Impact of an online multicomponent very-low-carbohydrate program in women with polycystic ovary syndrome: a pilot study

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Objective: To study the impact of a very-low-carbohydrate (VLC) diet for 16 weeks in overweight or obese women with polycystic ovary syndrome (PCOS).
Design: Single-arm prospective pilot study.
Setting: We recruited participants using medical records from an academic medical center.
Patient(s): Twenty-nine overweight or obese women (body mass index, 25–50 kg/m^2) with PCOS.
Intervention(s): We taught participants to follow a VLC diet and provided information about a variety of behavioral skills including mindfulness and positive affect using an online 16-week intervention.
Main Outcome Measure(s): Changes in body weight, glycated hemoglobin, and PCOS-related quality of life.
Result(s): The intervention led to positive health outcomes including decreases in percent weight (mean difference = −7.67, SD = 6.10) and glycated hemoglobin level (mean difference = −0.21%, SD = 0.27), an increase in sex hormone binding globulin level (mean difference = 9.24 nmol/L, SD = 16.34), and increases in PCOS-related quality of life measures, including menstrual predictability (mean difference = 2.10, SD = 2.76) and body hair (mean difference = 1.14, SD = 1.04). The low-density lipoprotein cholesterol level increased (mean difference = 0.23 mmol/L, SD = 0.49).
Conclusion(s): The results suggest that a VLC dietary intervention has potential to promote both weight loss and glycemic control in overweight and obese adults with PCOS, two key components in the prevention of type 2 diabetes.
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Key Words: Polycystic ovary syndrome, very-low-carbohydrate diet, weight

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Six to nine percent of women have polycystic ovary syndrome (PCOS), a burdensome endocrine disorder in women of reproductive age characterized by anovulation and hyperandrogenism (1). The recommended guidelines for diagnosis of PCOS based on the Rotterdam criteria requires the exclusion of other diagnoses known to cause ovulatory dysfunction or hyperandrogenism and the inclusion of at least two of the following three manifestations: ovulatory dysfunction; hyperandrogenism; and polycystic

ovaries (2). Polycystic ovary syndrome significantly impairs fertility and quality of life in addition to increasing the risk of obesity, type 2 diabetes, hyperlipidemia, and cardiovascular disease. The risk of type 2 diabetes is three to seven times higher in women with PCOS (2), and for obese women with PCOS, the risk is even higher (3).

Lifestyle modification to bring about weight loss is a key recommendation for women with PCOS in position statements from the Androgen Excess and PCOS Society (4, 5), Endocrine Society's clinical practice guidelines (6), and international evidence-based guidelines (7). Weight loss may improve both reproductive and metabolic outcomes. It typically reduces insulin levels, insulin resistance, and androgen levels, each of which may contribute to improved ovulatory function, pregnancy rates, live birth rates, and glycemic control (4–6, 8–10).

Despite this consensus in recommendations for lifestyle-driven weight loss, experts disagree on the ideal dietary approach for PCOS, including whether a lower carbohydrate diet may be beneficial (4, 10). Carbohydrates have been shown to increase insulin secretion, which then stimulates ovarian androgen production and inhibits the release of fatty acids from cells; the hyperinsulinemia present in PCOS likely contributes to hyperandrogenism (11, 12). Thus, reducing insulin levels through diet may provide a critical nonpharmacologic treatment option for women with PCOS (12–16). A very-low-carbohydrate (VLC) diet may be able to lower insulin levels and be effective for weight loss (17).

We, therefore, conducted a 4-month, 16-session, single-arm prospective pilot study using a VLC diet intervention in overweight and obese women with PCOS to test the hypothesis that a VLC diet would lead to clinically significant weight loss (primary outcome), improvements in glucose control (secondary outcome), as well as other health improvements. To assist with dietary adherence and promote improved mental health, we integrated the dietary component of the intervention with positive affect practices, on the basis of the positive pathways to health theoretical model (18) and mindful eating strategies, which, among other effects, may reduce hedonic eating, a significant barrier for following dietary advice (19).

MATERIALS AND METHODS

Potential participants were identified from electronic outpatient medical records at Michigan Medicine, a large health care system in Southeastern Michigan, United States. The inclusion criteria focused on a subtype of PCOS, based on a self-reported diagnosis of PCOS together with the presence of medically documented hyperandrogenism and oligomenorrhea–anovulation (for women not on birth control). Hyperandrogenism was defined as an elevated total testosterone level of $\geq$50 ng/dL or free androgen index of $>$1.5 (ratio of testosterone/sex hormone binding globulin [SHBG] $\times$ 100) or self-reported severe acne or hirsutism for those not currently on hormonal birth control and a history from the prior 10 years of an elevated total testosterone level of $\geq$50 ng/dL or free androgen index of $>$1.5 (ratio of testosterone/SHBG $\times$ 100) or severe acne or hirsutism for those currently on hormonal birth control. Oligomenorrhea–anovulation was defined as spontaneous intermenstrual periods of $\geq$45 days or a total of $\leq$8 menses per year. Additionally, records reviewed for up to 10 years or baseline results were used to rule out other causes of hyperandrogenism or ovulatory dysfunction: total testosterone level of $<$100 ng/dL, dehydroepiandrosterone sulfate level of $<$600 μg/dL, fasting 17-hydroxyprogesterone level of $<$2.0 ng/mL, hyperprolactinemia (prolactin level of $<$25 ng/mL), and follicle-stimulating hormone levels of $<$20 mIU/mL (optional). Additional inclusion criteria were body mass index (BMI) of 25–50 kg/m^2, age of 21–40 years, regular access to the internet, ability to engage in light physical activity, willingness to engage with the intervention, and approval of participation by their primary care provider or PCOS specialist. The exclusion criteria were as follows: pregnant or planning to get pregnant in the next 6 months; breastfeeding or less than 6 months postpartum; type 1 or 2 diabetes; and planned or a history of weight loss surgery. Preliminary eligibility was confirmed by an online screening survey. Additionally, participants were asked to fill out an online consent form, complete a more detailed online survey about their physical and psychological well-being, and perform a 3-day food diary using MyFitnessPal (Under Armour, Inc.). Participants went to one of over 20 of the Michigan Medicine health system's MLabs for their baseline blood draw to confirm their eligibility and weighed themselves on a scale we mailed to them from BodyTrace (San Francisco, CA). After 4 months, participants repeated the online survey, 3-day food diary, blood draw, and self-weighing.

The intervention was entirely remotely delivered and a technology-supported multicomponent program. It consisted of instructional multimedia modules provided via e-mail every week for 16 weeks. A description of each module is presented in Table 1. The weekly e-mails included a short survey to assess adherence and health concerns, short embedded videos to teach the weekly topics, downloadable handouts, and links to external resources on the web. For those who preferred not to watch videos, transcripts were provided in a portable document format. The modules were not live-streamed and remained indefinitely viewable for participants at a time convenient for them. Modules tended to require approximately 10–30 minutes to complete.

The dietary component consisted of a VLC diet, which has been used successfully in the research of the project principal investigator (PI) (L.R.S.) for type 2 diabetes (20–22). We advised participants to reduce their carbohydrate intake to 20–35 net (nonfiber) grams per day, maintain their current protein intake within the requirements suggested by the Institute of Medicine (23), and derive their remaining calories from fat. Common foods included animal foods (e.g., cheeses, meats, and eggs), healthy fats, nuts, seeds, and low-carbohydrate vegetables and fruits. Additional components to assist participants with behavior change included the following: dietary self-monitoring using MyFitnessPal (optional throughout the trial but strongly encouraged, required for 3 days at baseline and month 4); body weight self-monitoring using a digital scale; goals for physical activity and sleep; training in positive affect and mindfulness; text

TABLE 1

Description of weekly sessions.

Module	Dietary topics	Supplementary strategies topics
No. 1	Study overview, diet rationale, changing snacks and breakfasts, tracking diet	Positive affect: acts of kindness
No. 2	Changing lunches, starting a favorite foods diary, ketone testing, tips for dining out, fluids and salt	Mindfulness: introduction and practice exercise for mindful eating
No. 3	Changing dinners, clean out the pantry, sugar substitutes, food cravings	Positive affect: noticing "feel good" moments
No. 4	Watch your protein, coping with eating off the meal plan, eating on a budget	Mindfulness: more awareness of hunger and fullness
No. 5	Resisting peer pressure to eat off the meal plan	Mindfulness: awareness of food cravings and triggers
No. 6	Adding in physical activity and sleep	Positive affect: gratitude
No. 7	Preparing ahead	Mindfulness: mini meditations
No. 8	Troubleshooting barriers to dietary adherence (technical errors, psychological obstacles, and external realities)	Mindfulness and positive affect: self-compassion
No. 9	Eating on the meal plan when traveling	Positive affect: personal strengths
No. 10	Gray zone foods, paying attention to foods that may not be part of the meal plan	Mindfulness: mindfully responding to stress
No. 11	Increasing food variety, eating at restaurants	Mindfulness: relaxing breath
No. 12	How tastes change	Positive affect: planning positive activities
No. 13	Troubleshooting food sensitivities	Positive affect: positive reappraisal
No. 14	More about sugar	Mindfulness: enjoying your foods
No. 15	Troubleshooting hunger, thirst	Positive affect: accomplishing small, doable goals
No. 16	Recovering from slips, sticking to goals	

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messages; mailed materials (cookbooks and urine ketone strips); menus; and social support through existing online support groups, similar to our previous research in type 2 diabetes (21, 22). The diet coach (R.M.) contacted participants at least every other week and provided personalized feedback and encouragement; she was also available via e-mail for participant questions at any time. The project PI (L.R.S.) edited all messages for clarity and accuracy before the coach sent them to participants. The research was approved by the University of Michigan Institutional Review Board, HUM00113697.

Outcomes

Weight and metabolic outcomes. The primary outcome was body weight loss with exploratory metabolic outcomes including changes in glycated hemoglobin (HbA1c), hormones, and lipids. The results were converted to International System of Units per standard protocols. We used a remote scale for body weight measurements because this has been found to be correlated .99 with in-person, clinic-based measurements (24, 25).

Psychological outcomes. We assessed PCOS health-related quality of life, including subscales related to menstrual symptoms, menstrual predictability, emotions, body hair, and infertility (26); Patient-Reported Outcomes Measurement Information System measures of global physical and mental health as well as fatigue and sleep (27); and the Food Craving Inventory, which assesses cravings for unsweetened carbohydrates/starches (e.g., corn bread, popcorn, rolls, biscuits, sandwich bread, rice, baked potato, and pasta) and sweets (e.g., brownies, cookies, candy, chocolate, donuts, cake, cinnamon rolls, ice cream, pancakes or waffles, and breakfast cereal) (28). We further assessed three factors that prior research has shown to mediate weight loss achieved with programs employing mindfulness techniques similar to those used in the current study (19, 29, 30). We, therefore, assessed reward-based eating, or the lack of control over eating, lack of satiety, and preoccupation with food (e.g., "I feel out of control in the presence of delicious food") (31); body responsiveness, or responsiveness to bodily sensations, including perceived disconnection between psychological and physical processes and the importance of interoceptive awareness or listening to bodily sensations for self-regulation (e.g., "I am confident that my body will let me know what is good for me") (32); and mindful eating, or the nonjudgmental awareness of physical and emotional sensations associated with eating (e.g., "I notice when there are subtle flavors in the foods I eat") (33).

Self-reported diet. Participants used MyFitnessPal to report their daily food consumption, from which total calories and net carbohydrates were calculated (total carbohydrates minus fiber). Participants tracked their diet for 3 days at both baseline and the 4-month follow-up. To avoid days that were only partially recorded, we included only days that the tracked caloric intake was at least 500 kcal (34). We mailed participants urinary acetoacetate test kits (to test for a ketone that can be measured in urine; Ketostix, Abbott) and asked whether they observed ketones in their urine during the first month of the intervention.

Changes in prescribed medication. Participants reported on any changes in what diabetes medications they were prescribed.

Intervention feasibility and acceptability. We assessed intervention feasibility by examining our ability to reach our recruitment target (approximately 30 participants), maintain enrollment, and limit loss to follow-up. Satisfaction with the program was rated from 1, *not at all satisfied,* to 7, *very satisfied*. To assess potential acceptability, we also asked participants to answer, "How long can you see yourself following your assigned diet?" In the 4-month survey for all participants, we asked open-ended questions for the participants' perspectives about the program and its impact. We also invited all participants to take part in a phone interview.

Statistical Analysis

Quantitative. The primary outcome, change in body weight from baseline to 4 months, was measured by percent weight loss as well as by the percentage of participants who lost a clinically significant amount of weight, defined as at least 5%. Previous research suggests that a variety of health conditions, such as hypertension and fertility, improve with only 5% weight loss, and thus, 5% has become the standard level for clinically significant weight loss (35). When reporting the proportion of participants who met weight reduction thresholds, we conservatively used the total sample size assuming that participants who did not complete the program did not achieve the threshold. This imputation method was also used for self-report of dietary adherence and presence of ketones in the urine. We examined histograms, quantile–quantile plots, and skewness statistics to ascertain whether our quantitative outcomes and changes in those outcomes were normally distributed. The baseline summary characteristics for quantitative variables included means and SDs for variables that were normally distributed and medians and interquartile range for skewed variables. To examine differences between participants who completed the intervention and follow-up and those who dropped out or were lost to follow-up, we used independent *t* tests for normally distributed variables, the Mann-Whitney rank tests for skewed distributions, and the χ^2 tests for proportions. To test our hypotheses that the intervention changed outcomes over time, we used paired *t* tests when the before and after differences had a normal distribution and the Wilcoxon signed rank tests when the differences were skewed. We performed all analyses using Stata version 16. We completed an intention-to-treat analysis with all available data (no imputation for missing data; in this case similar to a completer's analysis) and a per-protocol analysis for participants who adhered to the intervention protocol. We defined adherence as reporting a score of 5 or higher (scale of 1–7) for the level of dietary adherence on a minimum of 13 out of the 16 weekly check-ins.

Qualitative. We interviewed a subset of participants over the phone 1–2 months after they had completed the trial. These semistructured interviews were recorded, transcribed verbatim, and analyzed with a thematic approach. Two coders analyzed the transcripts using NVivo 12 Plus software, independently reviewing the same three transcripts to create preliminary codes, identifying themes and patterns throughout the interviews. Through discussion between coders and the project PI (L.R.S.), a final thematic coding structure was developed. Coders applied this structure to all transcripts, double coding six and independently coding the remaining eight, meeting to discuss discrepancies regularly. Once all transcripts were coded, codes were categorized by broader themes through discussion to consensus. We also explored the open-ended 4-month online survey responses.

RESULTS

Of the 29 women with PCOS recruited (all during 2019), 21 (72.4%) completed both baseline and 4-month measurements. Because this was a pilot study, the sample size was not calculated to provide adequate power to detect group difference. The study participant flowchart is provided in Figure 1. The participants were 82.76% White, 3.45% Asian, 10.34% Black or African American, and 3.45% with a Hispanic ethnicity. The mean age was 31.21 years (SD = 5.13), seven participants (24%) were on birth control at baseline (three oral contraceptive pills, three hormonal intrauterine devices, and one copper intrauterine device), and all lived in Southeast Michigan. The summary characteristics of the sample at baseline are presented in Table 2. Of the eight (27.5%) individuals who did not complete the study, one dropped out of the study (no reason provided), and the other seven engaged to varying degrees throughout the study but did not complete follow-up measurements (lost to follow-up, no reason provided). There were no significant statistical differences in retention by baseline age, weight, BMI, HbA1c, glucose, insulin, homeostatic model assessment 2 for insulin resistance, androgens, or metabolic markers, such as low-density lipoprotein (LDL), high-density lipoprotein, and triglycerides.

Weight and Metabolic Outcomes

Table 3 summarizes the effects from 0 to 4 months in all participants with final outcomes as well as per-protocol participants. We aimed to reduce bias by having outcomes assessed by masked assessors, to reduce assessor bias. The mean percent weight loss was 7.67% (SD = 6.10, $t = -6.16$, $P<.001$), with 15 of 29 participants (51.72%) losing at least 5% of their body weight, 14 of 29 participants (48%) losing at least 7% of their body weight, and 10 of 29 participants (34%) losing at least 10% of their body weight. The mean BMI reduction among the intention-to-treat participants was 2.64 kg/m^2 (SD = 2.14, $t = -6.05$, $P<.001$). In addition to these statistically significant reductions in body weight and BMI, we observed statistically significant improvements in HbA1c and SHBG. We also observed a statistically significant increase in LDL level. The results for changes in androgens and metabolic markers are presented in Table 3.

Psychological Aspects

Overall, all measured psychological aspects improved in the whole sample, and nearly all improved in the per-protocol subanalysis (Table 3).

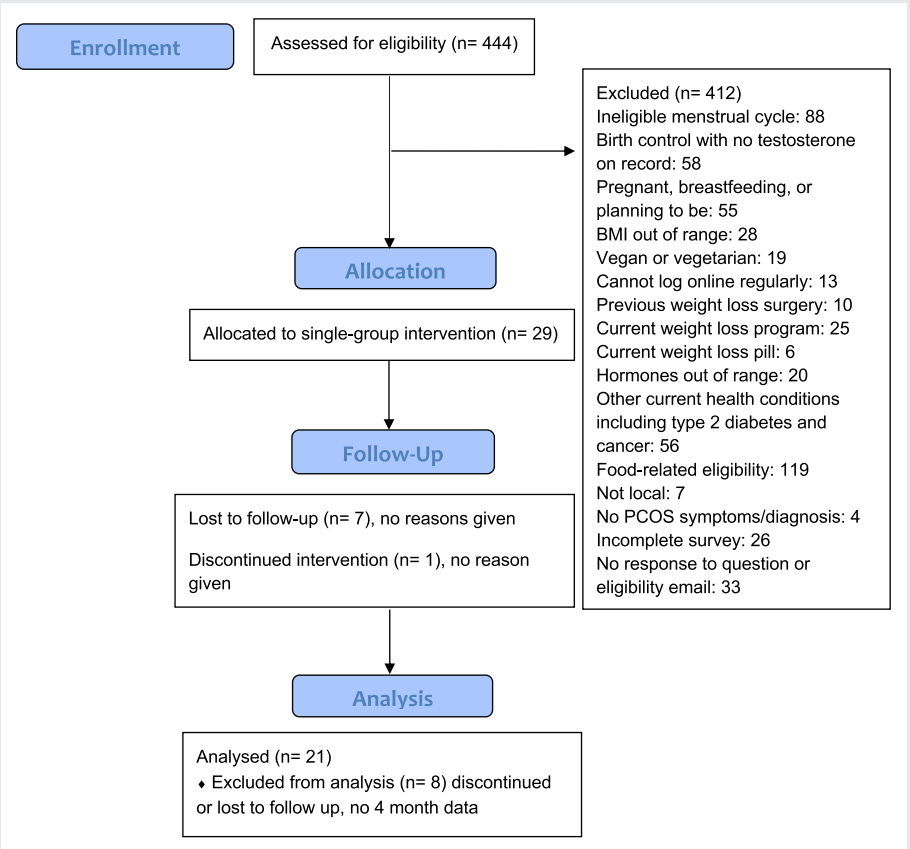
Dietary Self-Report

Participants significantly reduced both total calories and net (nonfiber) grams of carbohydrates. Most participants (25 out of 29) observed ketones in their urine during the first month of the intervention, and 15 out of 29 met our criteria for adherence on the weekly self-report survey, which was used to complete the per-protocol analysis, for which results were largely similar (Table 3).

Medication Changes

Twelve of the 21 study completers (57 %) reported taking metformin at the start of the study. Of these, one increased her

FIGURE 1



Study participant flowchart.

Missel. PCOS and very-low-carbohydrate diet. Fertil Steril Rep 2021.

dose, and one stopped for reasons unrelated to treatment. Three women reported taking spironolactone at baseline. One increased their dose during the first week of the study, one remained on the same dose, and one stopped that medication.

Intervention Feasibility and Acceptability

After 9 days, 13% of those we mailed as part of trial recruitment had filled out an online screening survey expressing interest, and we were able to make our recruitment target with that initial group. Among participants who answered the follow-up survey (n = 21), program satisfaction was high (median = 7.00 on a 7-point scale, interquartile range = 1.0), and everyone reported a score of 5 or higher. Only 14% (3/21) reported that they would stop the assigned diet as soon as the study was over, with all the rest reporting that they intended to continue the diet for at least another few months, and 48% (10/21) stated that they did not plan to ever stop following a VLC diet.

Adverse Events

Several adverse events were reported throughout the course of this trial. Two participants developed kidney stones, one within 2 weeks of starting the intervention and the other 2 months into the intervention. A different participant reported continuous muscle cramping and blurry vision 2 months into the intervention; symptoms subsided after consulting with their physician.

Qualitative Findings

Through the subsequent thematic analysis of interviews (Supplemental document, available online) with 14 participants and 21 open-ended survey responses, several themes emerged. We report the most prominent themes here.

Subjective changes in health. Participants experienced a variety of positive health changes, including weight loss, improved glucose control, increased energy and menstrual regularity, and reduced "brain fog," abdominal pain, acne, facial hair, heart burn, and premenstrual syndrome. Some negative health changes included transitory headaches, muscle cramps, trouble sleeping, menstrual irregularity, and two participants who reported kidney stones.

Weight loss. Several participants positively commented on their significant weight loss. One lost so much weight that she was no longer eligible for gastric bypass surgery: "I was

TABLE 2

Baseline sample characteristics.

Variable	All participants N = 29	Intention-to-treat participants N = 21	Noncompleters N = 8	*P* value[a]
Age, mean (SD)	31.21 (5.13)	31.38 (4.81)	30.75 (6.23)	.77
Race, N (%)				.12
White	24 (82.76)	19 (90.48)	5 (62.50)	
Asian	1 (3.45)	0 (0.00)	1 (12.50)	
Black or African American	3 (10.34)	1 (4.76)	2 (25.00)	
Hispanic	1 (3.45)	1 (4.76)	0 (0.00)	
Weight (kg), mean (SD)	99.66 (20.35)	98.76 (20.61)	102.04 (20.85)	.71
BMI (kg/m^2), mean (SD)	36.01 (7.01)	35.77 (7.04)	36.64 (7.36)	.77
HbA1c (%), mean (SD)	5.43 (0.28)	5.41 (0.25)	5.46 (0.36)	.69
Glucose (mmol/L), mean (SD)	5.06 (0.56)	5.05 (0.60)	5.10 (0.49)	.84
Insulin (pmol/L), mean (SD)	105.21 (61.13)	94.17 (46.76)	134.18 (85.89)	.12
Testosterone (nmol/L), mean (SD)	0.01 (0.01)	0.01 (0.01)	0.01 (0.01)	.39
[b]SHBG (nmol/L), median (IQR)	32.00 (24.00, 40.00)	28.00 (25.00, 40.00)	32.50 (18.50, 41.50)	.73
LDL (mmol/L), mean (SD)	2.58 (0.71)	2.68 (0.67)	2.33 (0.80)	.25
HDL (mmol/L), mean (SD)	1.33 (0.32)	1.31 (0.28)	1.40 (0.44)	.51
[b]Triglycerides (mmol/L), median (IQR)	1.15 (0.93, 1.65)	1.19 (0.93, 1.94)	1.06 (0.94, 1.33)	.41
HOMA2-IR, mean (SD)	2.25 (1.24)	2.00 (0.97)	2.91 (1.67)	.08
[b]MyFitnessPal—total calories (kcal), median (IQR)	1,558.33 (1,284.67, 1,819.00)	1,516.00 (1,284.67, 1,817.00)	1,646.42 (1,268.50, 1,972.67)	.66
[b]MyFitnessPal—total calories (kJ), median (IQR)	6,520.07 (5,375.05, 7,610.70)	6,342.94 (5,375.05, 7,602.33)	6,888.61 (5,307.40, 8,253.64)	.66
MyFitnessPal—net carbohydrates (g), mean (SD)	151.08 (86.17)	146.45 (91.15)	163.23 (75.69)	.65
MyFitnessPal—protein (g), mean (SD)	66.50 (22.85)	62.83 (19.98)	76.15 (28.31)	.16
[b]MyFitnessPal—fat (g), median (IQR)	67.00 (52.00, 81.00)	69.33 (52.00, 87.00)	60.50 (50.67, 76.50)	.53
Reward-based eating, mean (SD)	2.65 (0.55)	2.68 (0.61)	2.54 (0.34)	.56
Body responsiveness				
Perceived disconnection, mean (SD)	3.92 (1.02)	3.79 (0.98)	4.28 (1.13)	.28
Interoceptive awareness, mean (SD)	3.88 (1.07)	3.76 (1.07)	4.24 (1.08)	.32
Food Craving Inventory—starches, mean (SD)	2.57 (0.46)	2.60 (0.46)	2.45 (0.49)	.47
Food Craving Inventory—sweets, mean (SD)	2.63 (0.77)	2.68 (0.77)	2.48 (0.80)	.56
Mindful eating, mean (SD)	2.43 (0.54)	2.39 (0.58)	2.55 (0.37)	.51
PCOSQ—menstrual symptoms, mean (SD)	3.49 (0.94)	3.49 (0.85)	3.48 (1.24)	.97
[b]PCOSQ—menstrual predictability, median (IQR)	2.00 (1.00, 3.50)	2.50 (1.50, 3.50)	1.50 (1.00, 3.00)	.32
PCOSQ—emotions, mean (SD)	3.15 (1.23)	3.10 (0.91)	3.30 (1.91)	.70
PCOSQ—body hair, mean (SD)	3.05 (1.58)	3.18 (1.57)	2.72 (1.67)	.49
[b]PCOSQ—weight, median (IQR)	1.29 (1.00, 2.14)	1.14 (1.00, 1.71)	1.86 (1.00, 2.43)	.31
PCOSQ—infertility, mean (SD)	3.91 (2.15)	4.29 (2.05)	2.92 (2.20)	.13
PROMIS—global mental health, mean (SD)	44.88 (5.92)	45.24 (5.62)	43.94 (6.96)	.61
[b]PROMIS—global physical health, median (IQR)	45.10 (42.40, 48.20)	45.10 (42.60, 48.40)	42.60 (42.10, 44.35)	.10
PROMIS—fatigue, mean (SD)	54.63 (7.60)	54.38 (8.19)	55.31 (6.20)	.77
PROMIS—sleep disturbance, mean (SD)	52.00 (6.00)	51.41 (5.36)	53.55 (7.63)	.40

Note: We used independent *t* tests to compare means for normal distributions, the Mann-Whitney rank tests to compare skewed distributions, and the χ^2 tests to compare proportions. BMI = body mass index; HbA1c = glycated hemoglobin; HDL = high-density lipoprotein; HOMA2-IR = homeostatic model assessment 2 for insulin resistance; IQR = interquartile range; LDL = low-density lipoprotein; N = number; PCOSQ = The Polycystic Ovary Syndrome Health-Related Quality of Life Questionnaire; PROMIS = Patient-Reported Outcomes Measurement Information System; SD = standard deviation; SHBG = sex hormone binding globulin.

[a] The *P* value compares participants who did and did not complete the majority of follow-up measurements.

[b] Median and interquartile range (IQR) used for these outcomes, which have skewed distributions.

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considering the bypass surgery… I did start to go through some of the checklist items and I'm like, I really don't want to do this but if, you know, if this is the last resort because other diets weren't working for me… that's when I was meeting with [my physician]… So now I'm no longer eligible to be a part of that. <laughs> So I'm like, well, that's great."

TABLE 3

Effects of the intervention over 4 months.

	Intention-to-treat participants, N = 21			Per-protocol participants, N = 15		
Variable	**Mean (SD)**	***Test statistic***	***P value***	**Mean (SD)**	***Test statistic***	***P value***
Weight loss, %	−7.67 (6.10)	−6.16	<.001	−9.94 (4.26)	−9.03	<.001
Weight, kg	−7.23 (5.91)	−6.00	<.001	−9.49 (4.65)	−7.91	<.001
BMI, kg/m^2	−2.64 (2.14)	−6.05	<.001	−3.47 (1.68)	−8.00	<.001
[a]HbA1c, %	−0.21 (0.27)	−3.29	.001	−0.25 (0.28)	−3.00	.003
[a]Glucose, mmol/L	−0.19 (0.65)	−1.71	.09	−0.19 (0.73)	−1.62	.10
[a]Insulin, pmol/L	6.57 (118.03)	−0.90	.37	−26.08 (69.15)	−1.82	.07
Testosterone, nmol/L	−0.002 (0.01)	−1.76	.09	−0.002 (0.01)	−1.12	.28
[a]SHBG, nmol/L	9.24 (16.34)	2.54	.01	7.20 (12.36)	1.91	.06
LDL, mmol/L	0.23 (0.49)	2.15	.04	0.29 (0.50)	2.17	.049
[a]HDL, mmol/L	0.05 (0.24)	1.44	.15	0.08 (0.24)	1.54	.12
[a]Triglycerides, mmol/L	−0.30 (0.84)	−1.25	.21	−0.37 (0.96)	−1.17	.24
[a]HOMA2-IR	0.08 (2.24)	−0.89	.38	−0.53 (1.49)	−1.82	.07
[a]MyFitnessPal—total calories, kcal	−456.73 (486.38)	−3.60	<.001	−456.58 (583.11)	−2.73	.01
[a]MyFitnessPal—total calories, kJ	−1,910.95 (2,035.03)	−3.60	<.001	−1,910.31 (2,439.71)	−2.73	.01
[a]MyFitnessPal—net carbohydrates	−105.46 (95.00)	−3.77	<.001	−125.06 (103.21)	−3.11	.002
MyFitnessPal—protein	1.65 (23.71)	0.32	.75	7.68 (24.04)	1.20	.25
MyFitnessPal—fat	−3.28 (33.26)	−0.45	.66	4.01 (35.87)	0.42	.68
Reward-based eating	−0.56 (0.71)	−3.65	.002	−0.56 (0.74)	−2.95	.01
Body responsiveness						
Perceived Disconnection	0.92 (1.28)	3.30	.004	0.71 (1.34)	2.04	.06
Interoceptive Awareness	0.97 (1.64)	2.71	.014	1.29 (1.70)	2.93	.01
Food Craving Inventory—starches	−0.66 (0.64)	−4.68	<.001	−0.56 (0.68)	−3.17	.01
Food Craving Inventory—sweets	−0.61 (0.82)	−3.43	.003	−0.55 (0.91)	−2.35	.03
Mindful eating	0.46 (0.63)	3.33	.003	0.54 (0.62)	3.42	.004
PCOSQ—menstrual symptoms	1.11 (1.56)	3.26	.004	1.33 (1.66)	3.12	.01
PCOSQ—menstrual predictability	2.10 (2.76)	3.49	.002	2.30 (2.53)	3.52	.003
PCOSQ—emotions	1.92 (1.17)	7.52	<.001	1.85 (1.26)	5.70	<.001
PCOSQ—body hair	1.14 (1.04)	5.03	<.001	0.93 (1.09)	3.32	.01
PCOSQ—weight	2.52 (1.70)	6.81	<.001	2.69 (1.77)	5.87	<.001
PCOSQ—infertility	1.08 (1.43)	3.46	.003	1.27 (1.41)	3.47	.004
PROMIS—global mental health	3.36 (5.74)	2.68	.01	2.58 (5.66)	1.77	.10
PROMIS—global physical health	5.14 (4.31)	5.46	<.001	4.93 (4.25)	4.49	<.001
PROMIS—fatigue	−5.98 (6.65)	−4.12	<.001	−4.51 (6.81)	−2.57	.02
PROMIS—sleep	−2.01 (7.59)	−1.21	.24	−2.34 (7.97)	−1.14	.27

Note: All data available used for intention-to-treat analysis, with n = 24 for weight, n = 20 for LDL cholesterol, and n = 21 for all other markers. The results were converted from conventional units to International System of Units. A paired *t*-test was used when the differences between before and after were normal distributions; the Wilcoxon signed rank was used when the differences between before and after were skewed distributions (noted with [a]). The per-protocol analysis included the 15 participants we rated as adhering to the intervention. BMI = body mass index; HbA1c = glycated hemoglobin; HDL = high-density lipoprotein; HOMA2-IR = homeostatic model assessment 2 for insulin resistance; LDL = low-density lipoprotein; N = number; PCOSQ = The Polycystic Ovary Syndrome Health-Related Quality of Life Questionnaire; PROMIS = Patient-Reported Outcomes Measurement Information System; SD = standard deviation; SHBG = sex hormone binding globulin.

Missel. PCOS and very-low-carbohydrate diet. Fertil Steril Rep 2021.

Menstrual regularity. Participants had improvements in their menstrual cycles, including naturally spontaneous menstrual cycles not brought on by medication. One participant said she was "getting a cycle every month which I haven't gotten in almost, I would say, it's been 9 years." Another said she learned to "take back control over my body. Polycystic ovary syndrome can make you feel a little alienated from your own body because of symptoms, hormone fluctuations, pain, and irregularity. When I closely stuck to the diet, I was actually quickly noticing an improvement in all of those things."

Skin improvements. Participants described having less acne and improved skin, such as "I started seeing my skin glow." Another stated, "My complexion has never been, ever, ever, never not since I was maybe 11 have I had times where I've not had like a blemish, and I have that today…I have also had a reduction in the deep cystic acne I would get in my thighs, armpits chest and back."

Glucose control. Participants had improved glucose control and steady glucose levels, and some were able to stop taking their metformin. One explained, "My blood sugar when I started and before that even was prediabetic and now I'm

not prediabetic. [The program] changed my whole health, so I'm grateful." Another described her motivation to join the study and the positive effects after participating, saying, "I needed to lose some weight and I was very worried about my A1C and my blood sugar, and I did not like the metformin; it has weird side effects. So, I wanted to figure out a way to change my lifestyle so that I wouldn't have to take it forever-….That's what the study has done for me because… I don't have to take my metformin anymore, and I feel better than I have in years with no GI [gastrointestinal] distress. There's no more fatigue after eating. I don't have any blood sugar spikes. It's just great."

Altered beliefs about food. Several participants discussed changing thoughts on food, with one participant observing that she went "from the place of where I'm sugar addicted to being not dependent on sugar. So, just going to food for nourishment and enjoying the flavors." Another noted, "I learned that I [had been] using snacks as a coping mechanism a lot, so I've been feeling better about knowing when to eat and how much." Some described how learning about the physiological impact of food was beneficial, such as "…understanding the role that insulin and sugar plays in my weight has been incredibly helpful for me. I feel that knowing this will help me continue to stay on track. Some people are lactose intolerant; I feel like I am sugar intolerant."

One participant was surprised about "how tasteful the food is in this program. Following the recipes and adding more vegetables to my diet, that's been really surprising, because vegetables aren't exactly really good-tasting… it surprised me how good [vegetables go] with certain foods and certain proteins." Participants brought up several strategies that they used to support their dietary adherence, including preparing meals in advance, having a list of easy-to-prepare "go-to" meals, learning how to read food labels, and being aware of ways to substitute ingredients to make food compatible with the meal plan. One noted, "Finding the powdered pork rinds was a total game changer because then I could still make chicken fingers <laughs>, so if I wanted something totally like comfort food, it was still possible to do that."

Physician support. Participants had either neutral or positive physician support. One participant said, "He seemed interested, he was saying that he had other patients on keto who had had success with it in losing weight. But he did make a comment like, 'I love bread too much, I couldn't give that up,' which I think is just kind of funny. But yeah, I would say he definitely wasn't unsupportive of it." Another's physician was "very impressed… and excited because I'm finally getting healthy. Over the years, he has suggested diet and exercise, which I have done but a typical calorie in, calorie out diet… I was still finding it very hard to lose weight, and it wasn't working the way he wanted it to work. So I think it always frustrated him that he'd always tell me to try harder… He's now asking how I did it, how I've lost so much weight and how I got my cholesterol down so far so quick and he wants to suggest it to other people that might be in similar conditions that I was in."

DISCUSSION

This trial provides compelling proof of concept that an online, multicomponent VLC diet and lifestyle intervention is feasible, acceptable, and potentially efficacious in treating women with PCOS. Participant satisfaction was high, and numerous objective and subjective factors improved. Finally, interviewed participants noted a variety of mostly positive health changes.

For example, we observed significant improvements in body weight, which is consistent with previous trials implementing a ketogenic diet in patients with PCOS (16, 36). Weight loss results in several key benefits for women with PCOS, including improvement of metabolic parameters, reduced risk of developing cardiovascular disease, and reduced risk of type 2 diabetes (37). Previous trials have retained a similarly small number of participants, in trials between 2 and 3 months, with similar reductions in weight and improvements in glucose control. The intervention from our research is designed to be online and, therefore, easy to access, in which previous published research did not emphasize (35, 38). Overall, this suggests that a VLC dietary intervention could be used to manage some of the negative outcomes associated with PCOS.

Our glucose control results are consistent with a previous single-arm prospective carbohydrate restriction trial in PCOS, which observed a significant reduction in HbA1c (38). Additionally, the results from our trial show a greater HbA1c reduction than was observed in a short-term trial using a Dietary Approaches to Stop Hypertension diet (39). These findings may be due to the reduced postprandial glycemia and hyperinsulinemia that results from carbohydrate restriction (40).

The trial has several strengths and limitations. A strength of the trial is that we measured psychological outcomes very broadly, finding improvements in global mental health, global physical health, and PCOS-related quality of life measures, including menstrual predictability and body hair. Another strength of this trial is that the intervention is completely online, which may facilitate the feasibility of a future study that could recruit participants nationally and reach racial/ethnic and socioeconomic groups often underrepresented in weight loss studies (41). In terms of limitations, although the results from this study are promising, long-term implications are unclear because of the short, 4-month timeline, small sample size, and lack of experimental control. Larger, long-term, randomized controlled trials comparing our diet with other dietary approaches are necessary to better understand the long-term feasibility and efficacy of this approach to treatment for PCOS and explore some of the outcomes such as the elevation in LDL cholesterol (LDL-C) level. However, during weight loss, stored cholesterol can be mobilized from adipose tissue, temporarily increasing the LDL-C level, so this is likely not a concern (42). Moreover, LDL-C is a controversial indicator of cardiovascular risk, and VLC diets typically improve outcomes more strongly related to cardiovascular risk, such as triglycerides, small dense LDL, and large buoyant LDL (43).

In addition, our participants were primarily White, and to what extent results generalize to people of color is unclear.

Moreover, because this was a multicomponent program, which combined a VLC diet with a variety of other factors, such as instruction in positive affect and mindful eating skills, it is unclear which components of the intervention led to the outcomes. Additionally, other factors related to PCOS play a role in the increased insulin resistance these women experience and may not be modulated by weight loss. In future research, trials could examine the impact of this intervention for women with normal BMIs. We also did not assess how long participants had been taking metformin and whether this may have caused prior weight loss. A larger, future trial may be able to be powered to detect the potential confounding influence of metformin. Finally, the combined lost to follow-up and dropout rate for this trial was moderate (27%), although this falls within the average dropout rate (27%–35%) in previous diet and lifestyle studies for those diagnosed with PCOS (44). Time commitment was cited as the main reason for dropout in trials that evaluated the effects of lifestyle modification in women with PCOS (37). Further evaluation of dropout rates is needed to improve the effectiveness of future dietary interventions for PCOS.

CONCLUSION

Polycystic ovary syndrome is commonly diagnosed earlier in life than type 2 diabetes, as it is discovered during the early reproductive years (45). Given that PCOS is known to place women at a higher risk of developing type 2 diabetes, early management has the potential to effectively reduce risk and prevent or delay progression to type 2 diabetes. This multicomponent VLC dietary intervention was feasible, acceptable, and efficacious in promoting weight loss and other positive changes in overweight patients with PCOS.

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