health, medical conditions, or medications.
- Weight measurement and computerized tests of behavioral impulsivity and other cognitive tasks.

- Blood draw/labs to confirm eligilbity: T2DM, Hba1c in range; TSH in normal range, normal liver and kidney function). If Hba1c is measured more than 4 weeks before the class start date, it will be repeated at the baseline blood draw.

All screening evaluations will be completed within 8 weeks prior to class start date.

6.2.2 Enrollment, Baseline, and/or Randomization

Enrollment

Participants will become enrolled upon randomization, after meeting all screening criteria and completing all of the baseline assessment procedures.

Baseline Assessments

Those who complete the consent visit and whose screening labs are within range will complete the following baseline assessments from home/online: Qualtrics questionnaire (to assess baseline eating behavior, mood, stress, etc), 24-hour diet recall, and baseline blood draw at LabCorp convenient to them. Those whose screening Craving EMA was completed more than 4 weeks before the class start date will repeat this assessment in order to get baseline data more proximal to when the intervention starts.

Blood draws and lab tests will be done at LabCorp.

Test	Rationale	Screening	Baseline	Follow-up (3 & 6 mos)
HbA1c	Overall glucose control	x	x	x
C-peptide (for those on insulin)	Confirms T2DM in those on insulin	x		
TSH	Rule out untreated thyroid disorder	x		
Comprehensive Metabolic Panel	Rule out liver and kidney dysfunction	x		
Glucose, Plasma (fasting)*	Used to calculate HOMA-IR		x	x
Insulin*			x	x
hsCRP	Examine effects of the diet on cardiometabolic and inflammatory markers		x	x
Lipid Panel			x	x
NMR LipoProfile® (Without Graph)—includes lipids			x	x

24-hour dietary recall: Despite limitations of self-report measures in assessing dietary intake, they remain an important tool to assess dietary adherence. 24-hour diet recall provides a measure that complements the ketone measure by providing overall diet composition information that cannot be obtained from ketone measures. We will use the University of Minnesota's Nutrition Data System for Research (NDSR) software to perform 24-hour diet recall (http://www.ncc.umn.edu/products/). This is a widely-used dietary analysis program that enables the collection of multiple 24-hour diet recalls and encompasses multiple foods appropriate for diets of type 2 diabetic patients. Dietary recalls will be administered by trained dietetics volunteers by co-investigator Dr. Cindy Leung, a nutrition epidemiologist with extensive history of conducting 24-hour recalls. Recalls will be entered into the NDSR software immediately after completion. Dietary recalls will be conducted without prior notification to avoid changes in diet on the reporting day.

Craving EMA: We hypothesize that a key behavior mechanism by which training in mindfulness can

improve diet adherence is through reducing eating behavior in response to food cravings. This mobile, real-time EMA approach allows us to capture eating-related behavior and that is often brief and automatic and therefore poorly suited to traditional retrospective questionnaires. Participants will complete EMA of food cravings and craving-related eating via smartphones prior to, during, and following the intervention, a total of up to 6 times. During each of these craving-assessment periods, participants will receive mobile cravings assessment via text 3 times per day for 3 days. The text message will ask them to complete a short questionnaire regarding whether they have experienced any food-related cravings in the past few hours, whether they have eaten in response to these cravings, and what they ate. They will also be asked to rate their stress level during the day.

Computerized Cognitive Measures: The computer session will comprise approximately 20-30 minutes of the tasks described below. These tasks can be adjusted to be shorter than their stated length by reducing the number of trials administered. This is a common practice in neuropsychological science research. We will create a 20-30 minute battery from the following tasks:

- Delayed Discounting[37];. The DD (1 minute) assesses the extent to which individuals value delayed versus proximal rewards. Individuals who discount delayed rewards at a high rate are more likely to engage in substance abuse, overeating, or problem gambling. This 5-trial adaptation of the original Delayed Discounting,[38] task has been validated and is an effective way to assess discount rates while reducing participant burden. The primary outcome is the participant's point of indifference, which is computed with intertemporal choice tasks that present a series of discrete choices between a larger quantity of a reward that is delayed and a smaller amount of that commodity that is available immediately.
- Go/No-Go;[39] The Go/No-Go task (~12 minutes) is a computer task that measures sustained attention and response control, also termed behavioral inhibition. Participants are asked to watch a rectangle (oriented either vertically or horizontally), and press the spacebar as quickly as possible when the rectangle's color becomes green. In contrast, when the rectangle becomes blue, participants are asked to restrain from pressing the spacebar. The primary outcome is the number of trials correctly identified, and response time, where faster performance and better capacity to inhibit responses to blue rectangles relative to green, indicates better response inhibition.
- Food Stroop.[40] The food Stroop task (~5 minutes) is an adaptation of the classic Stroop task, and thus provides an easily quantifiable measure of food preoccupation. Subjects are asked to color-name food- and weight-related words written in different-colored inks, compared with neutral words.
- Relative Reinforcing Efficacy (RRE) of Food.[41] This task (~3 minutes) measures the relative reinforcement value of tasty foods as participants indicate how much they would be willing to pay. These choices reflect decisions that people face in the real world when experiencing the motivation to eat.
- Dot Probe.[42] This modified visual probe task (~4 minutes) measures selective attentional processing of images of food relative to neutral images. The task consists of 10 practice trials and 4 blocks that each consisted of 100 experimental trials, of which 60 are target trials (food–neutral picture pairs) and 40 are filler trials (neutral–neutral picture pairs).

Online questionnaires/self-report measures: We will use a targeted battery of questionnaires assessing food cravings and other eating-related behaviors, as well as standard measures of psychological distress. These will be completed via Qualtrics, and can be completed at home, via the internet. Participants who prefer to come to the lab to complete these using a study computer may schedule a time to do with study staff during business hours.

- Perceived Stress Scale (PSS).[43] 10-item measure assessing the degree to which someone perceives stress.
- Patient Health Questionnaire (PHQ-8).[44] A standardized, well-validated 8-item measure of depressive symptoms.
- Reward-Based Eating Drive (RED).[45] The 9-item RED scale assesses three aspects of drive to eat (loss of control, lack of satiety, and preoccupation with food). Items are answered on a Likert scale from 1 (not at all like me) to 5 (very much like me). The title of the RED questionnaire provided to participants is “Eating Experiences.” Example items include "I feel out of control in the presence of delicious food" and "When I start eating, I just can't seem to stop."3
- Food Craving Questionnaire - Trait Reduced Version (FCQ-T-R).[46] The 15-item FCQ-T-R assesses (1) preoccupation with food (i.e., obsessive thought about food and eating), (2) loss of control (i.e., difficulty regulating eating behavior when exposed to food cues), (3) positive outcome expectancy (i.e., believing eating to be positively reinforcing), and (4) emotional craving (i.e., tending to crave food when experiencing negative emotion).2
- Stress-related Eating. [47] The 2 items used in the Midlife in the United States (MIDUS) study asked participants to indicate how they usually experience a stressful event using the following two items: “I eat more of my favorite foods to make myself feel better” and “I eat more than I usually do". Items are answered on a scale from 1 (a lot) to 4 (not at all). Responses are reverse-coded and summed, with higher scores indicating greater use of food in response to stress. Item correlations are good (= .80, = .81).4
- Palatable Eating Motives Scale.[48] The 19-item PEMS assesses four motives for eating tasty food (Social, Conformity, Enhancement, and Coping motives) and is modeled after the Drinking Motives Questionnaire (M. L. Cooper, 1994). Items are answered on a 5-point scale with the following options: Almost Never/Never; Some of the Time; Half of the Time; Most of the Time; Almost Always/Always.1
- 1-item Stress Eating.[18] This 1-item measure has been shown to predict weight gain and worsened metabolic factors in times of stress. This item asks, “how much do you tend to eat when you are under moderate stress?” and is responded to on a 5-point scale from much less than usual to much more than usual.5
- Weight Efficacy Lifestyle Questionnaire – Short Form (WEL-SF).[49] The ability to adhere to a diet in the face of difficult situations, such as dietary lapses, socializing, and peer pressure is integral to long-term maintenance of intervention effect. We will assess dietary adherence self-efficacy using the 8-item which assesses abilities to adhere to dietary prescriptions in a variety of situations.
- Loss of control over Eating – Brief (LOCES-Brief).[50] This 7-item measure assess perceived control over one’s eating. Items are assessed on a 100mm visual analogue scale ranging from “not at all hungry” or “not at all anxious” etc., to “extremely hungry” or “extremely anxious” etc.
- Food Acceptance and Action Questionnaire (FAAQ).[51] This 10-item questionnaire applies constructs of acceptance and mindfulness to eating behavior. Higher scores indicate greater acceptance of motivations to eat. Items are answered on a 6-point Likert scale ranging from 1 (very seldom true) to 6 (always true). A summary score is calculated by summing the scores from all items – higher scores indicate greater acceptance of motivations to eat.9
- Control of Eating Questionnaire (CoEQ).[52] This 21-item measure assesses food craving for sweet and savory, dietary restraint, and mood over the previous 7 days. Items are assessed on a 100mm visual analogue scale that varies in its anchors to capture the experience of food craving assessed by a given item.7

- Dutch Restrained Eating Scale.[53] This 10-item subscale of the Dutch Eating Behavior Questionnaire assesses the frequency of restrained eating behavior. Items are assessed on a 5-point likert scale ranging from 1 (never) to 5 (very often).8
- Five Factor Mindfulness Questionnaire (FFMQ).[54] We will use the short-form of the FFMQ which assesses general tendencies to be mindful in experiences of daily life.
- Promis-29 (www.nihpromis.org): A collection of 4-item short forms assessing anxiety, depression, fatigue, pain interference, physical function, sleep disturbance, and ability to participate in social roles and activities as well as a single pain intensity item. The PROMIS measures a system of highly reliable, precise measures of patient–reported health status for physical, mental, and social well–being.
- Self-Compassion Scale Short Form (SCS-SF13).[55] The SCS-SF is a 12-item measure that assesses dimensions of self-compassion including self-kindness, self-judgment, common humanity, isolation, mindfulness, and over-identification.

Weight

- One of the goals of dietary adherence for persons with T2DM is weight loss. We will use the same scale to weigh participants at each time point.

Randomization

Participants will be randomized to intervention groups after completion of all screening and baseline assessment steps, and before initiation of intervention. Randomization will be done approximately 2 weeks prior to the start of classes in order to minimize post-randomization drop-out due to life circumstances that might affect participant ability to attend classes (e.g. such as job loss/change, family emergency, etc).

6.2.3 Blinding

Not applicable for this study.

6.2.4 Follow-up visits and other data collection

Follow-up assessments at 3 and 6 months include the following (all described above in the baseline assessment section):

- Blood draws/laboratory tests
- Weight measurement
- Computerized tests of behavioral impulsivity and cognitive tasks
- Health history/medication changes
- Online battery of self-report questionnaires; may be completed at in-person visit if preferred (described above)
- 24-hour dietary recall
- Craving EMA

We aim to complete the 3 and 6 month visits with all participants within a 2-3 week window at these timepoints.

At-Home Ketone Monitoring: Participants will be given a home ketone monitoring device (Precision Xtra® System) and ketone strips, which measure beta-hydroxybutyrate. This is a glucometer device that also measures ketones from finger-stick blood if ketone strips are inserted instead of glucose

strips. The device store data, which will be checked periodically during class sessions to confirm accuracy of self-reported measurements. *Frequency*: Participants will be asked to measure ketones before dinner 3 times a week for approximately 4 weeks during the intervention (to provide more intensively self-monitoring when starting the diet) and twice weekly thereafter to monitor ketosis/diet adherence. We will use the EMA system to send requests to check ketone levels and report values back. During study visits, participants will be asked to bring in the meter and staff will download data on devices to provide a check on accuracy of participant reported measures.

6.2.5 Completion/Final Evaluation

The assessments to be performed at the final evaluation at are listed above (section 6.2.4).

The only potential reason for early termination that we anticipate are participant-driven, including having to move out of the Bay Area, or dislike of/unwillingness to continue to follow the study diet. We will take steps to help participants implement the study diet in a way that works well for them, in order to prevent these kinds of early terminations. Participants who experience a life event (e.g. job change, family crisis) that affects their ability to continue to attend the intervention classes will be encouraged to continue to follow the study diet and other intervention steps to the best of their ability. They will be offered course materials and handouts in order to facilitate their ability to maintain behavioral changes that they made to date. Participants who discontinue the study intervention early will be asked to remain in the study and complete follow-up assessments as originally planned. If a participant moves out of the Bay Area or otherwise is unable or unwilling to come for a study follow-up visit, study staff will work with them to complete questionnaires online and have a blood draw at a LabCorp location convenient to them.

7. SAFETY ASSESSMENTS

7.1 Specification of Safety Parameters

The key study intervention involves diet changes, which in general is a minimal risk intervention step. The risk of hypoglycemia in persons receiving medications such as insulin or sulfonylureas is a possible serious potential adverse event, however. We anticipate that with the precautions described in detail below, the risk of serious hypoglycemia will be very low. While we encountered no serious adverse events in pilot testing, there has been little careful long-term assessment of adverse events with carbohydrate restricted diets in T2DM, which means there is some uncertainty in predicting the likelihood of adverse events. Other anticipated risks include those associated with venipuncture, psychological testing, and loss of confidentiality. None of these risks are anticipated to occur at a frequency exceeding 5%.

Expected risks to the subject from the carbohydrate-restricted diet are as follows:

1. Hyperlipidemia: There have been reports this approach, which involves increases in proportion of calories from fat, causing increases in LDL cholesterol, a risk factor for heart disease. However, several clinical trials of carbohydrate restricted diets for obesity, including three of up to one-year duration, have not shown this relationship:

1. Dansinger ML, Gleason JA, Griffith JL, Selker HP, Schaefer EJ. Comparison of the Atkins, Ornish, Weight Watchers, and Zone diets for weight loss and heart disease risk reduction: a randomized trial. *JAMA.* 2005;293(1):43-53.

2. Foster GD, Wyatt HR, Hill JO, et al. A randomized trial of a low-carbohydrate diet for obesity. *N Engl J Med.* 2003;348:2082- 2090.

3. Stern L, Iqbal N, Seshadri P, et al. The effects of low- carbohydrate versus conventional weight loss diets in severely obese adults: one-year follow-up of a randomized trial. *Ann Intern Med.* 2004;140(10):778-785.

We will monitor serum fasting lipid profiles at baseline, 3, and 6 months (also 12 months in R33 phase) to assess this potential risk.

2. Hypoglycemia: The carbohydrate restricted diet may lead to decreases in glucose levels. In persons receiving medications such as sulfonylureas or insulin, this could increase the risk of hypoglycemia if appropriate medication adjustments are not made while the participant is transitioning into nutritional ketosis (once in nutritional ketosis, beta-hydroxybutyrate as a preferred CNS fuel offers some protection against symptomatic hypoglycemia.[56]). In our pilot study, we used a medication reduction algorithm that resulted in no episodes of hypoglycemia. For the proposed study, we will use a similar algorithm.

Initial HbA1c	Initial medication reduction
6.5-7.0%	• Continue: Metformin, TZD • Reduce by 50%: Basal insulin • Stop: Secretagogue, prandial insulin, pre-mixed insulin, acarbose, GLP-1 ag/DPP4 inhibitor
7.1-8.0%	• Continue: Metformin, TZD • Reduce by 50%: Basal insulin, pre-mixed insulin, secretagogue, GLP-1 ag/DPP4 inhibitor • Stop: Acarbose, prandial insulin
8.1-12%	• Continue Metformin, TZD, secretagogue, basal insulin, GLP-1 ag/DPP4 inhibitor • Reduce by 50%: Pre-mixed insulin, • Stop: Acarbose, prandial insulin

TZD: thiazolindinedione; secretagogue: sulfonylureas and megltinides; GLP-1 ag: glucagon like peptide 1 agonist; DPP-4 inhibitor: dipeptidyl peptidase 4

For the first 6 weeks of the trial, participants on non-insulin medications will be asked to check blood glucose (BG) fasting and pre-dinner. If taking insulin, participants will be asked to check BG before each injection (standard of care). BGs will be reviewed on a weekly basis by study physicians, including an endocrinologist. If the majority of BG values drop below 110, or there are other concerning BG patterns, we will reduce/stop medications in the following order:

1. Pre-mixed insulin
2. Secretagogue
3. GLP-1 ag/DPP4 inhibitor
4. Basal Insulin
5. TZD
6. Metformin

Study physicians will review these medication adjustments as well as any symptoms reported by participants using information collected from participants on a weekly basis, and will communicate

suggested changes in diabetes medications to participants. Study participants will be able to contact study staff using a study phone number for questions or problems, and staff will be able to reach study physicians by pager for more urgent problems. As in our pilot study, primary care physicians for participant will receive information about the study before the participant begins the study. Study physicians will help to make sure that primary care physicians informed of any suggested changes to medication regimens, and will consult with primary care physicians where indicated.

3. *Other theoretical risks* of the carbohydrate restricted diet include nephrolithiasis and increased bone turnover. The potential for these side effects is derived from pathophysiologic theory, studies of the diet using intermediate endpoints, and extrapolation from similar diet approaches, such as the ketogenic diet for epilepsy. Because kidney stones and bone fractures have not been reported as an actual adverse effect of this diet in the research literature, we cannot estimate their frequency. We will be recording adverse events that occur during the study.

4. *Minor adverse effects*: With this diet, several minor side effects may occur and include constipation, headache, muscle cramps, diarrhea, general weakness, and rash. Most of these occur at diet initiation, are short-lived, and are generally alleviated by adequate fluid intake and other minor diet modifications that will be thoroughly addressed in the intervention. Participants will be instructed to speak to the instructor *or contact study staff* if they experience discomfort, such as constipation, diarrhea, weakness, muscle cramps, or dizziness. There is extensive instruction during class on how to address any potential side effects stemming from the diet.

7.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

Unanticipated problems will be recorded in the Salesforce study database throughout the study. We will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. We will monitor serum fasting lipid profiles at baseline, 3, and 6 months (also 12 mos in R33 phase). Events will be followed for outcome information until resolution or stabilization.

Safety parameters will be reviewed and analyzed per the schedule below.

Data type	Frequency of review	Reviewer
AEs and rates (including out-of-range lab values)	Monthly	PI, Internal QA Reviewer
	Semi-annually	Independent Monitors
	Annually	NCCIH
SAEs (unexpected and related)	Per occurrence	PI, Independent Monitors, NIH/NCCIH
SAEs (expected or unrelated)	Per Occurrence	PI, Internal QA Reviewer
	Annually	Independent Monitors, NIH/NCCIH
Unanticipated Problems	Monthly	PI, Internal QA Reviewer
	Per Policy	IRB

Study progress and safety will be reviewed monthly (and more frequently if needed). Progress reports, including patient recruitment, retention/attrition, and AEs will be provided to the Monitoring Committee semi-annually. An Annual Report will be compiled and will include a list and summary of AEs. In

addition, the Annual Report will address (1) whether AE rates are consistent with pre-study assumptions; (2) reason for dropouts from the study; (3) whether all participants met entry criteria; (4) whether continuation of the study is justified on the basis that additional data are needed to accomplish the stated aims of the study; and (5) conditions whereby the study might be terminated prematurely. The Annual Report will be sent to the Independent Monitor and will be forwarded to the IRB and NCCIH. The IRB and other applicable recipients will review progress of this study on an annual basis

7.3 Adverse Events and Serious Adverse Events

An **adverse event (AE)** is generally defined as any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome or disease which either occurs during the study, having been absent at baseline, or if present at baseline, appears to worsen. Adverse events are to be recording regardless of their relationship to the study intervention.

A **serious adverse event (SAE)** is generally defined as any untoward medical occurrence that results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly.

Laboratory values that will be collected to assess safety: We will monitor serum fasting lipid profiles at baseline, 3, and 6 months (also 12 months in R33 phase). Abnormal lipid values are defined using the Common Terminology Criteria for Adverse Events (CTCAE) v 4.0 criteria provided below (https://evs.nci.nih.gov/ftp1/CTCAE/Archive/CTCAE_4.02_2009-09-15_QuickReference_5x7_Locked.pdf).

Adverse Event: Hypertriglyceridemia
Short Name: Hypertriglyceridemia
MedDRA Code: 10020870

Grade	Description
1	150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42mmol/L
2	>300 mg/dL - 500 mg/dL; >3.42 mmol/L- 5.7 mmol/L
3	>500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L
4	>1000 mg/dL; >11.4 mmol/L; life-threatening consequences
5	Death

Adverse Event: Cholesterol high
Short Name: Cholesterol high
MedDRA Code: 10008661

Grade	Description
1	>ULN - 300 mg/dL; >ULN - 7.75 mmol/L
2	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L
3	>400 - 500 mg/dL; >10.34 - 12.92 mmol/L
4	>500 mg/dL; >12.92 mmol/L

AEs to be collected as solicited events at study visits include recent hospitalizations and hypoglycemic episodes. Unsolicited events will be recorded in the study Salesforce database. AE data that is formally assessed at study visits will be compared to existing unsolicited events in participant records to avoid double capture.

7.4 Reporting Procedures

Serious Adverse Event reporting will be in accordance with the UCSF IRB Regulations (http://irb.ucsf.edu/sites/hrpp.ucsf.edu/files/post-approval-reporting-summary-sheet.pdf) and Code of Federal Regulation Title 21 Volume 5 Part 312.32.

Incidents or events that meet the OHRP criteria for unanticipated problems require the creation and completion of an unanticipated problem report form. OHRP recommends that investigators include the following information when reporting an adverse event, or any other incident, experience, or outcome as an unanticipated problem to the IRB:

- Appropriate identifying information for the research protocol, such as the title, investigator's name, and the IRB project number;
- A detailed description of the adverse event, incident, experience, or outcome;
- An explanation of the basis for determining that the adverse event, incident, experience, or outcome represents an unanticipated problem;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem.

Adverse Event Reporting

SAEs that are unanticipated, serious, and possibly related to the study intervention will be reported to the Independent Safety Monitor(s), UCSF IRB, and NCCIH in accordance with requirements.

- Unexpected fatal or life-threatening AEs related to the intervention will be reported to the NCCIH Program Officer, and Independent Safety Monitor(s) within 3 days of the investigator becoming aware of the event. Other serious and unexpected AEs related to the intervention will be reported within 5 working days.
- Anticipated or unrelated SAEs will be handled in a less urgent manner but will be reported to the Independent Safety Monitor(s), IRB, and other oversight organizations in accordance with their requirements and will be reported to NCCIH on an annual basis.
- All other AEs documented during the course of the trial will be reported to NCCIH on an annual basis by way of inclusion in the annual report and in the annual AE summary which will be provided to NCCIH and to the Independent Monitors. The Independent Safety Monitor(s) Report will state that all AEs have been reviewed.

7.5 Follow-up for Adverse Events

Adverse Events will be followed for outcome information. Study personnel will follow-up with participants on a regular basis (frequency to be determined by the nature of the problem) until the problem has resolved or stabilized. These contacts may be made by the PI or other study physician or personnel (including staff, Project Director) and will be done via phone and/or email or text as the PI deems appropriate depending on the event and situation, and taking into account participant preference as reasonable.

7.6 Safety Monitoring

While the overall risks of this study are low, due to clinical trial design and the use of a treatment that has a low but possible risk of serious adverse effects, we will employ a two-person data safety-monitoring board with outside reviewers. The outside reviewers will not otherwise be part of the study team, and will include an experienced clinical investigators and statistician. The reviewer's CVs will be submitted to NIH, and agreement will be obtained from NIH that the reviewers are suitably qualified before beginning the study. The PI will ensure continuous and close monitoring of participant safety. The PI will report to the DSMB. Study progress and safety will be reviewed weekly by the PI and core study team. A report that will be submitted to the outside reviewer will be compiled every 6 months and will include a list and summarization of adverse events. In addition, the report will address (1) whether adverse event rates are consistent with pre-study assumptions; (2) reason for dropouts from the study; (3) whether all participants met entry criteria; and (4) whether continuation of the study is justified on the basis that additional data are needed to accomplish the stated aims of the study. If the DSMB requires an interim analysis based on the occurrence of severe adverse events, we will develop plans for conducting these in consultation with the statistician on this RCT. The outside monitoring reports will be increased in frequency if two or more Serious Adverse Event's (SAE's) with attribution to study related procedures as possibly, probably or definitely related occur in a six-month period of time. In this situation, SAE's will be reported monthly, and study procedures will be reviewed to determine if changes are needed to reduce the risk of SAEs.

Steps Emanating from Data Review: The DSMB will be able to recommend amendments to the protocol, changes in study procedures, changes to the data collection plan or study forms, or study termination due to safety or other issues. Should recommendations be made to amend the study protocol or terminate the study, these recommendations and planned responses will be forwarded to the NIH program officer within 10 working days. Should the protocol be amended as a result of data review, the UCSF IRB will be notified and the amendment approved prior to study amendment implementation unless the protocol amendment must be implemented to protect the immediate safety of the study subjects. In such a case, the protocol amendment will be immediately implemented and the UCSF IRB will be notified directly after protocol amendment implementation.

The PI will be the primary individual responsible for data and safety monitoring. The DSMB Chair will not be named as a co-investigator on this RCT and will serve as a secondary safety monitor determine what steps should be taken to manage AEs and SAEs if/when they occur. In the event that a SAE is identified, the DSMB Chair will schedule a full meeting of the DSMB and review the results of the SAE report from the UCSF CHR prior to this meeting. The decisions of the IRM and the DSMB will assist Dr. Hecht with developing plans to implement this RCT in a manner that minimizes research-related risks to participants.

DSMB Reviews. Annual DSMB meetings will be held via teleconference. Where a SAE occurs, a special closed meeting of the DSMB will be convened to determine what changes if any are necessary and if the RCT should be stopped.

8. INTERVENTION DISCONTINUATION

Stopping Guidelines: No interim analyses are planned and we do not anticipate stopping the study early. The primary clinical outcome variable, HbA1c, is a surrogate marker for long-term risk of clinical events in diabetes, but is not an outcome that would justify early termination rules for a study of this size and duration. However, the occurrence of any serious adverse events related to intervention or

assessment procedures will be reviewed at length by the DSMB in separately scheduled, closed meetings (if or when severe adverse events occur) to determine whether the study should be stopped. Where the DSMB considers issues related to participant safety, the DSMB Chair will moderate closed sessions and take a formal vote from DSMB members as to whether the trial should continue given the occurrence of the adverse event(s).

9. STATISTICAL CONSIDERATIONS

9.1 General Design Issues

Our overall hypothesis is that improved ability to manage food cravings and emotional eating is a key mechanism through which mindfulness-enhancements can improve dietary adherence. In the initial R61 phase, we will look for preliminary evidence for several hypothesized pathways by which the MBI components will influence dietary adherence.

We have several hypothesized pathways by which the MBI components will influence dietary adherence. These pathways and their associated measures are as follows:

1. Primary: Enhanced ability to address food cravings/decreased impulsivity. We have three key measures: (1) frequency of eating in response to cravings (EMA); (2) frequency of eating high carbohydrate/sweet foods in response to cravings (EMA); (3) the Delayed Discounting task or Relative Reinforcing Value of Food task.
2. Decreased stress- and emotion-related eating. We will use two key measures: (1) Palatable Eating Motives Scale (PEMS), for stress-related eating. (2) The Emotional Overeating Questionnaire for other emotion-related eating. We will also use the EMA method above to assess eating in response to emotions.
3. Improved resilience (resumption of dietary adherence) when dietary non-adherence occurs. Our key measure will be the time from a ketone measure of < 0.2 mmol/L to higher levels of > 0.2 mmol/L, indicating a return to nutritional ketosis after a period of consuming foods that depress ketosis.

9.2 Sample Size and Randomization

Target sample size: 180; 60 participants in the first/R61 phase. 120 in the second/R33 phase.

Our primary hypothesized mechanism is change in frequency of eating in response to cravings. Based on preliminary data, we expect that participants will report that on average, they have eaten in response to cravings on 50% of days on EMA measures at baseline (SD 11%). Our key concern is whether the Ed+MBI group has a significant decrease in days of eating in response to cravings. With N=30 persons in each arm, we will be able to detect a statistically significant decrease with 80% power (alpha=.05), if the group experiences eating in response to cravings on 44% of days or less. We will also test whether there are differences in decreases in cravings between groups.

Based on typical diet interventions for obese persons, we estimate that this will decrease to 30% of days in the Ed group, and 20% of days in the Ed+MBI group, for a mean difference of 10% (SD of 11%). With 30 people in each arm, this will provide us with a power of 80% to detect a statistically significant difference, using a two-tailed test, alpha=.05. For this phase, in which we are screening for evidence of effect on the proposed mechanism, we believe that a one-sided test, corresponding the hypothesis that the Ed+MBI group will have a greater effect on craving related eating than Ed alone, we will have 88% power. Note that we are not accounting for potential drop-outs in the analysis. We

anticipate that almost everyone will get through at least 4 weeks of intervention, which will provide initial data that can be used on all participants. In our pilot study of persons with T2DM and carbohydrate restricted diets, 94% completed the full 13 session program. Even if there is 20% dropout with no usable data, we will have 80% power to detect a statistically significant difference between groups in craving related eating, using a one-sided test.

Though of lesser concern at this early stage, we aim to test whether our hypothesized mechanisms are correlated with dietary adherence measures and will use linear regression. Using our overall sample of N=60, we will have greater than 80% power to detect a significant correlation if the true correlation coefficient (r) is .43 or greater. If we look just at the Ed+MBI group, we will have 80% power to detect a significant correlation is the true correlation coefficient (r) is .53 or greater.

Treatment Assignment Procedures

Participants will be randomized in a 1:1 fashion to one of two study groups (Ed or Ed+MBI), using block sizes of 4-6, and stratifying by BMI (above and below BMI of 25). We do not have a sample size goal for each stratum, but we want to ensure that the two arms have approximately equal numbers of normal weight participants.

Randomization to intervention group and maintenance phase track will be done via the Salesforce database. The randomization table will be programmed by a database manager, who is not otherwise involved in any enrollment or other participant procedures. Randomization will be done via the Project Director, Dr. Moran, who will not have access to the randomization table. When a participant ID number is entered into the database by study staff, a group assignment is revealed. This provides a computerized group assignment that cannot be altered by study staff and the group assigned is immediately recorded in the study database.

9.3 Definition of Populations

Intent to treat (ITT): Intent to treat is defined as the population that has been randomized, regardless of class attendance.

Per protocol: Per protocol is defined as the population that has been randomized and attended who attend at least 2/3 of weekly group sessions (8/12).

9.4 Interim Analyses and Stopping Rules

No interim analyses will be performed and we do not anticipate stopping the RCT early. The primary clinical outcome variable, HbA1c, is a surrogate marker for long-term risk of clinical events in diabetes, but is not an outcome that would justify early termination rules for a study of this size and duration. However, the occurrence of any serious adverse events related to intervention or assessment procedures will be reviewed at length by the DSMB in separately scheduled, closed meetings (if or when severe adverse events occur) to determine whether the RCT should be stopped or enrollment suspended. Where the DSMB considers issues related to participant safety, the DSMB Chair will moderate closed sessions and take a formal vote from DSMB members as to whether the trial should continue given the occurrence of the adverse event(s).

9.5 Outcomes

9.5.1 Primary Outcome

Primary mechanistic outcome(s): Our primary hypothesized mechanism is reduction in **frequency of eating in response to cravings** as a result of enhanced ability to address food cravings with mindfulness training. Our key measure of this mechanism is frequency of eating in response to cravings using ecological momentary assessment (EMA). This outcome will be measured at baseline, mid-intervention (approximately weeks 7, 13, and 19) and at final follow-up/end of study (week 26).

9.5.2 Secondary Outcomes

Secondary mechanistic outcomes: We have four additional mechanistic measures to assess our hypothesis that mindfulness training will enhance dietary adherence:

- Enhanced ability to reduce craving-related eating/decreased impulsivity as measured by the Delayed Discounting or Relative Reinforcing Value of Food task.
- Decreased stress-related eating as measured by the Palatable Eating Motives Scale (PEMS) subscale for stress-related eating as a coping mechanism.
- Decreased emotion related eating as measured by the Emotional Overeating Questionnaire.
- Improved resilience (resumption of dietary adherence) after dietary non-adherence occurs. Our key measure will be the time from a ketone measure of < 0.2 mmol/L to higher levels of > 0.2 mmol/L, indicating a return to nutritional ketosis after a period of consuming foods that depress ketosis.

Secondary clinical outcomes:

- Glycemic control, using HbA1c. We view improving HbA1c as the primary clinical outcome that we seek to improve in subsequent studies.
- Fasting glucose
- Homeostatic model assessment (HOMA) index of insulin resistance (computed from insulin and fasting glucose measures)
- Weight
- Adherence to diet measured by 24-hour diet recall and by ketone measures

9.6 Data Analyses

Overall analysis approach: Preliminary analysis will be performed to confirm that key data variables are clean and complete in prepared datasets. Baseline patient characteristics will be compared between intervention groups to assess whether important characteristics were evenly distributed during randomization. General analytic approaches will include estimation of odds ratios and risk differences plus chi-square tests for categorical variables compared across groups, rates of change with confidence intervals plus McNemar's test for categorical variables compared pre/post-intervention within groups, and t-tests and multiple regression for comparing continuous variables between groups. Secondary analyses will use random-intercept-random-slope mixed effects models for all repeated measures over time, with linear splines used to estimate initial improvements, subsequent maintenance, and possible eventual backsliding.

The principal analysis will use intent-to-treat methods in which all observations will be included for individuals based on initial group assignment, regardless of adherence to the treatment protocol. As a secondary analytic method, we will also perform as-treated analyses with those who attend at least 2/3

of weekly group sessions (8/12). We recognize the challenge of missing data in assessing clinical trial outcomes. We will take extensive steps to limit missing data. Our team has extensive experience in study retention; in our SUCCEED T2DM study, outcome assessment was completed in 97% of participants at 12 weeks. For our primary mechanism measure, eating in response to cravings using EMA, data can be obtained even for persons who move or have to travel. Finally, we will employ mixed-effects models and multiple imputation methods to address missing data if there is still a substantial amount.

For each of these measures, our primary analysis will be comparison of changes from baseline to follow-up time points between groups (see overall analysis approach above). We will also assess changes from baseline to follow-up within each group to help assess the potential effect of each intervention arm on these measures. We will also test for preliminary evidence that each of these proposed mechanisms is associated with dietary adherence. Dietary adherence will be measured two ways: (1) proportion of blood ketone measures $\geq$ 0.3mmol/L: (2) proportion of kcal from carbohydrate, using 24-hour diet recall. Each of our mechanism measures are continuous variables. We will therefore assess correlations between each of the mechanism measures and the dietary adherence measures, using linear regression. Finally, we will perform initial analysis of whether there are differences in two important clinical outcomes between intervention groups: HbA1c (to examine glycemic control) and weight. These clinical outcomes should result from our intermediate behavioral outcome of improved dietary adherence. We do not expect to have adequate sample-size in either phase of this study to address this question, but believe that preliminary assessment of these outcomes should be performed in case there are dramatic differences between groups even with limited sample size.

10. DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

Data will be collected by trained research assistants and study coordinators, using paper forms, as well as via online questionnaires using *Qualtrics.* All surveys and forms will be de-identified and coded with a unique subject number that will not contain personally identifiable information, such as subject initials or birthdates.

10.2 Data Management

The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data. The investigators will maintain adequate case histories of study subjects, including accurate case report forms (CRFs), and source documentation.

Data collection and accurate documentation are the responsibility of the study staff under the supervision of the investigator. All source documents and laboratory reports will be reviewed by the study team and data entry staff, who will ensure that they are accurate and complete.

This study will use a Salesforce database. The database will be secured with password protection. The statistician will receive only coded information that is entered into the database under those identification numbers. Electronic communication with outside collaborators will involve only unidentifiable information. The database incorporates an electronic audit trail to show change(s) to data after original entry including the date/time and user making the change. Paper data collection forms will be used to collect a limited amount of data (e.g. health history and medications, weight), which will be entered into the Salesforce database after undergoing systematic review for

completeness, accuracy, and adherence to study protocols.

10.3 Quality Assurance

10.3.1 Training

All study staff will complete CITI human subjects training. This will be tracked and reviewed by the Project Director yearly or more frequently, with submission of each IRB modification or renewal (i.e. at least yearly). Study staff will also receive training from Dr. Moran on all study screening, enrollment, and assessment procedures, including data collection review and entry procedures. Trainings will incorporate both didactics as well as observation and modeling of appropriate procedures and conduct.

10.3.3 Metrics

Much of our data will be electronically and automatically captured (e.g. lab results), but we plan several steps to ensure data quality. EMA data will be reviewed on a weekly basis and questionable responses will be clarified with participants. For Qualtrics questionnaires, we will utilize range checks and other automated steps to prevent or check unusual responses; programing will be performed to require responses to key data elements. Lab results will be reviewed for clinical reasons before providing to participants, and unexpected values will be followed-up to ensure accuracy. The accuracy of hand-entered data will be checked via automatic checks for out-of-range values.

QA review and data verification will be performed by someone other than the individual originally collecting the data, or by double-data entry. We will review data at least monthly in order to take corrective action as needed for any trends in errors. We will use our study database to plan upcoming follow-up visits and ensure that these are appropriately scheduled. The database will also be used to identify any visits that are at risk of being overdue so that follow-up steps can be taken. A statement reflecting the results of the ongoing data review will be incorporated into the Annual Report for the Independent Safety Monitor(s).

10.3.4 Protocol Deviations

Protocol deviations will be captured by regular review of cases during the enrollment process by Dr. Moran to ensure that eligibility criteria are met. Key points of review include post-consent visit and baseline lab completion as well as before randomization. Checks will also be programmed into Salesforce to ensure that enrollees have completed necessary steps to enrollment. Deviations in data collection procedures will be captured via the following standard procedure: after each participant visit, the study staff member who conducted the visit will review the folder and data collection forms. A second review will be done by another staff member who wasn't involved in the data collection before data entry. Any discrepancies or potential problems will be documented and reviewed with Dr. Moran (or, over time and with training and supervision, with one of the lead study coordinators). Dr. Moran will periodically spot-check random participant folders to ensure compliance with procedures.

10.3.5 Monitoring

Protocol compliance and monitoring will be done via review of records and forms after each participant visit before data entry. Review will be done by a study staff member who was not involved in the data collection for that participant, and any discrepancies or potential problems will be reviewed by the Dr. Moran (Project Director). Dr. Moran will periodically spot-check random data collection forms to ensure compliance with procedures.

11. PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

The protocol and the informed consent document (Appendix A) and any subsequent modifications will be reviewed and approved by the IRB or ethics committee responsible for oversight of the study.

11.2 Informed Consent Forms

A signed consent form will be obtained from each participant, using IRB-approved consent forms and procedures. The consent form will describe the purpose of the study, the procedures to be followed, and the risk and benefits of participation. A copy will be given to each participant and this fact will be documented in the participant record.

11.3 Participant Confidentiality

Participants will be assigned unique, coded, confidential identifiers (code numbers), which will be used to label all data forms, data entries and biological specimens, including LabCorp lab slips and results. Identifiable information, such as name, will not appear on these materials. The key linking the subject's identity to their unique coded identifier will be kept in a confidential manner in a database on a secure UCSF server, with access only by the principal investigator and the research staff. No names or individual identities will be used in publications resulting from the study. Physical records will be kept in an area accessible only to research staff. Research data will be stored on a secure, HIPAA-compliant server and drive with monitored and controlled access for study staff and investigators. The web-based survey will be hosted on secure servers. In addition, participants will enter only a study ID number, thus no identifying information will be associated with their questionnaire data. Online data collection avoids or minimizes the transfer of personally identifiable information, and uses industry best practices for protection of data. On the ERN forums, users are identified by self-selected screen names. Other users cannot see their email address or other identifying information. Participants must use an email address to register to use the ERN app. Participants will told that if they choose, they can use an anonymous email address that is not connected to their identity for this process, and staff will offer to assist them in acquiring such an address if they wish. If they choose to do this, then the risk of privacy loss resulting from a breach in Claritas's security is reduced.

11.4 Study Discontinuation

The study may be discontinued at any time by the IRB, the NCCIH, the OHRP, or other government agencies as part of their duties to ensure that research participants are protected.

13. PUBLICATION OF RESEARCH FINDINGS

Conference abstracts and manuscript will be made available for review by study co-investigators included on the publication prior to submission.

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15. SUPPLEMENTS/APPENDICES

i. Consent form