The University of Michigan PCOS Intervention Using Nutritional Ketosis

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The PINK Study (PCOS Intervention using Nutritional Ketosis): Diet and lifestyle management for women with polycystic ovary syndrome

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Proposal

1.0 Objective and Specific Aim/Hypothesis for this IRB application:

The goal of this proposed research is to pilot our existing LCD intervention for type 2 diabetes to use in overweight or women with PCOS.

Aims: Test the feasibility, acceptability, and preliminary efficacy of the intervention. We will randomize 30 overweight or obese women with PCOS to the 4-month intervention. Outcome measures include:

- **intervention feasibility** (recruitment and retention);
- **acceptability** (satisfaction with the intervention); and
- **preliminary efficacy** as determined by our primary outcome (body weight), as well as and other measures (including glycemic control, insulin resistance, lipids, testosterone, inflammation, and quality of life).

Information gained from this study will be used to finalize the intervention and prepare our team to propose a larger-scale, longitudinal, randomized controlled trial. Ideally, this follow-up trial would also examine long-term adherence and other health implications, including clinical complications. This later research would be appropriate for NIDDK (where Dr. Saslow already has a K01 with Dr. Aikens as mentor).

2.0 Background Information:
SIGNIFICANCE

Polycystic ovary syndrome (PCOS) is a common and costly disorder. Polycystic ovary syndrome (PCOS) is the most common endocrine disorder for women of reproductive age [1]. ***Women with PCOS have a 3-7 times higher risk for type 2 diabetes [2], and obese women with PCOS have an even higher risk of type 2 diabetes [3, 4].*** Obesity and PCOS tend to co-occur; about 30-60% of women with PCOS are obese [5] and over 10% of obese women have PCOS [6].

Position statements of the Androgen Excess and PCOS Society call for lifestyle management to be the primary treatment for metabolic complications in women with PCOS [7, 8] and the Endocrine Society's **clinical practice guideline calls for diet and lifestyle interventions for all overweight or obese women with PCOS** [9]. Weight loss, a critical outcome in diet and lifestyle interventions for women with PCOS, may also improve reproductive and metabolic outcomes: reduce insulin, insulin resistance, and androgen levels; improve ovulatory function and pregnancy and live birth rates; and improve glycemic control [7-12]. While experts largely agree that physical activity should be included in such interventions [13, 14], the ideal diet is still debated, especially whether a lower carbohydrate diet is beneficial [12, 15]. The hyperinsulinemia of PCOS likely contributes to the hyperandrogenism, which is why insulin-sensitizing drugs have been proposed as

therapies for PCOS [16]. **Reducing insulin through diet, however, may provide a critical nonpharmacological treatment for overweight or obese women with PCOS** [17-21].

3.0 Methodology:

Participant recruitment and eligibility. We will contact the pool of potentially eligible participants, based on electronic medical records at the University of Michigan, sending them a letter describing the study, which we will also follow up with a phone call. We will also use flyers posted throughout our institution as well as advertise locally, in our referral areas, on our web site and on a variety of other institutional web sites including https://umhealthresearch.org/ and national websites such as PCOS support groups. We will also promote the study to other physicians and healthcare providers.

Inclusion criteria: The most generally agreed upon approach to diagnose PCOS is through the Rotterdam criteria. We will include women in one PCOS subtype, those having these two symptoms:

- Hyperandrogenism - (a) If not on current birth control: hyperandrogenism defined as current elevated total testosterone >= 50 ng/dL or free androgen index > 1.5 (ratio of testosterone/SHBG x 100) or severe acne or hirsutism (b) if on current birth control: history from the past 10 years of hyperandrogenism defined as past elevated total testosterone >= 50 ng/dL or free androgen index > 1.5 (ratio of testosterone/SHBG x 100) or severe acne or hirsutism
- oligomenorrhea-anovulation defined as spontaneous intermenstrual periods of ≥ 45 days or a total of ≤ 8 menses per year.

We will include participants who, according to the medical records or their self-report, have an existing PCOS diagnosis, plus the following labs from the past 10 years (either from UM medical records, the medical records they choose to send us, or tests that we order for them at baseline):

- total testosterone < 100 ng/dL (required)
- dehydroepiandrosterone sulfate (DHEAS) < 600 µg/dL (required)
- fasting 17-hydroxyprogesterone (17-OHP) level < 2.0 ng/mL (required)
- hyperprolactinaemia (prolactin < 25ng/ml) (required)
- follicle-stimulating hormone (FSH) levels < 20 mIU/mL (optional)

Participants must also be overweight or obese (BMI 25-50), be 21-40 years old, have regular access to the internet, be able to engage in light physical activity, and willing and able to follow the assigned intervention. Their participation in the trial will need to be approved by their primary care physician or another healthcare provider who functions as their primary care physician, such as an endocrinologist.

Exclusion criteria: a non-English speaker; inability to complete baseline measurements; a substance abuse, mental health, or medical condition that would interfere with participation (such as current chemotherapy); pregnant or planning to get pregnant in the next 6 months; type 1 or type 2 diabetes; baseline aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2 times normal; baseline renal disease defined as BUN > 30 mg/dL or serum creatinine >1.4 mg/dL; baseline uncorrected thyroid disease (TSH <0.45 mIU/ML or >4.5 mIU/ML); breastfeeding or less than 6 months post-partum; planned or history of weight loss surgery; vegan or vegetarian; currently enrolled in a weight loss program or other investigative study that might conflict with this research; taking medications known to cause weight gain or loss; taking hypoglycemic medications other than metformin or medications known to affect metabolism; or patients with other etiologies of anovulation and hyperandrogenism, e.g., Cushing's disease, thyroid dysfunction, elevated prolactin levels, sighs of congenital adrenal hyperplasia, organic intra cranial lesion such as a pituitary tumor, or suspected adrenal or ovarian tumor secreting androgens.

After passing preliminary eligibility based on an online screening survey (using an online consent form), we will ask participants to (1) have their primary physician approve their participation in the trial, (2) answer online surveys about self-reported physical and psychological well-being, (3) go to one of more than 20 local locations to get their blood measured, (4) perform a 3-day food diary, and (5) weigh themselves on the bodyweight scale that we will mail them.

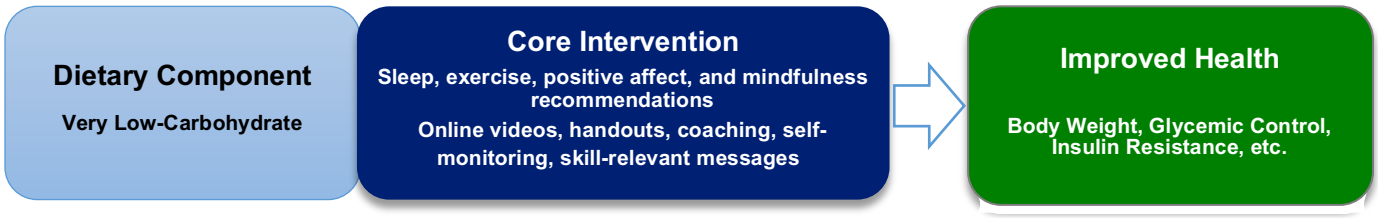
At month 4 the steps listed above (2-5) will be repeated. In addition, all enrolled participants will be invited to voluntarily participate in an interview at the end of their 4-month intervention. These interviews will explore their perspectives about the feasibility and acceptability of the intervention, as well as barriers and facilitators of their participation. This interview will take place over the phone with study staff and will last approximately 20-30 minutes. The interview will be recorded, saved onto encrypted devices, and then deleted from the recording device. Interviews will be transcribed and then coded by multiple coders to find common, broad themes. We plan to use Production Transcripts (https://www.productiontranscripts.com/qualitative-research-transcription/) to transcribe all interviews and NVivo software for qualitative coding.

Intervention. Participants will be e-mailed links to the coursework every week for 16 weeks. We chose this time frame so as to be able to develop a sufficiently robust intervention for the future larger, longer trial. In addition, as HbA1c can take about 3 months to reflect changes in blood glucose control and participants may take 1 month to fully change their diet to be LCD, 4 months should yield an accurate estimate of the changes in their blood glucose control.

The weekly links will connect participants to: a) a short survey to assess intervention-related behavioral adherence and any health concerns, b) a short embedded video to teach the topics, c) downloadable handouts distributed online to accompany the videos, and d) links to external resources on the web pertaining to the week's information. As some participants prefer not to watch videos, the transcripts of the embedded videos will be provided as well, in an easy-to-read downloadable pdf format.

The lessons will not be delivered synchronously in real time, but will be able to be watched and read whenever is convenient. Participants will be encouraged to complete the lessons in one sitting although they will be able to log into the lesson again at a later point if they would prefer. Lessons will vary in length, but on average they will take about 10 to 30 minutes to complete, including watching the short video and reading the handouts. We will track how often and when participants log into the lessons, thus allowing us to assess engagement with the curriculum.

Some of the intervention topics and approaches are described below:



Dietary Component: An LCD. Participants will be encouraged to eat an LCD, the same one Dr. Saslow has recommended in her previous research [22, 23], to reduce carbohydrate intake to between 20-35 non-fiber grams of carbohydrates a day. Participants will be encouraged to eat a normal amount of protein (to keep their protein levels as they were before the intervention began, as long as they were meeting the minimum amount suggested by the Institute of Medicine [24]) and to derive their remaining calories from fat. Generally, calories will be derived from animal foods, cheeses, eggs, fats, nuts, seeds, and low-carbohydrate vegetables. This intervention was created in consultation with experts in the LCD and has been iterated in six previous trials for adults with prediabetes or type 2 diabetes.

Core Intervention:

a) Dietary self-monitoring using a free application. We will ask participants to track their diet using a free online and mobile application, MyFitnessPal (which our participants have found easy to use, has a wide variety of foods in its database, and has over 150 million users). If by the time we begin the trial there is an easier-to-use diet-tracking program more tailored to the very low-carbohydrate diet, we will consider using that program instead.

b) Body weight self-monitoring using a digital scale. We will ask participants to track their body weight with an easy-to-use remote scale provided by the study. The scale connects via its own cellular network and therefore does not require any Wi-Fi passwords or setup by participants, simplifying ease of use. We will use this information to monitor participant success and tailor coaching support.

c) Goals for physical activity and sleep. We will describe the health benefits of physical activity [25]. Using the Diabetes Prevention Program [26] as a guide, participants will be encouraged to engage in moderately intense physical activity for at least 150 minutes a week. The intervention will also describe the connection between lack of sleep and weight gain [27], impaired insulin signaling [28], and type 2 diabetes [29]. Participants will be encouraged to practice sleep hygiene and aim for 7-9 hours a night of sleep.

d) Training in positive affect and mindfulness (extra psychological supports). We will teach these skills, how they are expected to help, research supporting them, and suggestions for practicing them.

e) Text messages. Reminders about targeted behaviors are tied to greater behavioral adherence [30, 31]. Thus, to deliver convenient reminders, as Dr. Saslow has done in her previous research, we will send automatic, motivational, and educational skill-relevant messages about 5 times a week to participants [32, 33].

f) Mailed materials. To attempt to help participants change their diet and increase their self-efficacy for new foods, at baseline participants will receive an assortment of difficult-to-find foods that are allowed on their diet (such as coconut and almond flour) and at baseline and 1 and 3 months later we will mail them lay-press cookbooks. Possible materials are pictured to the right.

g) Menus, including written meal plans and grocery lists, will be provided, as these have been found to be more effective for weight loss than an intervention without such support [34].

h) Access to intervention coach. Coaches have generally been found to be effective additions to behavioral interventions [35]. If participants have questions, they will be able to e-mail their coach whenever they would like in order to receive prompt replies. Phone-based support will also be available on request. We have used this approach successfully in three other online trials of this program for adults with type 2 diabetes. For example, we have a coaching manual that the coach can refer to for common issues. All written coaching messages are vetted by Dr. Saslow before they are sent.

i) Social support. We will encourage participants to join already existing online, well-moderated support groups for people following an LCD, especially groups for women with PCOS, such as one of the many Facebook or reddit groups. (We will provide a list.) We decided to refer participants to existing groups to ensure long-term access to the groups, a realistic and cost-effective way to provide an intervention at scale.

Participant safety. To be responsive to intervention-related health issues that may arise, as in our previous research, we will also inquire about physical symptoms in each weekly e-mail. We will consult with and refer to the participants' primary care physicians as needed. Although we are excluding potential participants with type 1 or 2 diabetes, it is worth noting that diabetic ketoacidosis is a life-threatening complication of poorly controlled diabetes. An LCD reduces the risk of diabetic ketoacidosis; the level of ketones expected in an LCD is an order of magnitude lower than the level seen in diabetic ketoacidosis, and this low level of ketones does not pose a threat to health [36].

To cope with blood pressure changes (as such an approach tends to lower blood pressure), we will teach participants about the signs of low blood pressure, how to self-manage symptoms, and when symptoms may warrant reaching out to their primary care physician for possible medication management.

4.0 Statistical Design:

Power considerations. As an exploratory study designed to help us understand feasibility and potential efficacy, this trial is not meant to be adequately powered for testing hypothesized effects. Rather it will help us understand the potential efficacy for weight loss and our benchmarks for feasibility (retention, adherence, satisfaction) and other secondary outcomes.

Data analytic plan. As we have no control group, we will simply examine means and standard deviations of changes and whether we have reached our benchmarks for the trial. See below for details.

Intervention outcomes at 4 months

Intervention feasibility and acceptability	
Outcome	**Measure/Method**
Recruitment and retention	We will report numbers for recruitment and retention using a CONSORT diagram. Number and reasons for failure to complete follow-up assessments will be reported.
Intervention acceptability and satisfaction	At completion, participants will report the following: 1) satisfaction with each intervention component; 2) satisfaction with the intervention overall; 3) likelihood of referring the intervention to a friend; 4) intervention aspects perceived to be most useful; and 5) suggestions for improvement the intervention.
Intervention engagement	Frequency of lesson log-ins and adherence to the recommended diet based on dietary recall. In our previous study in adults with type 2 diabetes, by 4 months participants had logged into more than 95% of lessons.
Open-ended questions	We will ask participants open-ended questions about various aspects of their experience to explore, in an open-ended way, their opinion about the intervention and trial.
Preliminary efficacy	
Primary outcome	Body weight, as measured by a scale we will mail participant (which connects using its own cellular network to our study databases). We will examine the average percent weight loss as well as the percentage of participants in each group who lose a clinically significant amount of weight, at least 5%, which is thought to lead to metabolic improvements and reductions in the future risk of type 2 diabetes [10].
Exploratory metabolic and cardiovascular health outcomes	To reduce the future risk of type 2 diabetes, our goal is to improve glycemic control (glycated hemoglobin; HbA1c), insulin resistance (homeostatic model assessment from fasting blood glucose and insulin; HOMA), lipids (triglycerides and cholesterol), free testosterone [37], and inflammation (C-reactive protein) [38, 39]. These measurements will all occur at MLabs, a local laboratory run by Michigan Medicine.

Intervention outcomes at 4 months

Intervention feasibility and acceptability	
Other measures	PCOS-related quality of life [40], general quality of life (from Patient-Reported Outcomes Measurement Information System or PROMIS, which includes depressive symptoms, energy levels, pain, and sleep quality)[41], physical activity [42, 43], dietary adherence (macronutrient levels assessed with a 3-day food record), food cravings [44], stress eating [45, 46], dietary-based social support [47].

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