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Original Article

ORIGINAL ARTICLE

Time-restricted eating and autosomal dominant polycystic kidney disease: a pilot, randomized clinical trial

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ABSTRACT

Background. Autosomal dominant polycystic kidney disease (ADPKD) is the most commonly inherited progressive kidney disease. Time-restricted eating (TRE) is a fasting regimen that restricts eating to a particular window (typically 8 hours/day), which could slow cyst growth based on preclinical models.

Methods. A 12-month, randomized, controlled, behavioral dietary intervention compared TRE with a control group given healthy eating advice without TRE (HE), without caloric restriction. Participants underwent baseline and 12-month measurements, including adherence (percentage of participants adhering to the 8-hour window; primary outcome), and MRI to determine height-adjusted total kidney volume (htTKV) and adiposity.

Results. Twenty-nine participants (23 females, mean standard ± deviation 48 ± 9 years) with a body mass index of 31.1±5 kg/m^2 were randomized to TRE ($n = 14$) or HE ($n = 15$). Of the total participants, 71% ($n = 10$) of TRE and 87% ($n = 13$) of HE participants completed the intervention. The eating window was 9.6 ± 3.6 hours for TRE (60% achieving the 8-hour window) and 12.0 ± 2.0 for HE groups ($P = .07$). At month 12, both groups lost modest weight (−2.4 ± 6.4% and −3.6 ± 5.4% in the TRE and HE groups, respectively). Annual change in htTKV was 3.0 ± 8.5% and 4.6 ± 8.8% in the TRE and HE groups, respectively. Both change in weight ($r = 0.67$, $P < .01$) and change in visceral adiposity ($r = 0.54$, $P < .01$) were positively correlated with change in htTKV.

Conclusion. Both the TRE and HE group lost modest weight at 12 months. The targeted TRE adherence of ≥75% of participants was not achieved. Weight and adiposity loss may be more important drivers of kidney growth than the timing of eating.

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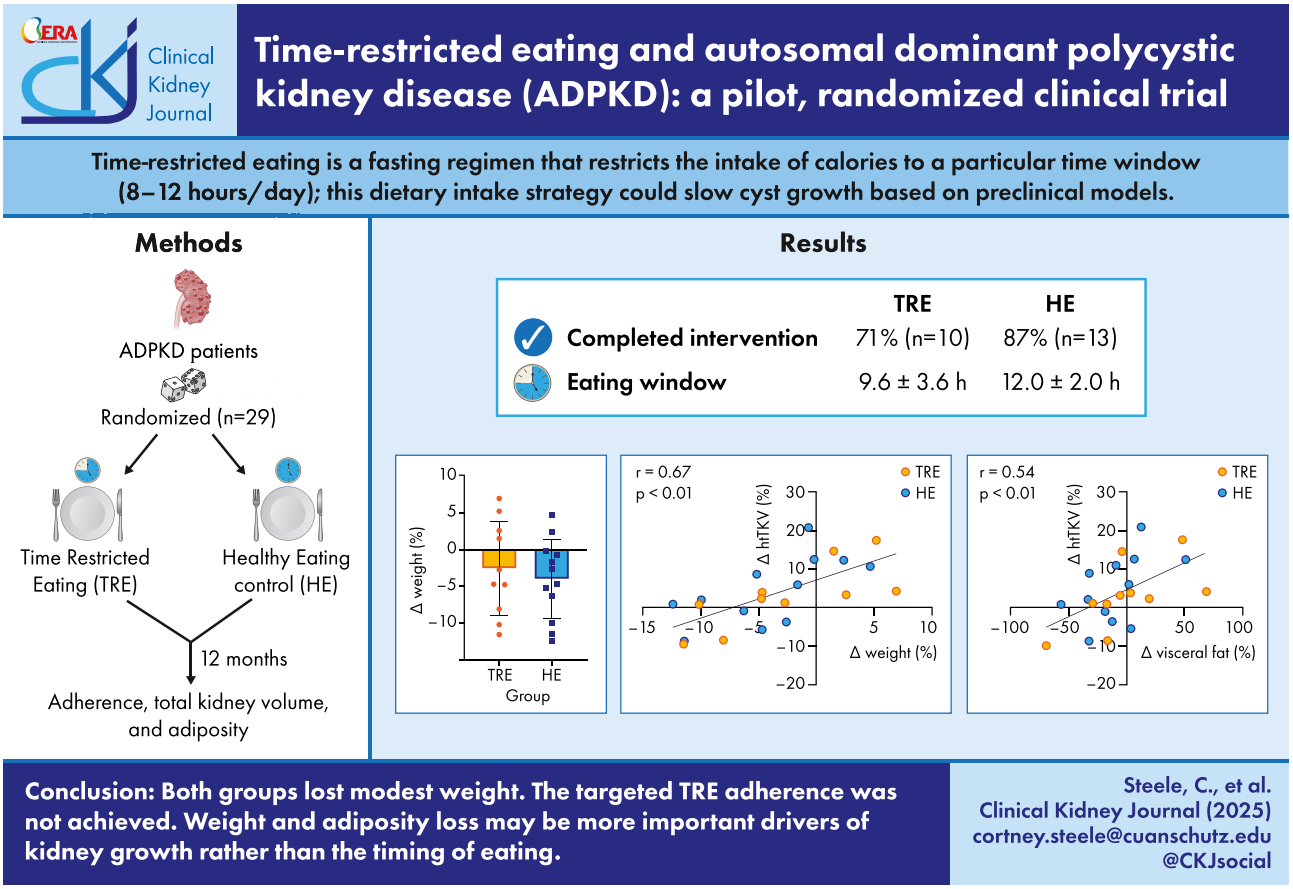
GRAPHICAL ABSTRACT



Keywords: diet, fasting, kidney, polycystic, weight loss

KEY LEARNING POINTS

What was known:

- Time-restricted eating (TRE) can reduce body weight and fat mass in people without autosomal dominant polycystic kidney disease (ADPKD).
- TRE reduces disease progression in animal models of ADPKD.

This study adds:

- In the present study, TRE and healthy eating advice without TRE (HE) interventions in adults with ADPKD resulted in similar modest weight loss over a 12-month period.
- Adherence to TRE varied across our study cohort, and randomized groups did not differ in change in anthropometrics, glucose metabolism, or caloric intake with the 12-month intervention.

Potential impact:

- Fasting may be beneficial to some individuals; however, this study confirmed an earlier report that weight loss is associated with height-adjusted total kidney volume, regardless of the dietary intervention.
- This was a feasibility study. Future research is needed to determine the efficacy of weight loss to slow kidney growth in ADPKD.

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is categorized by the progressive development and growth of kidney cysts, leading to end-stage kidney disease in the majority of patients [1, 2]. Evidence suggests that ADPKD alters metabolism, which likely promotes cyst development and growth [3–5]. The established metabolic consequences of obesity may, therefore, also impact disease progression for individuals with ADPKD [6].

Periods of fasting may modify numerous cellular and molecular mechanisms implicated in ADPKD. Among other pathways, fasting can stimulate the AMP-activated protein kinase (AMPK) pathway, inhibit the mammalian target of rapamycin-ribosomal protein S6 kinase (mTOR-S6K) pathway, and inhibit insulin-like growth factor 1 (IGF-1) [7]. Fasting promotes metabolic reprogramming via a shift from carbohydrate to fat metabolism, primarily mediated by AMPK [8]. This shift to ketogenesis could suppress the growth of cysts, which favor aerobic glycolysis and may not use ketones as an energy source [9].

Time-restricted eating (TRE) is a fasting regimen that restricts the intake of calories to a particular feeding window (typically 8–12 hours/day), while still meeting nutrient requirements. This dietary approach has been shown to promote weight loss and reduce body fat in those without ADPKD [10–12]. In non-ADPKD rodent models, TRE protected against weight gain despite comparable caloric intake to the control group [13, 14], improved mTOR and AMPK pathway function [14], and improved insulin sensitivity [15, 16]. Most recently, TRE reduced disease progression in the Han:SPRD rat model of polycystic kidney disease (PKD), including cyst volume, total body weight, mTOR activity, and proliferation markers [9]. However, the feasibility of a TRE intervention in humans with ADPKD has not been evaluated.

Therefore, this randomized, parallel-group trial in adults with ADPKD was designed to assess the acceptability and efficacy of a 12-month behavioral weight loss intervention utilizing TRE (8-hour window starting within 3 hours of waking) as compared to a healthy eating group (HE) without time restriction. We hypothesized that TRE would be an acceptable dietary intervention that would result in more significant weight loss, more favorable changes in body composition, and improved metabolic outcomes after 1 year as compared to HE.

MATERIALS AND METHODS

Experimental design

A 1-year, randomized, two-arm, single-blind pilot study was conducted in adults with ADPKD and normal to moderately declined kidney function (≥30 mL/min/1.73 m^2). The goal was to assess the feasibility of delivering a 1-year behavioral intervention involving TRE or HE. We hypothesized that ≥75% of participants in the TRE group would adhere to the 8-hour window (primary outcome). The Colorado Multiple Institutional Review Board approved the study protocol (20-1262), and all participants provided written informed consent prior to participation. This study was conducted in accordance with the principles expressed in the Declaration of Helsinki. The trial was registered at Clinicaltrials.gov: NCT04534985.

Participants

Subjects were recruited nationally and underwent telephone and laboratory screening for inclusion/exclusion criteria (Supplementary Table 1). History of a clinically diagnosed eating disorder including anorexia nervosa, bulimia [binge eating disorder score >20 on the Eating Attitudes Test (EATS-26)] [17] or severe depression (score >18 on the Beck Depression Inventory [18]) required assessment by a study physician before participation. Tolvaptan was not exclusionary, provided that patients were on a stable dose for at least 3 months at the time of study enrollment. Incident tolvaptan usage was not permitted during the study. Those who qualified were randomly assigned to either the TRE or the HE group. Members of the investigative team involved in the data analysis were blinded to the treatment status. Due to the nature of the intervention, study participants were not blinded. Both groups received a comprehensive, group-based, behavioral dietary intervention delivered virtually.

Dietary intervention

The behavioral dietary interventions were administered by the Colorado Nutrition and Obesity Research Center (NORC) Clinical Intervention and Translation (CIT) Core. The curriculum for both groups was developed and delivered in consultation with a board-certified endocrinologist. The curriculum for the TRE group was based on an ongoing study in healthy overweight and obese adults [19]. The participants were instructed to eat within an 8-hour window, beginning within 3 hours of waking. The curriculum for both groups emphasized current clinical recommendations for the management of ADPKD, as well as chronic kidney disease (CKD), including moderate dietary sodium restriction (2.3–3 g), appropriate hydration, protein intake of 0.8–1.0 g/kg ideal body weight, moderate daily phosphate restriction (800 mg), and moderation in caloric intake (without a specific goal) [20]. However, the HE control group received no instruction regarding the timing of eating. Neither group was explicitly instructed to reduce energy intake or given a calorie goal; however, moderation in caloric intake was discussed as one of the topics. An experienced registered dietitian taught all virtual sessions. Month 1 was an intensive phase with weekly sessions (60 min) focused on achieving dietary goals. Subsequent monthly sessions (30 min) were focused on maintenance.

Primary outcome measures

Feasibility and adherence

A 7-day photographic food record at baseline and month 12 was used to evaluate meal timing and determine eating window. Percent adherence to the 8-hour TRE window (±30 min) during the 7-day recording period at month 12 was the primary endpoint. Self-reported dietary adherence, effort to adhere, and self- efficacy to adhere were also assessed in the TRE group, using a 1–10 Likert scale [21]. In a subgroup of participants ($n = 19$) a continuous glucose monitor (CGM) (FreeStyle LibrePro) was worn for 1 week at baseline and 12 months. The CGM sensor was applied to the back of the participant's upper arm to measure glucose in interstitial fluid every 15 min. Group comparisons were assessed by calculating the area under the curve (AUC) and visually via plotting the data as heat maps.

Clinical measurements

Body weight was measured on a calibrated digital scale to the nearest 0.1 kg and height was measured to the nearest 1 mm using a stadiometer at baseline and 12 months at the University of Colorado PKD research clinic. Changes in body composition were further assessed via dual-energy x-ray absorptiometry (DXA; Hologic Discovery W, Bedford, MA), and abdominal adiposity was quantified using magnetic resonance imaging (MRI) as described below (baseline and month 12). Resting energy expenditure was measured between 6 and 10 AM after a 12-hour fast using standard indirect calorimetry with the ventilated hood technique [22].

Body weight was also collected remotely at the times of group web-based sessions using BodyTrace scales to guide these

Table 1: Baseline characteristics and demographics for all participants.

	Total ($n = 29$)	TRE ($n = 14$)	HE ($n = 15$)
Age (years)	48 ± 9	50 ± 9	47 ± 9
Weight (kg)	88 ± 16	90 ± 18	85 ± 15
Sex			
Male (%)	6 (21)	2 (21)	3 (20)
Female (%)	23 (79)	12 (79)	12 (80)
Race			
Non-White (%)	2 (4)	0 (0)	2 (7)
White (%)	27 (96)	14 (100)	13 (93)
Body mass index (kg/m^2)	31.1 ± 5.1	31.8 ± 6.0	30.5 ± 4.2
Waist circumference (cm)	103 ± 14	104 ± 16	101 ± 12
Hip circumference (cm)	113 ± 12	114 ± 14	112 ± 11
Waist-to-hip ratio	0.91 ± 0.07	0.91 ± 0.08	0.90 ± 0.07
Systolic blood pressure (mmHg)	122 ± 11	124 ± 12	120 ± 9
Diastolic blood pressure (mmHg)	79 ± 9	82 ± 8	76 ± 10
Resting heart rate (bpm)	73 ± 8	73 ± 8	72 ± 9
Resting energy expenditure (kcal/day)	1599 ± 278	1606 ± 254	1593 ± 309
Mayo class			
1A	4 (14)	1 (7)	3 (20)
1B	9 (31)	4 (29)	5 (33)
1C	12 (41)	7 (50)	5 (33)
1D	3 (10)	1 (7)	2 (13)
1E	1 (3)	1 (7)	0 (0)
Smoking status (%)			
Never smoker	23 (79)	10 (71)	13 (87)
Past smoker	6 (21)	4 (29)	2 (13)
Beck Depression Inventory	6.09 (4.86)[a]	7.00 (5.91)[b]	5.38 (3.99)[c]
EATS 26 questionnaire score	4.09 (3.22)[a]	3.70 (3.43)[b]	4.38 (3.15)[c]

Baseline characteristics are presented as mean ± standard deviation or *n* (%).
$n = 23$[a], $n = 10$[b], $n = 13$[c].

Table 2: Study compliance (percentage of remote visits attended).

Compliance data	Total ($n = 23$)	TRE ($n = 10$)	HE ($n = 13$)	*P*-value
Baseline to month 1 compliance	88 ± 18	92 ± 12	84 ± 21	.21
Baseline to month 3 compliance	83 ± 17	86 ± 13	81 ± 19	.42
Month 3 to month 12 compliance	74 ± 27	64 ± 26	81 ± 26	.14
Total compliance	77 ± 21	72 ± 18	80 ± 23	.34

Data are presented as mean ± standard deviation.
Welch two-sample *t*-tests were used to calculate *P*-values to determine if there were differences between groups.

sessions, as used previously [21]. Percentage weight loss and BMI were calculated at baseline, 3 months, and 12 months. If a final weight was not available at month 12, the last weight available after month 6 via BodyTrace measurements was used. Waist and hip circumference were also measured at baseline and 12 months.

Safety, acceptability, and tolerability

Fasting blood samples were collected for screening and repeated at 3 and 12 months for analyses including a complete metabolic panel, complete blood count, hemoglobin A1c (HbA1c), and lipid panel. Samples were collected in the morning following an overnight fast. Estimated GFR (eGFR) was calculated using the CKD–EPI equation [23]. Month 3 samples were collected at a contract laboratory for all non-local participants.

Blood pressure and other vital signs were also measured at baseline and month 12 (Omron HEM907XL). Participants were encouraged to report adverse events to study staff as they occurred and were called monthly to assess current status and symptoms. Additional parameters to assess tolerability were collected at baseline and months 3 and 12 as follows. Quality of life (QOL) was assessed with the RAND 36 Item Health Survey (RAND-36) [24] physical and mental health component summary score. Mood state was assessed with the Profile of Mood States 2 (POMS-2) [25]. Additionally, to gain insight into physical activity, self-reported physical activity was quantified at baseline, 3 months, and 12 months using the Stanford Physical Activity Questionnaire [26]. ASA24 was used to administer and analyze 24-hour dietary recalls. Participants' self-reported dietary data were excluded if they did not complete the diet questionnaire or had extreme self-reported energy intakes (i.e. <500 kcal per day).

Table 3: Adverse events related or possibly related to the intervention.

Adverse event	Total ($n = 23$)	TRE ($n = 10$)	HE ($n = 13$)
Hunger	15 (17%)	12 (27%)	3 (7%)
Fatigue	2 (2%)	1 (2%)	1 (2%)
Irritability	5 (6%)	4 (10%)	1 (2%)
Headache	1 (1%)	1 (2%)	0 (0%)
Gastrointestinal distress	11 (13%)	5 (11%)	6 (14%)
Dizziness	1 (1%)	1 (2%)	0 (0%)
Lightheadedness	9 (10%)	5 (11%)	4 (9%)
Electrolyte abnormalities	1 (1%)	1 (2%)	0 (0%)
Other	44 (49%)	15 (33%)	29 (66%)

Data are presented as number of events *n* (%).

Table 4: Adherence score for the TRE group.

Variable	Month 3	Month 12
Success* (days)	6.40 ± 0.70	4.90 ± 1.91
Diet adherence score	9.00 ± 0.94	6.60 ± 2.95
Diet adherence difficulty (1–10)	3.70 ± 3.09	6.20 ± 2.53
Diet adherence likelihood (1–10)	9.10 ± 0.88	7.60 ± 3.03
Days diet met	6.90 ± 0.32	5.60 ± 2.17
Days diet achieved	6.40 ± 0.70	4.90 ± 1.91
Overall adherence score (1–10)	9.10 ± 0.88	6.60 ± 2.95
Overall adherence difficulty (1–10)	3.70 ± 3.09	6.20 ± 2.53
Future adherence likelihood (1–10)	9.10 ± 0.88	7.60 ± 3.03

Data are presented as mean ± standard deviation.
*Average number of days successful in eating only during 8-hour window over the past 7 days.

Exploratory outcomes

Circulating markers

Serum IGF-1 (DG100B, R&D systems), IGFBP-1(DGB100, R&D systems), adiponectin (DRP300, R&D systems), CRP (V-plex, K151STD, Meso Scale Discovery), leptin, and insulin (1:2 dilution, Customized U-Plex Metabolic Group 1, Meso Scale Discovery) were measured at baseline and 12 months using fasting blood samples [21]. Insulin resistance was estimated with the HOMA-IR formula [25].

Protein expression in peripheral blood mononuclear cells (PBMCs) isolated from whole blood using a CPT Vacutainer (#362 753, BD Biosciences) [27]. Details regarding

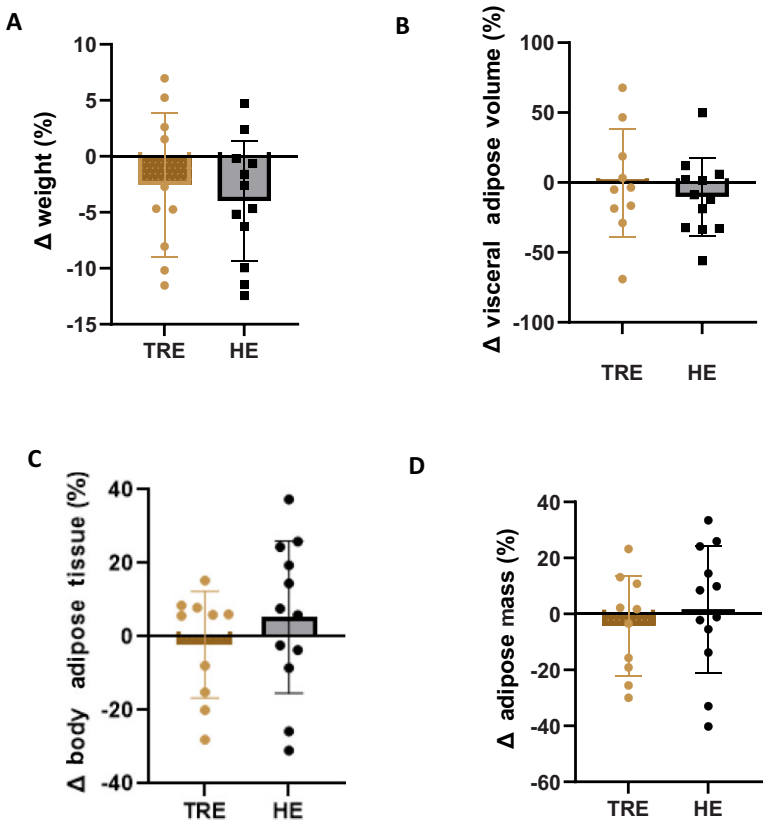


Figure 1: Weight loss and change in body composition with 1 year of TRE (gold) or an HE without TRE control intervention (black). (A) Percentage weight loss according to group randomization from baseline to 12 months, presented as mean and standard deviation with individual participants shown by dots. (B) Percentage change in visceral adipose volume measured via abdominal magnetic resonance imaging according to group randomization from baseline to 12 months, presented as mean and standard deviation with individual participants shown by dots. (C) Percentage change in the percentage of total adipose tissue measured via dual-energy X-ray absorptiometry (DXA) according to group randomization from baseline to 12 months, presented as mean and standard deviation with individual participants shown by dots. (D) Percentage change in total adipose mass measured via dual-energy X-ray absorptiometry (DXA) according to group randomization from baseline to 12 months, presented as mean and standard deviation with individual participants shown by dots.

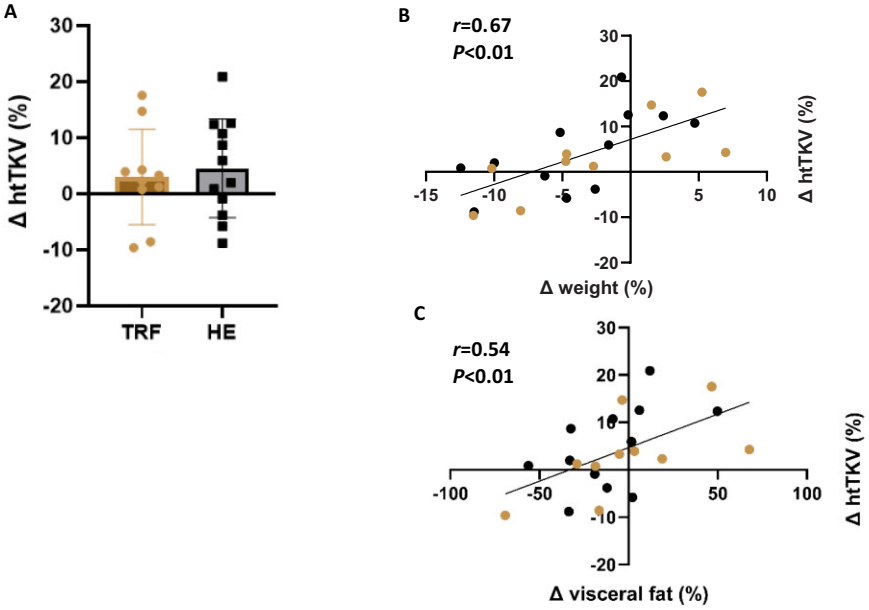


Figure 2: Change in height-adjusted total kidney volume (htTKV) and its association with weight and visceral adipose tissue loss. (A) Percentage change in htTKV measured via MRI according to group randomization [TRE (gold), or healthy eating advice without TRE control group, HE (black)] from baseline to 12 months, presented as mean and standard deviation with individual participants shown by dots. (B, C) Association of percentage change in body weight (B) and percentage change in visceral adipose volume (C) at 12 months with annual percentage change in htTKV. Among all participants, annual change in htTKV was correlated with change in body weight and visceral fat.

PBMC
processing are in the supplementary material.

Magnetic resonance imaging

A Siemens Skyra 3.0 T system was used to obtain an abdominal MRI at baseline and 12 months; the methodology has been described previously by our group [21]. Total kidney volume (TKV) was measured by stereology using Analyze software (Analyze 12.0, Mayo Foundation, Rochester, MN) by a single blinded investigator. Disease severity was categorized according to the Mayo Imaging Classification system [28]. The cystic index was also determined using a machine learning approach [29, 30]. As described previously, T2-weighted MRIs oriented in the axial plane with slice level at the L3 vertebra were used to segment subcutaneous adipose tissue, muscle, visceral adipose tissue, visceral organs, and bone via a semiautomated intensity threshold algorithm followed by manual correction by an expert imaging analyst using ITK-Snap [31].

Statistical analysis

As adherence was the primary outcome, the proposed sample size was based on the feasibility of recruitment for optimal cohort sizes, enrolled at a staggered rate throughout the study period rather than on a specific power. The goal was to recruit and randomize 30 total participants across three cohorts. Based on our previous weight loss trial [21], this was an ideal target cohort size for a pilot group-based lifestyle intervention delivered through a video chat platform. Blocked randomization was 1:1 with stratification by sex.

Statistical analyses were conducted in RStudio v6. Prism (GraphPad Software, version 7.03 for Windows, 2018, La Jolla, CA, USA) and RStudio v6 was used to generate figures. All AUC calculations used rGV with an AUC threshold of 80 mg/dL. SAS v9.4 calculated the Healthy Eating Index 2015 (HEI) from the ASA24 data. Welch's two-sample *t*-tests were used to compare the change in each variable between groups. An independent *t*-test was also used to compare mean differences between groups at baseline and 1 year. Paired *t*-tests determined mean differences between baseline and 1 year within groups. Proportions of study-related adverse events and questionnaire data were also compared between groups using a least squares mean test, χ^2 tests, or Fisher's exact test. Correlations were performed using Pearson's bivariate correlation. All statistical tests were assessed using a $P < .05$ threshold, determined *a priori*.

RESULTS

Participants

A total of 91 individuals (Supplementary Fig. 1) were assessed for eligibility, and 29 were then enrolled in the study after meeting the inclusion criteria (Supplementary Table 1). Table 1 presents the demographics and baseline characteristics of the participants. There were no differences in baseline characteristics between groups. Of the 29 randomized individuals, 23 completed the study, including 71% ($n = 10$) of those in the TRE group and 87% ($n = 13$) in the HE group. The most commonly reported previous medical condition was hypertension (Supplementary Table 2), and most participants were taking an antihypertensive medication at baseline (Supplementary Table 3).

Table 5: Anthropometrics, blood pressure, blood chemistries, and questionnaires of participants who completed the study.

	Total ($n = 23$)			TRE ($n = 10$)			HE ($n = 13$)			P-value comparison of change between groups
	Baseline	Month 3	Month 12	Baseline	Month 3	Month 12	Baseline	Month 3	Month 12	
Weight (kg)	86 ± 17	83 ± 18	83 ± 18	88 ± 20	85 ± 21	86 ± 20	85 ± 16	83 ± 16	80 ± 16	.66
BMI (kg/m^2)	30.3 ± 5.3	29.3 ± 5.2	29.5 ± 5.2	30.4 ± 6.2	29.1 ± 6.4	29.5 ± 5.2	30.2 ± 4.2	29.4 ± 4.2	29.2 ± 5	.37
Hip circumference (cm)	111 ± 13	NA	108 ± 13	112 ± 15	NA	109 ± 15	111 ± 11	NA	105 ± 8	.97
Waist circumference (cm)	101 ± 13	NA	95 ± 14	100 ± 15	NA	97 ± 16	102 ± 13	NA	91 ± 10	.28
Waist-to-hip ratio	0.90 ± 0.07	NA	0.88 ± 0.07	0.90 ± 0.07	NA	0.89 ± 0.09	0.92 ± 0.07	NA	0.87 ± 0.07	.15
Total fat mass (kg)	27 ± 11	NA	24 ± 14	28 ± 12	NA	24 ± 16	26 ± 11	NA	27 ± 12	.19
Total lean mass (kg)	57 ± 12	NA	49 ± 19	58 ± 13	NA	51 ± 23	56 ± 12	NA	52 ± 10	.45
Adipose tissue (%)	32 ± 9	NA	32 ± 10	32 ± 10	NA	31 ± 12	31 ± 9	NA	33 ± 9	.18
VAT mass (g)	551 ± 291	NA	580 ± 348	655 ± 309	NA	635 ± 356	464 ± 255	NA	538 ± 351	.06
SBP (mmHg)	101 ± 12	118 ± 12	118 ± 14	122 ± 14	119 ± 16	119 ± 16	119 ± 9	116 ± 9	118 ± 13	.44
DBP (mmHg)	76 ± 8	77 ± 8	75 ± 10	79 ± 7	78 ± 8	76 ± 6	74 ± 9	77 ± 8	75 ± 12	.39
Fasting glucose (mg/dL)	90 ± 5	83 ± 15	87 ± 7	89 ± 5	80 ± 16	87 ± 4	91 ± 6	85 ± 14	87 ± 9	.74
HOMA-IR	4 ± 2	4 ± 2	3 ± 2	4 ± 2	4 ± 2	4 ± 2	3 ± 2	3 ± 2	3 ± 2	.24
HbA1c (%)	5.3 ± 0.3	5.2 ± 0.3	5.3 ± 0.3	5.3 ± 0.3	5.3 ± 0.4	5.3 ± 0.4	5.2 ± 0.3	5.2 ± 0.3	5.2 ± 0.3	.43
Triglycerides (mg/dL)	119 ± 76	114 ± 49	108 ± 82	143 ± 100	137 ± 53	139 ± 115	100 ± 47	96 ± 39	84 ± 33	.69
Total cholesterol (mg/dL)	179 ± 35	185 ± 23	175 ± 32	176 ± 31	184 ± 24	183 ± 30	182 ± 39	186 ± 22	168 ± 34	.04
LDL cholesterol (mg/dL)	106 ± 30	110 ± 21	101 ± 25	98 ± 24	106 ± 24	103 ± 26	113 ± 33	114 ± 20	100 ± 26	.047
HDL cholesterol (mg/dL)	51 ± 11	54 ± 11	53 ± 14	54 ± 13	54 ± 13	56 ± 15	49 ± 10	53 ± 9	50 ± 14	.58
CKD–EPI eGFR (mL/min/1.73 m^2)	74 ± 24	71 ± 21	71 ± 22	72 ± 24	72 ± 24	65 ± 21	76 ± 24	70 ± 20	76 ± 22	.23
CRP (ng/mL)	4 ± 7	2 ± 2	5 ± 11	5 ± 8	6 ± 8	9 ± 16	4 ± 7	3 ± 3	2 ± 2	.16
IGF-1 (ng/mL)	70 ± 28	69 ± 21	68 ± 23	62 ± 12	70 ± 15	66 ± 20	75 ± 35	65 ± 24	69 ± 26	.63
IGF1-BP (ng/mL)	16 ± 10	25 ± 22	22 ± 18	16 ± 9	19 ± 16	18 ± 12	16 ± 11	26 ± 23	26 ± 21	.27
IGF-1 to IGF1-BP ratio	10 ± 19	7 ± 8	8 ± 14	5.3 ± 3.2	7.2 ± 6.9	5.4 ± 3.9	14.4 ± 24	6.9 ± 8.5	10 ± 19	.15
Leptin (pg/mL)	29 ± 25	14 ± 14	26 ± 27	28 ± 26	19 ± 18	28 ± 29	29 ± 26	20 ± 22	25 ± 28	.21
Adiponectin (μg/mL)	7 ± 4	8 ± 5	8 ± 5	6.7 ± 4.3	6.9 ± 5.2	7.7 ± 5.6	6.6 ± 4.1	8 ± 5	8 ± 5	.44
β-Hydroxybutyrate (mmol/L)	0.2 ± 0.1	0.2 ± 0.3	0.3 ± 0.2	0.3 ± 0.2	0.3 ± 0.5	0.3 ± 0.2	0.2 ± 0.0	0.2 ± 0.1	0.3 ± 0.2	.54
Serum chloride (mg/dL)	106 ± 2	104 ± 3	104 ± 3	105 ± 1	103 ± 2	103 ± 3	105 ± 2	105 ± 3	106 ± 3	.41
Leisure/physical activity in MET (hours/week)	13 ± 14	10 ± 13	12 ± 11	17 ± 20	9 ± 8	12 ± 11	10 ± 8	11 ± 16	13 ± 11	.72
POMS fatigue scale score	4 ± 4	5 ± 4	4 ± 3	4 ± 2	4 ± 3	4 ± 3	5 ± 5	6 ± 5	4 ± 4	.97
POMS vigor activity scale score	9 ± 4	9 ± 4	9 ± 4	9 ± 4	9 ± 4	8 ± 3	9 ± 3	8 ± 4	9 ± 4	.87
SF-36 mental health component summary score	78 ± 16	79 ± 15	79 ± 17	73 ± 21	78 ± 14	73 ± 20	81 ± 12	79 ± 17	83 ± 13	.28
SF-36 physical health component summary score	85 ± 12	90 ± 13	91 ± 11	87 ± 10	96 ± 7	94 ± 7	83 ± 13	86 ± 15	89 ± 13	.44

Data are presented as mean ± standard deviation.

There were no significant differences comparing change within groups at month 3 for any variables.

Welch two-sample t-tests were used to calculate P-values to compare the change at 12 months between groups (presented in the last column of the table).

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HOMA-IR, Hemostatic Model Assessment of Insulin Resistance; HbA1c%, hemoglobin A1c; LDL, low-density lipoprotein; HDL, high-density lipoprotein, CKD–EPI eGFR, estimated glomerular filtration rate by the Chronic Kidney Disease Epidemiology Collaboration equation; CRP, C-reactive protein; IGF1, insulin-like growth factor-1; IGF1-BP, insulin-like growth factor-1 binding protein; SF-36, 36-Item Short Form Survey; POMS, Profile of Mood States questionnaire; MET, metabolic equivalent of task; VAT, visceral adipose tissue.

Adherence and safety

Compliance, measured by remote visit participation (percent attended), was relatively high and did not differ between groups (Table 2). Adverse events that were related or possibly related to the intervention are described in Table 3. The most common event reported in the TRE group was hunger. The eating window was assessed via photographic records in 13 participants, including 5 in the TRE group and 8 in the HE group. Completion of the photographic records as instructed was more challenging than anticipated. Participants who did not complete the 7-day food photos in the final 3 months or were missing time stamp information were excluded due to inadequate data quality to assess adherence, limiting the sample size. At baseline, the eating window was 11.4 ± 1.5 hours for the TRE group and 12.3 ± 2.6 hours for the HE group ($P = .22$). At month 12, the eating window was 9.6 ± 3.6 hours for TRE [60% achieving the 8-hour window (<75% *a priori* definition of success)] and 12.0 ± 2.0 for HE ($P = .07$). Participants ranked their dietary adherence from 'not adherent at all' (1) to 'perfect adherence' (10) over the past 7 days. Participants ranked adherence as 9.9 ± 1 at month 3 and 6.6 ± 3 at month 12 (Table 4).

Clinical measurements and self-reported questionnaires

At month 12, the TRE group lost 2.4 ± 6.4% body weight and the HE group lost 3.6 ± 5.4% body weight ($P = .66$) (Fig. 1). Change in visceral adipose tissue ($P = .50$) and total body adipose tissue loss ($P = .35$) did not differ between the groups at month 12 (Fig. 1). Annual percentage change in height-adjusted total kidney volume (htTKV) was 3.0 ± 8.5% and 4.6 ± 8.8% in the TRE and HE groups, respectively (Fig. 2). Both change in weight ($r = 0.67$, $P < .001$) and change in visceral adipose volume ($r = 0.54$, $P = .009$) were positively correlated with changes in htTKV (Fig. 2). The association between change in weight and htTKV remained significant for both slow progressors (Mayo class 1A and 1B; $r = 0.75$, $P < .01$) and fast progressors (Mayo class 1C–E; $r = 0.69$, $P = .03$). The association between change in visceral adipose volume and htTKV remained significant only for slow progressors (Mayo class 1A and B; $r = 0.64$, $P = .03$). Change in other MRI measurements, including total abdominal adipose tissue, subcutaneous adipose tissue, and visceral adipose tissue, as well as cyst volume, did not differ between groups (Supplementary Table 4).

Change in anthropometrics, blood pressure, blood chemistries, and lifestyle questionnaires at 12 months did not differ between the groups (Table 5). The only exception was that the HE group had a greater reduction in cholesterol [−6.2 ± 12% compared with TRE 4 ± 11% over 12 months ($P = .04$)]; however, there were no differences when comparing total cholesterol at baseline ($P = .37$) or 12 months ($P = .30$) between groups ($P = .30$). Self-reported physical activity did not differ between groups at baseline ($P = .82$) or change over the 12-month period ($P = .39$).

Changes in β-hydroxybutyrate levels were not associated with changes in htTKV (Fig. 3). In a subset of participants, a continuous glucose monitor was worn for 7 days. The AUC at baseline did not differ between groups (14 710 ± 8446 and 22 148 ± 12 853 in the TRE and HE groups, respectively). At 12 months, the AUC also did not differ between groups (18 611 ± 6825 and 16 830 ± 4530 in the TRE and HE groups, respectively) (Fig. 4). There were no differences in change in phosphorylated AMPK or phosphorylated S6K in PBMCs between groups (Supplementary Table 5).

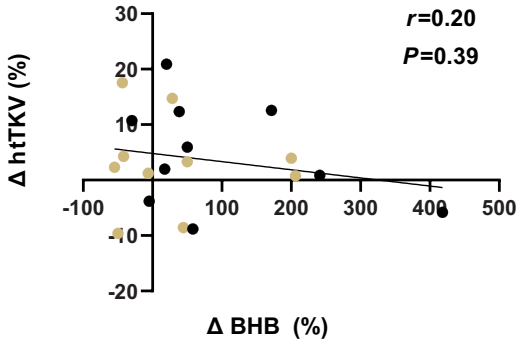


Figure 3: Change in height-adjusted total kidney volume (htTKV) and its association with β-hydroxybutyrate (BHB). Association of percentage change in β-hydroxybutyrate at 12 months with percentage change in htTKV. Interventions were TRE (gold) and HE advice without TRE (control; black).

Dietary intake and Healthy Eating Index

Self-reported carbohydrate intake was greater in the HE group at baseline than in the TRE group ($P = .01$), and fiber intake was also higher in the HE group than in the TRE group at baseline ($P = .01$). Change in dietary intake did not differ between groups. There were also no differences at baseline or 12-months for HEI between groups (Table 6).

DISCUSSION

This is the first study to evaluate the feasibility of delivering a 12-month behavioral intervention utilizing TRE or HE in individuals with ADPKD. In previous (non-ADPKD) studies, the TRE eating window has ranged from 8 to 12 hours, with several studies assigning a reduction in calories [19, 32–36]. Similar to our study, several other studies have allowed participants to eat *ad libitum* [11, 12, 37]. Overall, we found no differences in class attendance; however, only 60% of the individuals were able to adhere to the TRE window at month 12, below our *a priori* target of ≥75%.

Weight loss was similarly modest in the TRE and HE group at 3 months (−4.1 ± 4% and −2.8 ± 3%, respectively) and 12 months (−2.4 ± 6% and −3.6 ± 5%). Previous studies of TRE without caloric restriction have resulted in modest weight loss (1%–4%), comparable to the current results in individuals with ADPKD [11, 12, 38]. Concurrent recommendations of caloric restriction with TRE may result in greater weight loss (>5%) [33, 34, 19]. In this trial, we provided healthy eating guidelines without a calorie assignment in order to have the intervention group focus solely on the eating window and more clearly focus on the role of extended overnight fasting. Additionally, previous reports indicated participants had difficulty focusing on both caloric restriction and an eating window [19]. We included (a minority) of individuals with a normal baseline BMI, which could have also attenuated average weight loss.

The impact of TRE on HEI is variable, with reports of both improved diet quality and no change in HEI with TRE [39, 40]. Neither TRE nor HE improved HEI in the current study; however, it is important to note that there are inherent limitations to self-reported dietary data [41, 42], and poor response rates may have further limited our ability to detect a difference. Individuals were given assignments throughout the intervention to learn to track

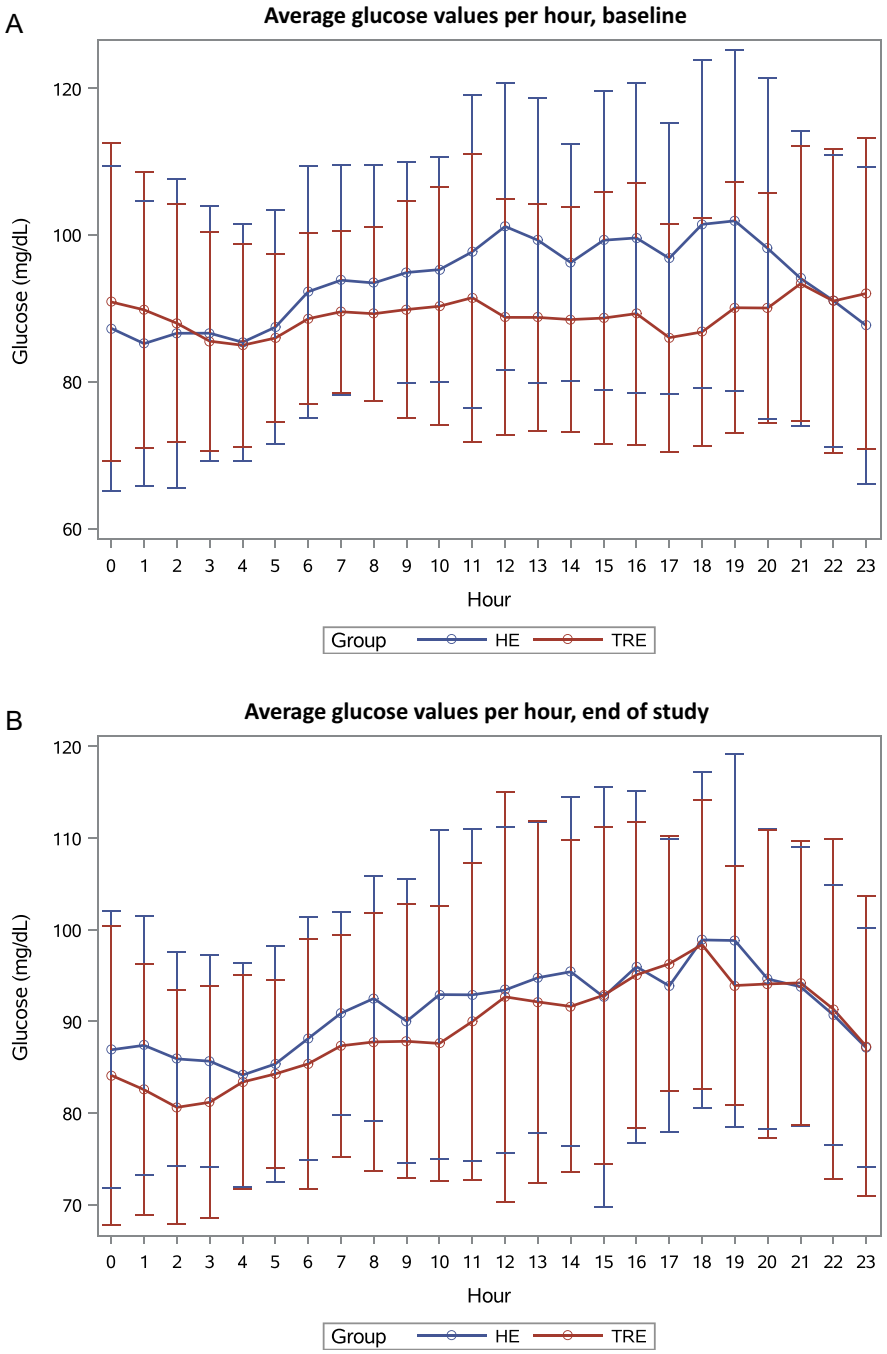


Figure 4: Continuous glucose monitor data in the TRE (red) and HE without TRE (control; blue) groups. (A) Average 7-day blood glucose per hour for the TRE ($n = 11$) and HE without TRE ($n = 8$) groups at baseline, presented as mean and standard deviation. (B) Average 7-day blood glucose per hour for the TRE ($n = 7$) and HE without TRE ($n = 7$) groups at 12 months, presented as mean and standard deviation.

dietary intake, which may have resulted in more accurate reporting in the later months. Unlike other studies, we did not provide guidelines for physical activity [19], and self-reported activity did not differ between groups at baseline or 12 months.

TRE improves mTOR and AMPK pathway function [14] as well as insulin sensitivity in non-ADPKD murine models [13, 15, 16], and reduces cystic disease progression in the Han:SPRD rat model of PKD [9]. Neither pS6K/S6K (mTOR activity) nor pAMPK/AMPK protein expression in PBMCs was altered with TRE or HE in the current study. As an exploratory outcome to facilitate power calculations for a subsequent clinical trial, we measured htTKV via MRI and observed no differences in annual percentage change between groups. However, consistent with our previous findings, changes in weight and changes in visceral adipose volume were positively correlated with changes in htTKV [21], despite the modest overall weight loss in the current study. These results suggest weight loss may exert a greater influence on ADPKD progression than fasting regimens [21].

Table 6: ASA24 dietary data.

	Total ($n = 23$)			TRE ($n = 10$)			HE ($n = 13$)			P-value comparison of change between groups
	Baseline[a]	Month 3[b]	Month 12[c]	Baseline[d]	Month 3[e]	Month 12[f]	Baseline	Month 3[g]	Month 12[h]	
Total energy (kcal)	1936 ± 615	1945 ± 693	1794 ± 536	1667 ± 612	1985 ± 696	1772 ± 711	2102 ± 578	1923 ± 723	1800 ± 547	.45
Carbohydrate intake (g)	218 ± 83	213 ± 85	183 ± 59	162 ± 68	219 ± 95	193 ± 98	253 ± 73	209 ± 84	180 ± 54	.19
Carbohydrate intake (%)	45 ± 10	44 ± 10	41 ± 7	39 ± 8	44 ± 9	43 ± 5	49 ± 9*	45 ± 10	41 ± 8	.19
Protein intake (g)	82 ± 32	77 ± 38	73 ± 24	82 ± 38	76 ± 46	80 ± 5	81 ± 27	78 ± 34	71 ± 28	.35
Protein intake (%)	17 ± 5	16 ± 4	17 ± 5	20 ± 4	15 ± 6	19 ± 7	16 ± 5	16 ± 3	16 ± 5	.35
Fat intake (g)	80 ± 33	92 ± 35	87 ± 31	71 ± 24	94 ± 29	77 ± 35	85 ± 38	90 ± 40	90 ± 32	.32
Fat intake (%)	37 ± 9	42 ± 7	43 ± 7	39 ± 9	43 ± 4	39 ± 2	35 ± 8	41 ± 9	45 ± 8	.32
Cholesterol (mg)	293 ± 282	262 ± 207	333 ± 248	360 ± 250	246 ± 231	495 ± 176	252 ± 302	271 ± 204	286 ± 256	.21
Sodium (mg)	3282 ± 1099	3211 ± 1731	2942 ± 560	2952 ± 1394	3252 ± 1699	2766 ± 120	3491 ± 869	3189 ± 1831	2992 ± 635	.36
Phosphorus (mg)	1327 ± 408	1368 ± 532	1327 ± 288	1279 ± 457	1382 ± 643	1110 ± 174	1357 ± 391	1368 ± 532	1390 ± 291	.23
Calcium (mg)	885 ± 449	941 ± 303	1159 ± 315	859 ± 319	956 ± 317	1120 ± 419	901 ± 526	934 ± 311	1170 ± 320	.18
Total fiber (g)	20 ± 10	26 ± 19	19 ± 10	12 ± 7	26 ± 14	13 ± 5	24 ± 10*	26 ± 22	21 ± 11	.43
Water (ounces)	117 ± 52	129 ± 55	130 ± 44	103 ± 39	139 ± 43	146 ± 46	125 ± 58	123 ± 61	126 ± 46	.37
Healthy Eating Index	56 ± 12	56 ± 13	59 ± 14	56 ± 13	54 ± 13	56 ± 3	55 ± 12	57 ± 13	60 ± 16	.38

Data are presented as mean ± standard deviation, *$P < .05$.

Independent t-tests were used to calculate P-values to determine differences between groups at all time points.

Welch two-sample t-tests were used to calculate P-values to compare the change at 12 months between groups (presented in the last column of the table).

$n = 21^{a}$, $n = 17^{b}$, $n = 9^{c}$, $n = 10^{d}$, $n = 6^{e}$, $n = 2^{f}$, $n = 11^{g}$, $n = 7^{h}$ participants that completed the 24-hour recall.

The HE group had a greater reduction in total cholesterol when compared with the TRE group over the 12-month period ($P = .04$). While triglycerides are sometimes reduced with TRE [43, 44], others have observed no differences in triglycerides, HDL, or LDL cholesterol, consistent with our results [11, 12, 38]. Consistent with other studies, HbA1c also did not change with TRE [11, 12, 19, 38]. Although improved insulin sensitivity measured via oral glucose tolerance test and HOMA-IR has been associated with TRE, we did not observe a difference in HOMA-IR [45, 46].

Our study has several limitations. First, we did not receive complete logs of dietary intake or food photos from many of our participants, limiting our sample size. Participants reported that taking photos of all food items and logging was time-consuming and burdensome. However, given that this was a feasibility study, this feedback is also critical in enhancing study design in the future and supports using alternative methods to assess adherence. The limited separation in the eating window between groups attenuated our ability to detect differences in secondary and exploratory outcomes. We aimed to examine the influence of TRE independently of caloric or macronutrient restriction. However, caloric or carbohydrate restriction may have a greater influence on ketosis, and this is a separate question that should be investigated further. Another limitation is that we did not objectively measure physical activity due to the scope of this pilot trial. As our primary goal was to assess the feasibility of TRE rather than efficacy, we opted for more heterogeneous and generalizable inclusion and exclusion criteria as opposed to limiting the study to those with more severe diagnoses of ADPKD. Lastly, similar to other ADPKD and dietary studies, our study population was predominantly non-Hispanic white and female, limiting the overall generalizability of the results.

In conclusion, the 8-hour eating window was difficult to adhere to in the TRE group and our target of ≥75% success was not achieved. Both the TRE and HE groups lost modest weight with the 12-month intervention. While annual change in htTKV did not differ across groups, it was correlated with change in weight and visceral adiposity, suggesting that these mechanisms may be more important drivers of kidney growth rather than the timing of eating. Future larger-scale trials powered for efficacy are necessary to further evaluate this hypothesis.

SUPPLEMENTARY DATA

Supplementary data are available at *Clinical Kidney Journal* online.

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DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

CONFLICT OF INTEREST STATEMENT

KL Nowak has been a consultant for Otsuka.

TRIAL REGISTRATION

ClinicalTrials.gov NCT04534985.

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