Supplemental Material

Curcumin Therapy to Treat Vascular Dysfunction in Children and Young Adults with ADPKD: A Randomized Controlled Trial

Kristen L. Nowak, Heather Farmer-Bailey, Wei Wang, Zhiying You, Cortney Steele, Melissa A Cadnapaphornchai, Jelena Klawitter, Nayana Patel, Diana George, Anna Jovanovich, Danielle E. Soranno, Berenice Gitomer, and Michel Chonchol

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Detailed Materials and Methods

Study Participants.

The study design and baseline participant characteristics of this clinical trial were recently reported (1). Eligible participants were recruited nationally and were enrolled at the University of Colorado Anschutz Medical Campus between November 2015 and December 2019. Enrollment in the trial concluded according to enrollment determined by power calculations (described below). Detailed eligibility criteria have been previously described (1). Briefly, participants eligible for inclusion were children and young adults 6-25 years of age with a diagnosis of autosomal dominant polycystic kidney disease (ADPKD) based on the presence of bilateral renal cysts in the setting of a family history of ADPKD or clinical diagnosis (2). Six was selected as the lower age limit due to the challenges for younger children to remain still for vascular testing and magnetic resonance imaging. Baseline estimated glomerular filtration rate (eGFR) was required to be >80 mL/min/1.73 m^2 (using CKiD [Chronic Kidney Disease in Children] Schwartz bedside equation for ages 6-17 (3) and the CKD-EPI [Chronic Kidney Disease Epidemiology Collaboration] equation for ages 18-25 (4)). Participants were excluded if they were currently using a curcumin supplement, had a history of smoking within 12 months, suffered from alcohol dependence or abuse, were hospitalized in the past three months, had active infection or antibiotic therapy, were pregnant, lactating, or unwilling to use adequate birth control, had a body-mass index ≥ 95^{th} percentile in ages 6-17 or >40 kg/m^2 in ages 18-25, or had contraindications to magnetic resonance imaging (MRI). Study participants who were using antioxidants and/or omega-3 fatty acids, discontinued use for the duration of the study beginning at least 4 weeks prior to study participation. Participants who used cannabis refrained from usage at least 2 weeks prior to baseline and end-of-study vascular testing. Demographic variables, including racial and ethnic categories, were collected by self-report, as required by the funding agency.

A minimum of three blood pressures were obtained in the seated position with an appropriately sized cuff using an automated machine (Omron Hem-907XL, Hoffman Estates, IL) following quiet rest. Hypertension was classified based on 1) current treatment for diagnosed hypertension; 2) average blood pressure ≥95th percentile for age, sex, and height in children <18 years of age, based on 2018 pediatric hypertension guidelines (5); or 3) average blood pressure ≥130/80 mmHg in young adults, based on 2107 American College of Cardiology/American Heart Association guidelines (6).

Study Design.

The trial was a 12 month, randomized, placebo-controlled (1:1 allocation), parallel group, double-blind study with the polyphenol curcumin (25 mg/kg body weight/day), delivered in powder form mixed with food (to improve adherence as compared to pills, particularly among young children). Randomization occurred using a computer-generated blocked randomization sequence secured by a statistician, with stratification by age group (6-13 or 14-25 years). The co-primary outcomes were change in brachial artery flow-mediated dilation (FMD_{BA}) and aortic pulse-wave velocity (aPWV) at 12 months as indices of vascular function. Secondary outcomes were changes in oxidative stress-associated suppression of endothelium-dependent dilation (change in FMD_{BA} with acute infusion of ascorbic acid) and changes in circulating/urinary markers of oxidative stress and inflammation. Change in height-adjusted total kidney volume (htTKV) by MRI at 12 months was an exploratory outcome. Additional exploratory outcomes were other kidney MRI parameters (described below).

After initial screening, participants meeting inclusion and exclusion criteria underwent baseline vascular measurements in the supine position following standard recommendations, as described below, as well as assessment of secondary and exploratory endpoints. All investigators, coordinators, analysts, and participants were blinded to group assignment; only the nursing staff (who monitored drug dispensing) not affiliated with the study and the

statistician were aware of the randomization. Measurements were repeated after 12 months of the intervention.

Procedures.

The details of the procedures in this trial were recently published (1) and are described in brief.

Vascular Measurements. All vascular measurements were made as a single measurement per study visit following standard recommendations including an overnight fast (7). Additionally, participants refrained from caffeine (12-hr), exercise (24-hr), alcohol (24-hr), and non-prescription medications (48-hr) before vascular testing. Testing sessions were performed at the same time of day (between 7—10am) in a climate-controlled room, following at least 10 minutes of rest in the supine position. A pediatric cuff was placed distal to brachial artery around the forearm just below the antecubital fossa. The cuff was rapidly inflated (Hokanson, Bellevue, WA) for 5-minutes to 250 mmHg and images were recorded for 2 minutes following rapid cuff release. FMD_{BA} was determined using duplex ultrasonography (Xario 200, Toshiba, Tustin, CA) with ECG-gated end-diastolic ultrasound images analyzed by a single blinded analyst using a commercially available software package (Vascular Analysis Tools 5.10.10, Medical Imaging Applications, Coralville, IA) (8-10). The baseline diameter was determined using a 30-second baseline image and the peak diameter was determined at using the largest post-cuff diameter using 6 consecutive frames. The coefficient of variation for within subject baseline and peak brachial diameter during assessment of FMD_{BA} are 4.8% and 5.2%, respectively (11). Shear rate was calculated using the occlusion diameter measured from 4 minutes 30 seconds to 4 minutes 45 seconds, the peak velocity measured in the 15 seconds following cuff release (Doppler Flow Analyzer 5.10.10, Medical Imaging Applications, Coalville, IA), and the equation (4 x mean blood velocity) / diameter. The angle of insonation was 60 degrees. Endothelium-independent dilation (brachial artery dilation to 0.4 mg of sublingual

nitroglycerin) was assessed in participants ≥18 years of age without contraindications as a standard index of smooth muscle cell sensitivity to exogenous nitric oxide as the 6 consecutive peak frames recorded from minutes 3-8 post nitroglycerin administration (Vascular Analysis Tools) (9, 10).

Pulse-wave velocity was measured using a transcutaneous custom tonometer (Noninvasive Hemodynamics Workstation [NIHem], Cardiovascular Engineering Inc., Norwood, MA) positioned at the carotid, brachial, radial, and femoral arteries to non-invasively assess aPWV (measured as carotid-femoral PWV), as well as carotid-radial PWV (an index of peripheral stiffness) (9, 10). Supine blood pressure was also measured using the auscultatory method. The distances to each side from the suprasternal notch were measured using a tape measure (carotid, brachial, radial) or a custom raised ruler (femoral; Cardiovascular Engineering Inc.) The distance from the suprasternal notch to the carotid was subtracted from the distance between the two recording sites, and aPWV was calculated as the distance divided by time between the feet of the waveforms, recorded at each site, as described previously (12). The intra-operator coefficient of variation for within subject aPWV for our laboratory is 7.2%. Additionally, as secondary indices related to arterial stiffness, carotid artery compliance, carotid artery β-stiffness index, carotid intimal medial thickness, carotid augmentation index, and carotid systolic BP were also measured using the Xario 200 and NIHem (8, 9).

The influence of oxidative stress on FMD_{BA} was assessed by infusing a supraphysiological dose of ascorbic acid that produces plasma concentrations known to inhibit superoxide production *in vitro*(13) and measuring FMD_{BA} during the “drip infusion” when peak plasma concentrations occur (as compared to isovolumic saline), in a sub-group of participants ≥18 years of age (n=12/group baseline; n=10/group 12 months), as described previously (9, 10). We have previously shown that this protocol effectively raises plasma ascorbic acid concentrations in a population with ADPKD (10).

Systemic Markers of Oxidative Stress and Inflammation. Interleukin-6 (IL-6; detection limit: 0.27-1.3pg/ml, intra-run CV: 2.9-4.5%, inter-run CV: 5.9-12.9%), tumor necrosis factor-α (TNF-α; detection limit: 0.36-0.76pg/ml, intra-run CV: 2.9-3.6%, inter-run CV: 5.2-13.5%) and interferon-γ (detection limit: 1.4-2.7pg/ml, intra-run CV: 3.3-5.8%, inter-run CV: 11.4-14.8%) (U-PLEX ProInflam Combo (human) [catalog #K15025K], Meso Scale Discovery; sample dilution 1:2) and C-reactive protein (CRP) levels (detection limit: 0.69-19.8pg/ml, intra-run CV: 2.2-4.1%, inter-run CV: 6.7-9.9%; catalog #K151 STD, Meso Scale Discovery; sample dilution 1:1000) were measured by ELISA. Targeted liquid chromatography-tandem mass spectrometry (LC-MS/MS) analysis of a marker of oxidative stress (8-iso-prostaglandin F2α ([8-isoprostane]) was also performed on spot urine samples using a validated assay and normalized by urine creatinine, as described in detail previously (9, 14).

Kidney MRI. A Siemens Skyra 3.0 T system (Siemens Healthcare USA, Tarrytown, NY) was used to obtain MRIs for volumetric measurements of the kidneys, in a similar manner described for the CRISP (The Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease) study (15). No contrast agents were utilized. TKV, adjusted for height to account for normal growth in children (htTKV) (16) was measured by a single blinded analyst by stereology using Analyze software (Analyze 11.0, Mayo Foundation, Rochester, MN). The analyst was not a radiologist; however, a radiologist was a study co-investigator and consulted during analysis as needed. The inter- and inter-operator coefficient of variation for TKV in our laboratory are 5.3% and 5.7%, respectively. In addition, total cyst volume, fractional cyst volume (percent of TKV measured as cystic), and kidneyl parenchyma (TKV – cyst volume) were measured. Disease severity was categorized according to the Mayo Imaging Classification system for those participants ≥15 years of age (17).

Adherence, Safety, and Study Monitoring.

Participants were monitored with regular phone inquiries (months 1, 3, 6, and 9) regarding medication supply, safety/adverse events, and adherence questions. The adherence and safety questionnaire was designed explicitly for this study based on the existing literature on curcumin. A comprehensive metabolic panel, including serum creatinine, aspartate aminotransferase [AST], alanine aminotransferase [ALT], was performed at months 1, 6, and 12. While there is no known effect on liver function tests, this monitoring was conservatively performed based on possible side effects of tolvaptan in patients with ADPKD. A contract lab (Quest) was used at month 1 and 6. For comparison of eGFR using the same equation across all ages (children and adults), the new full age spectrum (FAS) eGFR equation was used (this equation was not yet developed at the time the study began, thus not used for inclusion purposes) (18). Home pregnancy tests were required monthly for all females of possible childbearing potential (≥Tanner Stage 2) and all participants recorded monthly home blood pressure readings using a standardized machine provided by the study, which were reported during phone safety checks. Based on the questionnaire responses provided by the participant to the researcher via phone, suggestions were made to help increase compliance as needed (e.g., mixing the powder in alternative foods to improve taste). Participants were not discontinued from the study due to lack of compliance and there was no pre-specified cut-off for study compliance. Percent compliance was calculated at the final visit based on the total powder consumed relative to expected (bottles were returned and remaining powder was weighed).

The study was monitored with annual meetings (a total of 6) by an independent Data and Safety Monitoring Board consisting of a nephrologist, pediatrician and statistician. The protocol allowed the DSMB to recommend stopping the trial if the data showed a significantly increased risk of adverse events with treatment or it became clear that a successful completion

of the study was not feasible (due to excess patient dropout, missing data, lack of recruitment, etc.) No changes to the protocol were recommended resulting from any of the DSMB meetings.

Study Approval.

All procedures were approved by the Institutional Review Board of the University of Colorado Anschutz Medical Campus and adhere to the *Declaration of Helsinki*. The nature, benefits and risks of the study were explained to the volunteers and their written informed consent /assent was obtained prior to participation. The trial was registered at ClinicalTrials.gov (NCT02494141).

Data Sharing Information.

Data obtained through this study and presented in this manuscript may be provided to qualified researchers with academic interest in ADPKD. Data shared will be coded, with no personal health information included. The data dictionary and study protocol (with statistical analysis plan) will also be available. Approval of the request and execution of all applicable agreements (i.e. data use agreement) are prerequisites to the sharing of data with the requesting party. Data requests can be submitted starting 9 months after article publication and the data will be made accessible for up to 24 months. Extensions will be considered on a case-by-case basis. Data will be provided following review and approval of a research proposal and Statistical Analysis Plan, as well as execution of a Data Sharing Agreement.

Statistics*.*

All statistical analyses were performed by using SAS version 9.4 (SAS Institute, Cary, NC). If appropriate, data transformation was performed before further analysis. A linear regression model was fit to assess the curcumin effect vs. placebo (independent variable) on the outcomes by regressing each outcome variable at 12 months (dependent variable) on study group with adjustment for baseline values. For outcome variables with more than two time

points a linear mixed effects model with random intercept and random slope was used to assess the effect of curcumin. We examined the interaction of sex and group on the primary outcome variables as well as htTKV. The differences in FMD within each group during saline infusion versus vitamin C infusion on the same day were analyzed by a paired t-test. Study drug compliance was compared between groups using an independent samples t-test.

All participants were included in the final analysis using multiple imputation with the Expectation-Maximization method(19) based on a pre-specified intent to treat analysis. The number of imputations was 10 and the variables included in the imputation included age, sex, race/ethnicity, baseline angiotensin converting enzyme inhibitor/angiotensin receptor blocker use, baseline statin use, baseline hypertension, baseline mayo classification, and data at baseline and month 12 for: FMD/aPWV, heart rate, baseline brachial dimeter, shear rate, β-stiffness index, and FAS-eGFR. As a secondary analysis, a complete case analysis was performed, including all participants with end-of-study data regardless of level of study compliance. A complete case analysis was also used for all secondary and other outcomes. For the co-primary outcomes (i.e., FMD_{BA} and aPWV), a two-sided significance level was set at 0.025 for each outcome. For other outcomes, a two-sided significance level was designated at 0.05.

A sample size of 27 subjects per group was calculated based on 90% power and a two-side type I error rate of 0.025, adjusted for two primary endpoints, in order to detect a mean increase in FMD_{BA} of 1.5%, given a standard deviation of 2.0.(20) Similarly, a sample size of 27/group was determined to have 90% power to detect a mean decrease of aPWV of 100 cm/sec given a standard deviation of 125, which is a clinically and statistically significant reduction demonstrated in response to an alternative lifestyle intervention (21), with $\alpha = 0.025$, adjusted for two primary endpoints. To account for a potential dropout of 20%, 34 subjects/group were enrolled. A sub-group sample size of 10 young adults (of 18-25 years of age) per group was selected to provide 89% power to detect a 50% reduction in ΔFMD_{BA} with

ascorbic acid (given ΔFMD = +3.0±1.0% with ascorbic acid in the placebo group (20)), with a two-sided $\alpha = 0.05$. Change in htTKV was considered exploratory, thus power was not calculated. We compared the 1.5 percent change in FMD_{BA} used in our power calculations to the 95% confidence interval of the observed change in the trial.(22) A similar comparison was made for the other primary endpoint, aPWV.

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Supplemental Table 1. Changes in Vital Signs and Clinical Labs

Variable	Curcumin (n=28)				Placebo (n=29)				
	Baseline	**1 month**	**6 months**	**12 months**	**Baseline**	**1 month**	**6 months**	**12 months**	***P*-Value**
SBP, mmHg	116±13	N/A	N/A	116±11	116±14	N/A	N/A	117±12	0.62
DBP, mmHg	71±9	N/A	N/A	72±7	73±9	N/A	N/A	73±11	0.50
Resting HR, bpm	75±12	N/A	N/A	77±14	73±12	N/A	N/A	76±12	0.70
FAS eGFR, ml/min/1.73m^2	109±16	101±16**	101±14**	109±18	115±18	106±15**	104±15**	111±17	0.67
Sodium, mmol/L	138±1	140±2	139±2	139±2	139±2	139±2	139±2	139±2	0.62
Potassium, mmol/L	4.0±0.4	4.1±0.3	4.2±0.3**	3.9±0.3	3.9±0.3	4.1±0.3**	4.1±0.2**	3.8±0.2	0.74
Chloride, mmol/L	105±2	105±2	104±2	106±2	105±2	104±2	104±2	105±2	1.00
CO_2, mmol/L	25±2	26±3*	25±3	25±2	25±2	26±2	26±2	25±3	0.94
Glucose, mg/dL	89±7	91±9	89±7	90±7	87±6	87±13	86±9	89±7	0.80
Blood Urea Nitrogen, mg/dL	13±4	13±4	15±4	14±3	14±4	14±3	14±5	15±4	0.76
Calcium, mg/DL	9.5±0.4	9.5±0.4	9.5±0.5	9.5±0.4	9.5±0.4	9.5±0.4	9.5±0.4	9.5±0.4	0.95
Total protein, g/dL	7.1±0.4	7.0±0.4	7.1±0.6	7.0±0.4	7.0±0.4	6.9±0.4	7.0±0.5	7.0±0.5	0.76
Albumin, g/dL	4.4±0.3	4.5±0.3	4.4±0.4	4.4±0.3	4.3±0.3	4.4±0.3	4.3±0.5	4.4±0.4	0.83

Total bilirubin, mg/dL	0.5±0.3	0.5±0.3	0.6±0.4	0.6±0.3	0.7±0.6	0.7±0.5	0.8±0.5	0.7±0.5	0.28
AST, U/L	20±5	19±4	20±5	21±9	20±5	18±3	23±16	23±21	0.76
ALT, U/L	15±6.7	15±7	17±8	16±8	15±7	14±5	19±13	24±49	0.48
ALP, U/L	93±70	100±71	98±71	89±67	101±89	104±91	98±82	89±72*	0.55

Data are mean±S.D. or median (interquartile range). N=27 for curcumin for labs at 0, 1, and 6 months and n=28 for placebo group at 6 months. P-value in last column is group*time interaction based on a repeated measures analysis with a mixed model or the group effect in a linear regression model for the outcome variable at 12 months with adjustment for baseline values. * p≤0.05; ** p<0.01; Tukey-Kramer post-hoc test (adjusted for multiple comparisons) vs. baseline in the same group. SBP, systolic blood pressure; DBP, diastolic blood pressure/ FAS eGFR, estimated glomerular filtration rate by the Full Age Spectrum equation; CO_2, carbon dioxide; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase

Supplemental Table 2. Additional Kidney Parameters (Other Outcome Measures)

Kidney Parameters	**Curcumin** (n=28)		**Placebo** (n=29)	
	Baseline	**12 months**	**Baseline**	**12 months**
Total kidney volume, ml	626 (472, 862)	662 (463, 999)	518 (357, 916)	571 (392, 965)
Total cyst volume, ml	249 (135, 447)	281 (157, 484)	196 (98, 438)	202 (131, 498)
Fractional cyst volume, %	39±15	42±28	37±24	41±17
Renal parenchyma, ml	379±132	392±134	413±231	404±199

Data are mean±S.D or median (IQR).