Supplementary Table S1: Distribution of the Number of Samples for Each Participant

Number of samples	Metformin participants	Placebo participants	Total participants	Total samples
10	29	28	57	570
9	8	7	15	135
8	2	4	6	48
7	1	3	4	28
6	1	0	1	6
5	1	2	3	15
4	1	1	2	8
3	1	2	3	9
2	1	0	1	2
1	4	1	5	5
Total	**49**	**48**	**97**	**826**

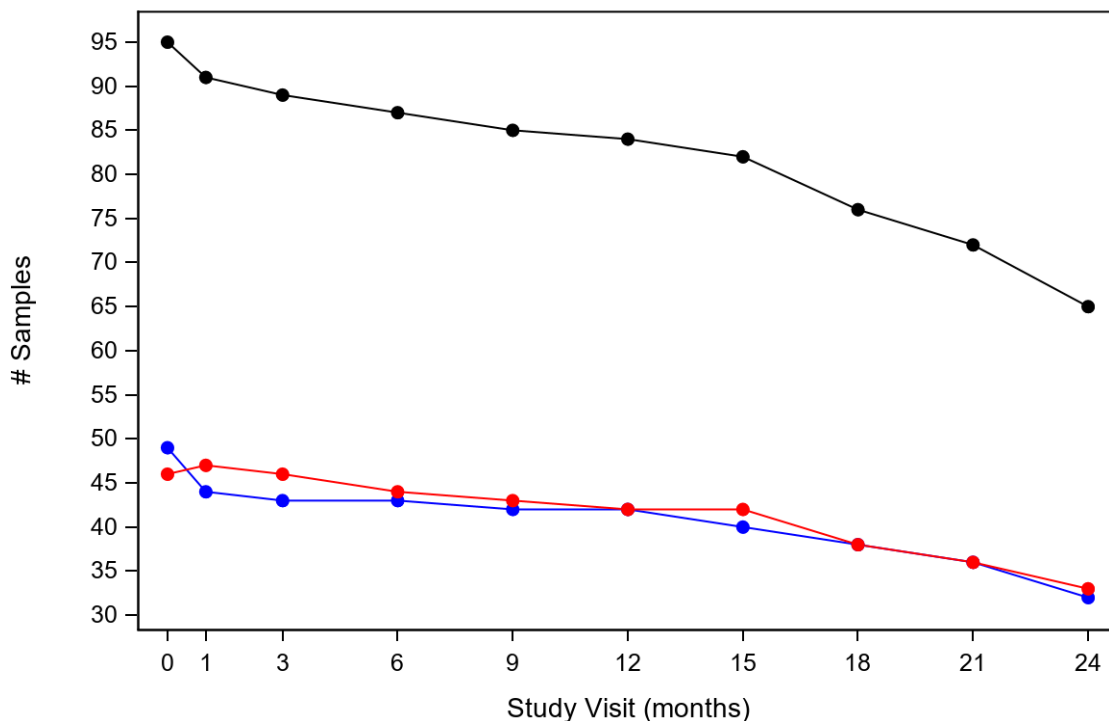## Supplementary Table S2: Baseline Characteristics by Randomized Arm

Characteristic *	Metformin (n=49)	Placebo (n=48)	Total (N=97)
Age (years) (at Screening)	41.8 (10.4)	42.1 (10.1)	41.9 (10.2)
Sex			
Male	11 (22.4%)	16 (33.3%)	27 (27.8%)
Female	38 (77.6%)	32 (66.7%)	70 (72.2%)
Race			
American Indian or Alaska Native	1 (2.0%)	0 (0.0%)	1 (1.0%)
Asian	2 (4.1%)	1 (2.1%)	3 (3.1%)
Black or African American	0 (0.0%)	1 (2.1%)	1 (1.0%)
White or Caucasian	46 (93.9%)	46 (95.8%)	92 (94.8%)
Ethnicity			
Hispanic or Latino	2 (4.1%)	6 (12.5%)	8 (8.2%)
Not Hispanic or Latino	47 (95.9%)	42 (87.5%)	89 (91.8%)
PKD genotype			
PKD1	37 (78.7%)	28 (60.9%)	65 (69.9%)
PKD2	7 (14.9%)	10 (21.7%)	17 (18.3%)
Other	1 (2.1%)	4 (8.7%)	5 (5.4%)
No mutation detected	2 (4.3%)	4 (8.7%)	6 (6.5%)
GFR calculated per CKD-EPI (ml/min/1.73 m²)	86.1 (20.6)	85.9 (19.0)	86.0 (19.7)
Vitamin B12 (pg/mL)	580.7 (350.8)	495.3 (202.3)	538.4 (288.8)
Glucose (mg/dL)	88.6 (8.4)	90.9 (9.1)	89.7 (8.8)
HbA1c (%)	5.2 (0.3)	5.2 (0.3)	5.2 (0.3)
Serum Creatinine (mg/dL)	0.9 (0.2)	0.9 (0.2)	0.9 (0.2)
Systolic BP (mmHg)	122.2 (13.1)	124.1 (13.0)	123.1 (13.0)
Diastolic BP (mmHg)	76.8 (8.9)	74.6 (8.5)	75.7 (8.7)
Weight (kg)	78.5 (16.9)	78.2 (17.4)	78.4 (17.0)
BMI	27.0 (5.9)	26.6 (4.5)	26.8 (5.2)
Mayo Imaging Class			
Class 2	2 (4.2%)	5 (10.4%)	7 (7.3%)
Class 1A	9 (18.8%)	6 (12.5%)	15 (15.6%)
Class 1B	13 (27.1%)	15 (31.3%)	28 (29.2%)
Class 1C	14 (29.2%)	12 (25.0%)	26 (27.1%)
Class 1D	6 (12.5%)	6 (12.5%)	12 (12.5%)
Class 1E	4 (8.3%)	4 (8.3%)	8 (8.3%)
Height-adjusted total kidney volume (mL/m)	625.8 (386.5)	750.9 (547.8)	688.4 (475.7)
Height-adjusted total hemorrhagic kidney cyst volume (mL/m)	24.5 (48.0)	22.1 (46.1)	23.3 (46.8)
Height-adjusted total simple kidney cyst volume (mL/m)	332.4 (347.9)	456.0 (493.3)	394.2 (429.1)
Height-adjusted total kidney cyst volume (mL/m)	356.9 (358.7)	478.2 (520.4)	417.5 (448.7)
Height-adjusted liver volume (mL/m)	1,224.1 (490.7)	1,019.0 (212.6)	1,121.6 (390.0)
Height-adjusted liver cyst volume (mL/m)	238.2 (452.0)	81.0 (166.7)	159.6 (348.0)
Site			
Tufts	24 (49.0%)	23 (47.9%)	47 (48.5%)
UMD	25 (51.0%)	25 (52.1%)	50 (51.5%)

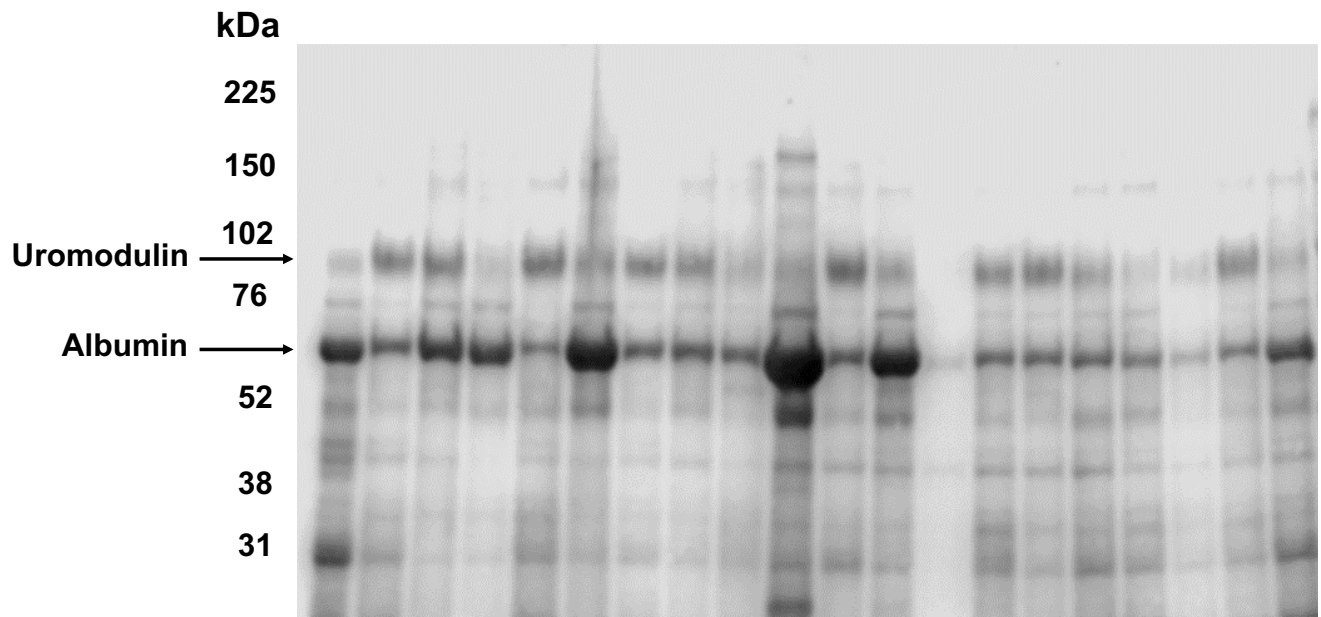| Characteristic [*]	Metformin (n=49)	Placebo (n=48)	Total (N=97)
Age at time of PKD diagnosis (years)	28.6 (12.4)	31.3 (11.2)	29.9 (11.9)
Diagnosis was due to			
Screening (family history)	11 (22.4%)	16 (33.3%)	27 (27.8%)
Incidental Imaging	12 (24.5%)	9 (18.8%)	21 (21.6%)
Pain	13 (26.5%)	10 (20.8%)	23 (23.7%)
Hypertension	3 (6.1%)	6 (12.5%)	9 (9.3%)
Routine Physical	5 (10.2%)	1 (2.1%)	6 (6.2%)
Hematuria	3 (6.1%)	2 (4.2%)	5 (5.2%)
UTI	2 (4.1%)	4 (8.3%)	6 (6.2%)
Method of diagnostic imaging			
Ultrasound	36 (73.5%)	33 (68.8%)	69 (71.1%)
CT	6 (12.2%)	8 (16.7%)	14 (14.4%)
MRI	4 (8.2%)	6 (12.5%)	10 (10.3%)
Unknown	3 (6.1%)	1 (2.1%)	4 (4.1%)
Family history of ADPKD			
No	9 (18.4%)	11 (22.9%)	20 (20.6%)
Yes	38 (77.6%)	34 (70.8%)	72 (74.2%)
Unknown	2 (4.1%)	3 (6.3%)	5 (5.2%)
Urine Biomarkers			
Urine Creatinine (Ucrea; mg/dL)	56.083 (46.851)	65.700 (45.053)	60.739 (45.999)
Urine Osmolality (Uosm; mmol/kg)	387.306 (234.674)	409.891 (206.320)	398.242 (220.520)
Urine Lactate (µM)/Ucrea	0.298 (0.350)	0.311 (0.406)	0.305 (0.376)
Urine Lactate (µM)/Uosm	0.038 (0.037)	0.039 (0.036)	0.039 (0.036)
Urine Lactate/Pyruvate	1.959 (2.339)	1.228 (0.668)	1.605 (1.773)
Urine Succinate (µM)/Ucrea	1.129 (1.018)	1.048 (1.095)	1.090 (1.051)
Urine Succinate (µM)/Uosm	0.131 (0.104)	0.132 (0.096)	0.132 (0.099)
Urine Pyruvate (µM)/Ucrea	0.239 (0.218)	0.234 (0.186)	0.237 (0.202)
Urine Pyruvate (µM)/Uosm	0.027 (0.018)	0.030 (0.014)	0.029 (0.016)
Urine Total Protein (mg/dL)/Ucrea	0.199 (0.199)	0.145 (0.123)	0.173 (0.168)
Urine Total Protein (mg/dL)/Uosm	0.028 (0.036)	0.022 (0.021)	0.025 (0.030)
Urine PKM2 (ng/mL)/Ucrea	0.153 (0.144)	0.144 (0.113)	0.149 (0.129)
Urine PKM2 (ng/mL)/Uosm	0.020 (0.022)	0.021 (0.014)	0.021 (0.018)
Urine LDHA (ng/mL)/Ucrea	0.063 (0.070)	0.050 (0.048)	0.057 (0.060)
Urine LDHA (ng/mL)/Uosm	0.008 (0.010)	0.008 (0.010)	0.008 (0.010)
Urine PDK1 (pg/mL)/Ucrea	5.532 (4.254)	4.019 (2.839)	4.799 (3.698)
Urine PDK1 (pg/mL)/Uosm	0.720 (0.710)	0.527 (0.295)	0.626 (0.555)

[*] *Continuous variables described as mean (SD) and categorical variables as n (%)*

Supplementary Figure S1 – Number of samples for each participant over time. Graph shows total number of samples collected and analyzed at each study visit (*black*), along with the number of samples for metformin-treated subjects (*blue*) and placebo group subjects (*red*) throughout the 24-month study period.

No. of participants by Arm										
Metformin	49	44	43	43	42	42	40	38	36	32
Placebo	46	47	46	44	43	42	42	38	36	33
Total	95	91	89	87	85	84	82	76	72	65

Supplementary Figure S2 – Representative image of urine protein staining from aliquots of 20 baseline participants' specimens subjected to SDS-PAGE and transfer to nitrocellulose membrane. Albumin (~67 kDa) and the Tamm-Horsfall glycoprotein (Uromodulin; ~100 kDa) are generally the two most abundant proteins expressed. However, overall and relative protein expression levels of these two major proteins are highly variable across the different study participants.

Supplementary Figure S3 – Scatter plot of the association between ln(urinary osmolality) and ln(urinary creatinine) for each sample. Samples from metformin-treated subjects are indicated by filled circles while samples from placebo group subjects are indicated by open diamonds. Linear least-squares regression fit of the data and equation is shown. The correlation of ln(UOsmolality) and ln(UCreatinine) is high (R^2 = 0.5902; P < 0.0001; N = 889).