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Baseline Characteristics and Patient-Reported Outcomes of ADPKD Patients in the Multicenter TAME-PKD Clinical Trial

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Abstract

Background Autosomal dominant polycystic kidney disease (ADPKD) has been associated with metabolic disturbances characterized by downregulation of AMP-activated protein kinase (AMPK), a critical sensor of the cellular energy status. Therapeutic activation of AMPK by metformin could inhibit cyst enlargement by inhibition of both the mammalian target of rapamycin pathway and fluid secretion *via* the CFTR chloride channel.

Methods We designed a phase-2, randomized, placebo-controlled, clinical trial to assess the safety, tolerability, and efficacy of metformin on total kidney volume in adults without diabetes (age 18–60 years) with ADPKD and eGFR of ≥50 ml/min per 1.73 m^2. There were no eligibility criteria relating to kidney volume. In addition to demographics and clinical/family history, baseline parameters included eGFR, total kidney and liver volumes measured by MRI, and patient-reported outcomes were ascertained by the Medical Outcomes Study Short Form-36, the Gastrointestinal Safety Rating Scale, and the HALT-PKD pain questionnaire.

Results We successfully randomized 97 participants recruited from two university-based clinical sites in Baltimore and Boston. The mean age of participants was 41.9 years, 72% were female, and 94% of participants were White. The majority of study participants had early stage disease, with a mean eGFR of 86.8±19.0 ml/min per 1.73 m^2. Approximately half of the study participants (48%) were classified as high risk for progression (Mayo imaging classes 1C, 1D, or 1E). There was no correlation between kidney and/or liver size and health-related quality of life (HRQoL) or gastrointestinal symptom severity.

Conclusions We report successful recruitment in this ongoing, novel, clinical trial of metformin in ADPKD, with a study sample comprising patients with early stage disease and nearly a half of participants considered at high estimated risk for progression. Participants reported a low gastrointestinal symptom burden at baseline, and HRQoL similar to that of the general population, with no differences in symptoms or HRQoL related to organomegaly.

Clinical Trial registry name and registration number Metformin as a Novel Therapy for Autosomal Dominant Polycystic Kidney Disease (TAME), NCT02656017

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Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common monogenic disorder resulting in kidney failure around the world (1). ADPKD is distinct from other cystic diseases because kidneys enlarge over time, resulting in hypertension, gross hematuria, and—ultimately—kidney failure (2). Observational studies have shown a correlation between the rate of growth of total kidney volume (TKV) and decline in GFR (3). ADPKD is also associated with numerous extrarenal manifestations, the most common being polycystic liver disease (4). Together, polycystic kidney and polycystic liver disease result in organomegaly, which substantially affects quality of life, with symptoms including increasing abdominal girth, pain, and gastroesophageal reflux (5).

To date, there is only one approved treatment for ADPKD, tolvaptan, which is a vasopressin 2 receptor antagonist that would be expected to target kidney cysts arising from the distal tubule and collecting duct.

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In clinical trials, tolvaptan was shown to slow cyst enlargement, primarily over the first year of treatment, and also to moderately slow decline in GFR by approximately 1 ml/min per 1.73 m^2 per year over a 3-year period (6,7). However, vasopressin 2 receptor antagonists have an obligate polyuric effect that make them difficult for some patients to tolerate (6). In addition, tolvaptan was associated with reversible liver injury in approximately 5% of clinical trial participants, with prescription use contingent on a stringent risk-evaluation and management-strategy program for liver function abnormalities (8). Given these limitations, there have been intense efforts to identify additional therapeutic targets.

Over the past several years, there has been an emerging link between metabolic dysregulation and ADPKD, including evidence implicating the Warburg effect (elevated levels of aerobic glycolysis with increased ATP production), mitochondrial abnormalities, and alterations in fatty acid metabolism (9–13). Numerous studies in mouse models demonstrated that targeting metabolic pathways has the potential of ameliorating cyst formation (9,14–19). One consistent finding is that metabolic disturbances in ADPKD are characterized by downregulation of the activity of AMP-activated protein kinase (AMPK), a critical sensor of the cellular energy status (9,16,17,19,20). The underlying mechanism(s) for suppression of AMPK activity in ADPKD are not fully resolved, but may relate to deficient functioning of polycystin proteins, which causes various metabolic perturbations, including dysregulated intracellular calcium homeostasis and increased cellular ATP in PKD-diseased kidney cells (9,21). Under normal circumstances, AMPK becomes activated under conditions of cellular energy depletion and other cellular stresses, which, in turn, leads to compensatory stimulation of energy-generating cellular pathways and inhibition of those that consume energy (21). Theoretically, therapeutic activation of AMPK in PKD could inhibit cell proliferation *via* inhibition of both the mammalian target of rapamycin pathway (22) and fluid secretion *via* the cystic fibrosis transmembrane conductance regulator chloride channel (21,23–25), both of which play important roles in cyst formation and progression.

Metformin has been used to treat type 2 diabetes for >50 years and has pleiotropic effects in cells, including serving as an AMPK activator (26,27). Briefly, metformin accumulates in mitochondria, where it is thought to inhibit Complex I of the respiratory chain, which suppresses ATP production, thereby increasing AMP/ATP and ADP/ATP ratios (28). This, in turn, stimulates AMPK activity in an attempt to restore the energy homeostasis. Other mechanisms of action relevant to ADPKD have also been proposed, including a decrease in cAMP levels by a direct inhibition of adenylyl cyclase and increasing fatty acid oxidation (26). Metformin's well-established safety profile and mechanism of action make this drug an attractive candidate for clinical testing. Preclinical studies have already demonstrated a salutary effect in two orthologous ADPKD mouse models (20).

However, there are several potential adverse effects of metformin treatment when applied to patients with ADPKD. Lactic acidosis is a rare, but potentially life-threatening, complication of metformin use, with greater frequency in those with lower GFR (29,30). Therefore, dose modification may be required in patients with ADPKD as GFR declines. Metformin is also associated with adverse gastrointestinal side effects including nausea, dyspepsia, and diarrhea (31). It is possible that these drug-related symptoms may be more common in patients with ADPKD, who often experience abdominal discomfort and dyspepsia due to organomegaly. The most appropriate and sensitive way to quantify these symptoms in patients with ADPKD who are treated with metformin is uncertain.

We have implemented a phase-2, multicenter, randomized, placebo-controlled trial to assess the safety, tolerability, and efficacy of metformin on TKV in individuals with ADPKD and eGFR ≥50 ml/min per 1.73 m^2. Here, we report experience with recruitment of participants and describe the characteristics of individuals enrolled in this clinical trial. We further examine patient-reported gastrointestinal symptoms and health-related quality of life (HRQoL) at baseline, and estimate their association with disease severity as reflected by total kidney and liver volumes.

Materials and Methods

Overview of Clinical Trial Design

The details of the TAME-PKD (Trial of Administration of MEtformin to tame PKD) trial design have been previously published (32). Briefly, the TAME-PKD trial is a 24-month, multicenter, parallel-group, phase-2, randomized, placebo-blinded, clinical trial of the tolerability and safety (primary outcomes), and efficacy (secondary outcome) of metformin in adults with ADPKD. The trial is funded by the US Department of Defense. Adults aged 18–60 years without diabetes but with ADPKD (determined by modified Pei–Ravine criteria) were recruited from two university nephrology practices based in Baltimore (University of Maryland Medical Center) and Boston (Tufts Medical Center) (33). The data coordinating and image analysis centers are at the University of Pittsburgh School of Medicine, and a metabolomics center is at the University of Southern California. All participants provided written informed consent, and the study protocol was approved by the institutional review boards of the participating institutions.

Patients were excluded from participation if they had diabetes (as defined by American Diabetes Association consensus criteria) (34); contraindications for magnetic resonance imaging (MRI); were taking medications known to interact with metformin (including nifedipine and furosemide); had an unclipped (>7 mm) or unstable cerebral aneurysm; active coronary disease; or any systemic illness, other than hypertension, likely to contribute to kidney disease. The initial eligibility criteria required an eGFR of ≥60 ml/min per 1.73 m^2; subsequent modifications were made in 2017 to permit enrollment of participants with an eGFR of ≥50 ml/min per 1.73 m^2, in accordance with revised Food and Drug Administration (FDA) guidelines on metformin dosing in patients with reduced GFR. There were no eligibility criteria relating to kidney volume. Recruitment began in June 2016 and was completed in December 2018.

Data Collection

Eligible participants who provided informed consent attended a prerandomization study visit with study staff. A structured medical and family history and symptom review was performed, and concomitant medications were recorded. Race was self-identified. BP was measured in a seated position, after at least 5 minutes of rest, with automated sphygmomanometers, using the calculated average of two measures. Serum creatinine was measured with an isotope dilution mass spectrometry–traceable assay, and GFR was estimated using the creatinine-based Chronic Kidney Disease Epidemiology Collaboration equation (35). Abdominal MRI was performed in coronal T1- and T2-weighted sequences, without the use of gadolinium. Images were transferred *via* a secured website to the image analysis center, where measurements of TKV and total liver volume (TLV) were performed using a regional growing and boundary delineation method on T2-weighted images. In addition, total kidney cyst and liver cyst volumes were estimated using the same measurement method. TKV and TLV were adjusted to measured standing height (height-adjusted TKV [htTKV] or height-adjusted TLV [htTLV]). Mayo imaging classification for each patient was assigned on the basis of htTKV and age, after initial classification of kidney cyst pattern as typical (class 1) or atypical (class 2), as previously described (36).

Baseline patient-reported parameters to assess tolerability in the clinical trial (from here on referred to as patient-reported outcomes) were ascertained using three validated instruments. General HRQoL was quantified with the Medical Outcomes Study Short Form-36 (MOS SF-36), and the mental and physical component scores were computed (37,38). *Z*-scores for the summary and component scores were computed with a range from one to 100, with higher scores indicating better HRQoL; mean scores for the normative population are 50, with an SD of ten. Gastrointestinal symptom burden was quantified using the Gastrointestinal Safety Rating Scale (GSRS) (39,40). This is a 15-item questionnaire which ascertains symptoms across five clusters (reflux, abdominal pain, indigestion, diarrhea, and constipation), with each symptom/item reported on a seven-point Likert scale. Scores were calculated for the entire scale, and for each symptom cluster. Pain was quantified by questions relating to back, radiating, and abdominal pain, on the basis of the HALT-PKD Pain Questionnaire (41). Patients were asked whether they had ever experienced any of these three categories of pain since ADPKD diagnosis, and were separately asked to rate the severity and frequency of these three categories of pain within the past 3 months.

Statistical Analyses

Means and SDs (or medians and interquartile ranges) of continuous measures and frequencies of categoric variables were calculated and presented for descriptive purposes. Differences between male and female participants are tested using *t* tests or Wilcoxon–Mann–Whitney tests for continuous variables (see table footnotes) and chi-squared or Fisher exact tests for categoric variables (see table footnotes). A one-sample *t* test was used to test the difference between the SF-36 mental composite score (MCS) and physical composite score (PCS) in study participants compared with the general population (mean, 50) for this instrument. We estimated Spearman rank correlation coefficients between scores on the SF-36 and GSRS with kidney and liver volumes. Analyses were performed using the entire cohort and stratified by sex to explore the strength of associations separately for male and female participants; we also performed *t* tests to compare patient-reported outcomes between patients with a history of back pain versus those without. Multiple linear regression was used to compare eGFR and kidney/liver volumes between the sexes, adjusting for age. Sample size estimations are described in detail elsewhere (32); with 48 participants per study arm and 15% attrition, we estimated a confidence interval width no larger than 21 for the primary tolerability outcome of total GSRS score. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

Results

Study Accrual

Between June 2016 and December 2018, a total of 108 patients with ADPKD were potentially eligible and provided consent for a screening research visit. Of these, four were determined to be ineligible for a variety of reasons, as indicated in Figure 1. Of the remaining 104 participants, an additional seven declined further participation before randomization, resulting in $N=97$ participants being randomized. Reasons that participants declined to enroll included withdrawal of consent, belief that participation would be burdensome due to length and/or frequency of follow-up required, or unwillingness to take study medication.

Participant Characteristics

Table 1 describes the characteristics of the 97 randomized participants. With regards to demographic characteristics, mean (SD) age was 41.9 (10.2) years, 72% were female, and 94% of participants were White. Of note, 26% had participated in an ADPKD clinical trial previously, primarily HALT-PKD. Regarding medical history, the mean age of ADPKD diagnosis was 29.9 (11.9) years, with 28% being diagnosed on the basis of planned screening in the setting of known family history, 24% diagnosed in the setting of pain, and 22% had ADPKD discovered as an incidental imaging finding during imaging for non-ADPKD indications. A large majority (74%) reported a known family history of ADPKD. Just over half the participants had a prior history of liver cysts, with a history of other common ADPKD complications (hernia, gross hematuria, upper tract urinary tract infection, stones) reported among 22%–44% of participants (see Table 1). In contrast, only nine participants reported an interventional treatment for kidney or liver cyst previously. Compared with female participants, males were younger ($P=0.04$), were more likely to be Hispanic ($P=0.04$), and were less likely to have had a prior upper tract urinary tract infection ($P<0.001$); there were no other significant differences in other demographics or PKD complications.

Mean eGFR was 86.8 ± 19.0 ml/min per 1.73 m^2, reflecting the eligibility criteria that excluded those with GFR <50 ml/min per 1.73 m^2. Median (interquartile range) htTKV was 609.8 (341.9–876.5) ml/m, and 7%, all females, had an

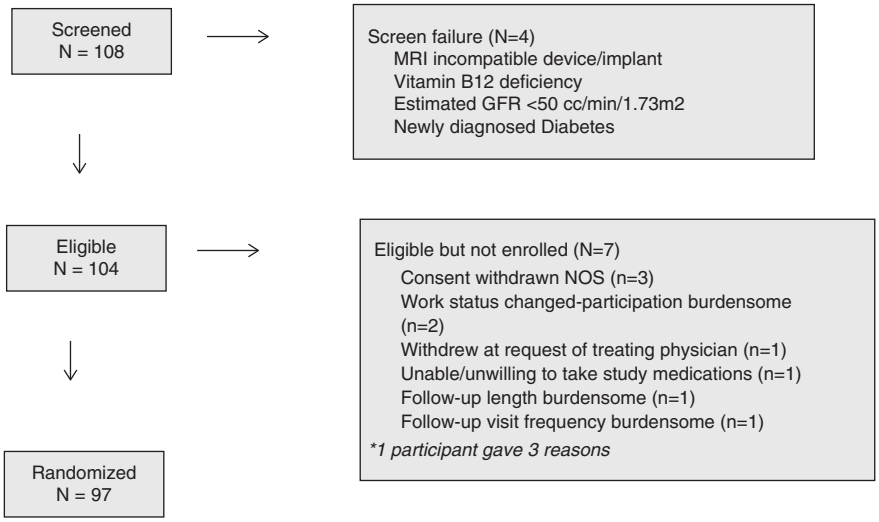

Figure 1. | **Flow of participants from screening to randomization**. NOS, not otherwise specified; MRI, magnetic resonance imaging.

atypical cystic pattern on MRI (Mayo imaging class 2). Nearly a half (48%) of participants were classified as high risk for progression (Mayo imaging classes 1C, 1D, or 1E) (36). BP was, on average, well controlled, and 62 (64%) participants were on antihypertensive treatment at baseline. Compared with female participants, males had higher systolic ($P=0.004$) and diastolic BP ($P=0.002$), and were more likely to have high-risk Mayo imaging classification ($P=0.01$), whereas eGFR, htTLV, and htTKV were not significantly different. After controlling for age differences between males and females, there remained no significant differences in eGFR, htTLV, or htTKV.

Patient-reported outcomes are described in Table 2. Mean reported HRQoL among these participants with ADPKD was similar to, or better than, that reported in the general population, as quantified by the MOS SF-36 instrument. For example, the mean MCS and PCS were 52.4±8.5 and 52.7±6.4, respectively, with general population mean values of 50.0 for each scale ($P=0.006$ for MCS and $P<0.001$ for PCS for one-sample t tests against mean=50, respectively). Patients also reported a low gastrointestinal symptom burden at baseline, with a mean total score on the GSRS of 1.4±0.4 and mean symptom domain scores ranging from 1.2 to 1.5 (Table 2). A slight majority (57%) reported having ever suffered from chronic or nagging back pain since being diagnosed with ADPKD, and a smaller proportion (39%) reporting having ever suffered from chronic or nagging abdominal pain. The proportion reporting back pain, radiating pain, and abdominal pain as "often" or more frequently within the prior 3 months was 30%, 7%, and 10%, respectively (Table 2). No significant differences in patient-reported outcomes and HRQoL were observed between male and female participants.

Correlation of Patient-Reported Outcomes and HRQoL with Organomegaly

Self-reported HRQoL was not related to organ enlargement. Specifically, neither the SF-36 MCS nor PCS was correlated with htTKV (Figure 2), TLV, nor combined total kidney and liver volumes ($P>0.05$ for all tests of correlation; Table 3). Likewise, neither the total nor domain-specific GSRS scores were significantly correlated with TKVs, TLVs, or combined kidney and liver volumes (Table 3). However, when patients with and without a history of chronic or nagging back pain were compared, the total GSRS score and scores for the reflux, abdominal pain, indigestion, and constipation domains were significantly, if modestly, higher among those with chronic/nagging back pain, indicating greater severity of these symptoms (Table 4). Likewise, the SF-36 MCS and PCS were significantly lower among those with chronic/nagging back pain, indicating lower HRQoL. There was a statistically significant clinical correlation in males only between constipation and TLV or combined kidney and liver volumes (Table 3). However, overall constipation was absent or mild in the study sample (median score of one out of seven for both males and females; Table 2).

Discussion

Here, we report successful recruitment in the TAME study, a randomized, placebo-controlled, clinical trial that will be the first to assess the safety, tolerability, and efficacy of metformin on inhibiting the growth of TKV in individuals with early to midstage ADPKD. Using two university-affiliated clinical sites with specialization in ADPKD research and large ADPKD clinical practices, we were able to identify 108 individuals for screening over approximately 2.5 years of recruitment. We ultimately randomized 97 of these participants with an eGFR of >50 ml/min per 1.73 m^2, meeting our prespecified accrual goal. Although robust recruitment was feasible with only two clinical sites, it is important to note that tolvaptan was approved by the FDA for the treatment of those with ADPKD at risk of rapid progression toward the end of the recruitment period. The absence of any FDA-approved therapy for ADPKD during most of the recruitment period undoubtedly facilitated successful enrollment in this clinical trial. With the availability of tolvaptan for clinical use and the potential risks inherent in enrolling patients treated with tolvaptan into randomized trials of investigational therapies with unknown risk of drug

Table 1. Demographic and clinical characteristics of study participants

Characteristic	All (*N*=97)	Females (*N*=70)	Males (*N*=27)	*P* Value
Demographics				
Age (yr), mean (SD)	41.9±10.2	43.3±10.1	38.5±9.7	0.04
Race, *n* (%)				0.15
American Indian/Alaska Native	1 (1)	1 (1)	0 (0)	
Asian	3 (3)	1 (1)	2 (7)	
Black	1 (1)	0 (0)	1 (4)	
White	92 (95)	68 (97)	24 (89)	
Hispanic ethnicity, *n* (%)	8 (8)	3 (4)	5 (19)	0.04
Participated in any clinical trial in the past	25 (26)	20 (29)	5 (19)	0.3
PKD history				
Age at PKD diagnosis (yr), mean (SD)	29.9±11.9	29.8±11.3	30.3±13.4	0.9
Basis of PKD diagnosis, *n* (%)				0.5
Screening (family history)	27 (28)	20 (29)	7 (26)	
Incidental imaging	21 (22)	16 (23)	5 (19)	
Pain	23 (24)	17 (24)	6 (22)	
Hypertension	9 (9)	5 (7)	4 (15)	
Routine physical	6 (6)	3 (4)	3 (11)	
Hematuria	5 (5)	3 (4)	2 (7)	
UTI	6 (6)	6 (9)	0 (0)	
Family history of ADPKD, *n* (%)	72 (74)	52 (74)	20 (74)	0.98
Liver cysts, *n* (%)	53 (55)	41 (59)	12 (44)	0.2
Gross hematuria, *n* (%)	32 (33)	25 (36)	7 (26)	0.4
Kidney stones, *n* (%)	21 (22)	16 (23)	5 (19)	0.6
Abdominal hernia, *n* (%)	20 (21)	13 (19)	7 (26)	0.4
Upper urinary tract infection, *n* (%)	42 (43)	38 (54)	4 (15)	0.001
Prior interventional treatment of cysts, *n* (%)	9 (9)	8 (11)	1 (4)	0.4
ADPKD severity and risk class				
eGFR (ml/min per 1.73 m^2), mean (SD)	86.8±19.0	86.9±19.3	86.7±18.7	0.96
eGFR <60 ml/min per 1.73 m^2, *n* (%)	11 (11)	9 (13)	2 (7)	0.7
Serum CO_2 (mEq/L), mean (SD)	26.9±2.3	26.7±2.4	27.5±1.9	0.15
Systolic BP (mm Hg), mean (SD)	123.1±13.0	120.8±13.3	129.2±10.1	0.004
Diastolic BP (mm Hg), mean (SD)	75.7±8.7	74.1±8.93	80.0±6.61	0.002
Body mass index (kg/m^2), mean (SD)	26.8±5.2	26.6±5.6	27.3±3.9	0.5
Treatment with antihypertensive medications, *n* (%)	62 (64)	43 (61)	19 (70)	0.4
Total kidney volume (ml), median (IQR)[a]	1022.3 (569.2–1489.9)	908.9 (527.8–1403.3)	1281.2 (922.2–1602.2)	0.02
Height-adjusted TKV (ml/m), median (IQR)[a]	609.8 (341.9–876.5)	542.6 (314.1–877.1)	692.5 (506.7–876.0)	0.09
Total kidney cyst volume (ml), median (IQR)[a]	552.9 (179.0–876.5)	470.5 (175.8–829.5)	731.9 (292.3–1032.7)	0.15
Total liver volume (ml), median (IQR)[a]	1794.5 (1540.6–2119.8)	1723.3 (1481.0–2150.9)	1894.9 (1672.2–2081.6)	0.2
Height-adjusted TLV (ml/m), median (IQR)[a]	1039.3 (885.3–1241.1)	1025.8 (869.8–1309.5)	1052.7 (949.6–1129.9)	0.8
Liver cyst volume (ml), median (IQR)[a]	11.7 (1.2–304.7)	12.2 (1.3–458.1)	10.3 (0.6–96.5)	0.3
Mayo risk class, *n* (%)[a]				0.01
Class II	7 (7)	7 (10)	0 (0)	
Class IA	15 (16)	11 (16)	4 (15)	
Class IB	28 (29)	25 (36)	3 (11)	
Class IC	26 (27)	16 (23)	10 (37)	
Class ID	12 (12)	7 (10)	5 (19)	
Class IE	8 (8)	3 (4)	5 (19)	

Continuous variables reported as mean±SD, median (IQR), and tested between females/males using t tests or Wilcoxon–Mann–Whitney tests, as appropriate. Categoric variables reported as n (%) and tested between groups using chi-squared tests or Fischer exact tests. PKD, polycystic kidney disease; UTI, urinary tract infection; ADPKD, autosomal dominant PKD; CO_2, carbon dioxide; IQR, interquartile range; TKV, total kidney volume; TLV, total liver volume.
[a]Information on TKVs, kidney cyst volumes, TLVs, liver cyst volumes, and Mayo risk class were missing for *N*=1 participant. All other measures were complete for all participants.

interactions, current and future clinical trials must either exclude such patients from participation, include tolvaptan as "standard of care" with balanced stratification across treatment and control groups, and/or target for recruitment a subgroup of patients with ADPKD who would be otherwise ineligible for tolvaptan therapy.

Table 2. Patient-reported outcomes before randomization among study participants

Characteristic	All (N=97)	Females	Males	P Value
Gastrointestinal symptoms rating scale, total score, mean±SD	1.38±0.43	1.41±0.45	1.30±0.39	0.3
Reflux	1.48±0.99	1.54±1.04	1.31±0.83	0.3
Abdominal pain	1.46±0.61	1.51±0.66	1.31±0.44	0.14
Indigestion	1.47±0.56	1.53±0.59	1.33±0.45	0.13
Diarrhea	1.20±0.44	1.20±0.44	1.20±0.45	0.9
Constipation	1.28±0.55	1.26±0.52	1.35±0.64	0.5
SF-36 mental composite score, mean±SD	52.4±8.46	51.9±8.77	53.7±7.63	0.4
SF-36 physical composite score, mean±SD	52.7±6.42	52.5±6.47	53.0±6.39	0.7
HALT pain questionnaire, *n* (%)				
Since diagnosis of PKD, ever experienced nagging or chronic pain in the back	55 (57)	43 (61)	12 (44)	0.13
Since diagnosis of PKD, ever experienced nagging or chronic pain in the back radiating into buttocks/hips/legs	32 (33)	28 (40)	4 (15)	0.02
Since diagnosis of PKD, ever experienced nagging or chronic pain in the abdomen	38 (39)	28 (40)	10 (37)	0.8
Back pain within prior 3 mo, *n* (%)				0.2
Never	26 (27)	17 (24)	9 (33)	
Rarely	18 (19)	14 (20)	4 (15)	
Sometimes	24 (25)	15 (21)	9 (33)	
Often	11 (11)	11 (16)	0 (0)	
Usually	12 (12)	8 (11)	4 (15)	
Always	6 (6)	5 (7)	1 (4)	
Pain radiating to buttocks/hips/legs within prior 3 mo, *n* (%)				0.8
Never	66 (68)	45 (64)	21 (78)	
Rarely	12 (12)	10 (14)	2 (7)	
Sometimes	12 (12)	9 (13)	3 (11)	
Often	4 (4)	3 (4)	1 (4)	
Usually	3 (3)	3 (4)	0 (0)	
Always	0 (0)	0 (0)	0 (0)	
Abdominal pain within 3 mo, *n* (%)				0.9
Never	49 (51)	35 (50)	14 (52)	
Rarely	11 (11)	8 (11)	3 (11)	
Sometimes	27 (28)	20 (29)	7 (26)	
Often	2 (2)	2 (3)	0 (0)	
Usually	7 (7)	4 (6)	3 (11)	
Always	1 (1)	1 (1)	0 (0)	

Continuous variables reported as mean±SD and tested between females/males using t tests. Categoric variables reported as n (%) and tested between groups using chi-squared tests or Fischer exact tests. SF-36, Short Form-36; PKD, polycystic kidney disease.

Lactic acidosis has been recognized as a serious, but very rare, complication of metformin therapy. The FDA has concluded that metformin can be used safely in patients with mild impairment in kidney function and even in some patients with moderate impairment in GFR, the latter potentially with dose reduction (31,42). Current FDA labeling recommendations suggest metformin is contraindicated in patients with an eGFR of <30 ml/min per 1.73 m^2, and should not be initiated in individuals with an eGFR of between 30 and 45 ml/min per 1.73 m^2. To adhere to these dosing recommendations, our inclusion criteria required participants to have an eGFR of >50 ml/min per 1.73 m^2 at randomization (accounting for expected eGFR decline over the 2-year treatment phase), which resulted in a study sample with early stage disease. In the TAME-PKD trial, there were no requirements for eligibility on the basis of kidney volumes. This study design decision was motivated by feasibility concerns to efficiently recruit participants without prior kidney volume measurements while avoiding a high screen-failure rate. This design element, when combined with the need to enroll those with preserved kidney function, also resulted in a study sample with roughly a half of participants considered at lower or uncertain estimated risk for disease progression on the basis of the Mayo imaging classification system (*i.e.*, class 2, 1A, or 1B).

Seven participants, all female, had atypical, Mayo imaging class 2A, MRI scans with cystic involvement that was segmental, asymmetric, or lopsided (36,43). In prior studies from the Mayo and HALT cohorts, the former had more males than females with class 2, whereas the reverse was observed in HALT (36,44). In all of these studies, there were relatively small numbers of patients with a class-2 classification, making it difficult to determine whether atypical imaging features have an association with sex. We noted other sex differences in clinical characteristics, with higher BP and a greater frequency of high-risk Mayo imaging class among males versus females. These findings are generally consistent with prior observations that male patients with ADPKD are at greater risk for ESKD compared with females (45). However, sex comparisons in this study sample may have been limited by the small number of males who were enrolled—a sex imbalance that was unexpected.

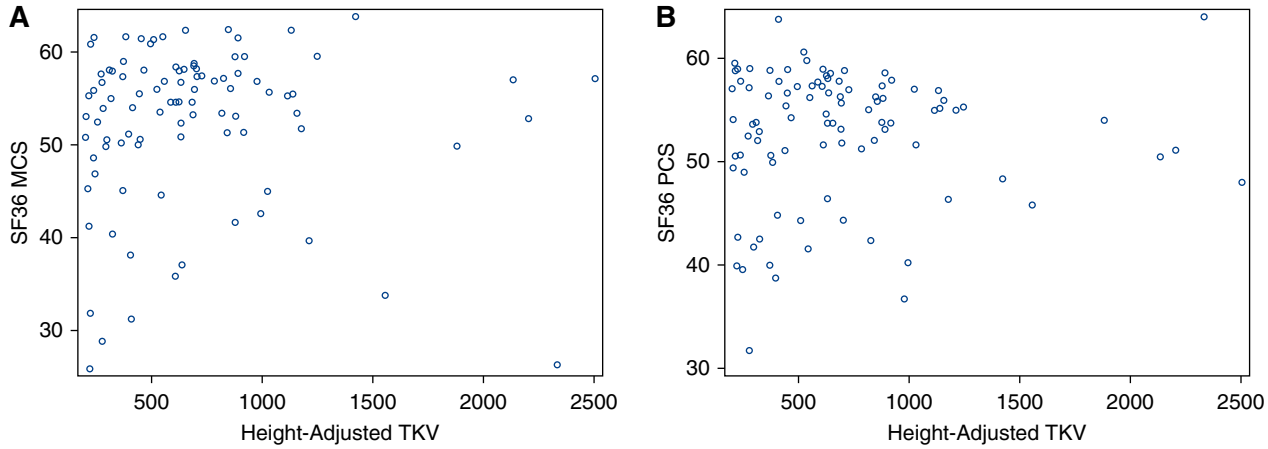

Figure 2. | **Height-adjusted kidney volume was not associated with health-related quality of life.** (A) Short Form-36 (SF-36) mental composite score (MCS) and height-adjusted total kidney volume (htTKV). (B) SF-36 physical composite score (PCS) and htTKV.

Because the major side effects of metformin relate to gastrointestinal symptoms, we used a validated symptom scale (the GSRS) to characterize such symptoms before randomization and during treatment and follow-up. We found that average symptom burden at baseline was quite mild and was unrelated to organomegaly, as quantified by total kidney and liver volumes. The meaning of the association between constipation and organomegaly in men is uncertain and perhaps a chance finding given that, on average, constipation was absent or mild in study participants. The mild nature of gastrointestinal findings in our study population may be explained by the relatively early stage and smaller kidney volumes in TAME compared with other recent clinical trials, such that differences in TKV in the range observed among these participants do not materially affect these symptoms (6). Alternatively, the types of

Table 3. Correlation (ρ) of patient-reported outcome with total kidney volume and total liver volume

Outcome	All Patients (N=97)		Females (N=70)		Males (N=27)	
	R_s	P Value	R_s	P Value	R_s	P Value
Total kidney volume (height adjusted)						
SF-36 MCS	0.17	0.09	0.20	0.10	−0.04	0.83
SF-36 PCS	0.00	0.98	−0.03	0.84	−0.03	0.90
GSRS total score	−0.08	0.43	−0.11	0.39	0.11	0.59
Reflux	−0.06	0.54	−0.03	0.79	−0.05	0.82
Abdominal pain	−0.13	0.22	−0.12	0.33	−0.06	0.76
Indigestion	−0.16	0.13	−0.19	0.12	0.08	0.69
Diarrhea	0.10	0.33	0.17	0.16	−0.07	0.72
Constipation	0.09	0.38	−0.02	0.90	0.37	0.06
Total liver volume (height adjusted)						
SF-36 MCS	−0.06	0.59	0.00	0.97	−0.31	0.12
SF-36 PCS	−0.08	0.42	−0.06	0.60	−0.15	0.45
GSRS total score	0.16	0.13	0.11	0.38	0.26	0.19
Reflux	0.15	0.14	0.15	0.21	0.08	0.69
Abdominal pain	−0.06	0.56	−0.10	0.40	0.09	0.64
Indigestion	0.18	0.07	0.17	0.16	0.17	0.40
Diarrhea	0.06	0.58	0.07	0.59	−0.02	0.94
Constipation	0.17	0.10	0.08	0.49	0.45	0.02
TKV+TLV (height adjusted)						
SF-36 MCS	0.04	0.68	0.08	0.53	−0.15	0.47
SF-36 PCS	−0.09	0.39	−0.09	0.44	−0.09	0.66
GSRS total score	0.12	0.26	0.08	0.50	0.28	0.15
Reflux	0.05	0.62	0.05	0.66	0.10	0.61
Abdominal pain	−0.03	0.77	−0.05	0.68	0.10	0.63
Indigestion	0.09	0.40	0.07	0.56	0.19	0.34
Diarrhea	0.17	0.09	0.22	0.07	0.04	0.83
Constipation	0.20	0.06	0.14	0.26	0.42	0.03

R_s, Spearman rank correlation coefficient; SF-36, Short Form-36; MCS, mental composite score; PCS, physical composite score; GSRS, Gastrointestinal Safety Rating Scale; TKV, total kidney volume; TLV, total liver volume.

Table 4. Comparisons of patient-reported outcomes by history of chronic back pain

Characteristic	No History of Back Pain	History of Back Pain	*P* Value
Gastrointestinal Symptoms Rating Scale, total score	1.21±0.29	1.50±0.48	<0.001
GSRS domain score			
Reflux	1.19±0.55	1.70±1.18	0.01
Abdominal pain	1.26±0.49	1.61±0.66	0.005
Indigestion	1.28±0.38	1.62±0.63	0.002
Diarrhea	1.24±0.53	1.18±0.37	0.49
Constipation	1.07±0.14	1.44±0.69	<0.001
SF-36 mental composite score	55.1±5.52	50.4±9.70	0.005
SF-36 physical composite score	55.1±4.49	50.9±7.08	0.001

GSRS, Gastrointestinal Symptoms Rating; SF-36, Short Form-36.

symptoms quantified by the GSRS, representing luminal gastrointestinal symptoms specifically, may be relatively unaffected by gradual organ enlargement over decades in ADPKD until very advanced disease is present.

We also noted that patient-reported HRQoL was, on average, similar to that reported in the general population for both mental and physical function. Furthermore, HRQoL as quantified by the MOS SF-36 general instrument was not associated with greater kidney or liver volumes. These findings are similar to those reported by Miskulin *et al*. (46) in the HALT-PKD study, in which average HRQoL scores in patients with ADPKD were not lower than the general population, even for those with eGFR <45 ml/min per 1.73 m^2 (47). The authors also reported no significant correlations between SF-36 scores and kidney volume; liver volumes were not examined in relation to HRQoL in that study. The preservation of HRQoL in patients with ADPKD in this trial, and the absence of any association with organ enlargement, may be due to a selected, highly functional study sample of patients with early stage ADPKD who were willing and motivated to participate in research, in contrast to an unselected sample. Patients with ADPKD and an earlier stage of the disease, such as those in TAME-PKD, may also accommodate to the slow organ enlargement and discomfort such that daily function is relatively preserved, at least until late stage disease. Alternatively, the SF-36 as a generic, disease-agnostic, patient-reported HRQoL instrument may be insensitive in detecting specific functional deficits related to symptoms specific to ADPKD. We did observe modestly higher gastrointestinal symptoms and modestly lower HRQoL in those who reported chronic back/flank pain on the HALT-PKD pain questionnaire; however, participant responses on chronic long-term symptoms, such as pain, which are present because of PKD, may be unreliable due to recollection bias.

In conclusion, recruitment in this ongoing, novel clinical trial of metformin in ADPKD successfully met its goal, with a study sample comprising patients with early stage disease and nearly a half of participants considered at high estimated risk for progression, despite preserved or mildly impaired kidney function. These participants reported a low gastrointestinal symptom burden at baseline, and HRQoL similar to that of the general population, with no differences in symptoms or HRQoL by kidney or liver size. Further studies will need to determine appropriate eligibility criteria in terms of disease stage and risk class to obtain the maximal possible risk-benefit ratio for metformin in ADPKD.

Disclosures

K. Bae is a consultant to Kadmon Corporation, Otsuka, and Sanofi. R. Perrone is a consultant to Otsuka, Palladiobio, Reata, Sanofi-Genzyme, and Vertex. R. Perrone serves as the editor of the renal cystic disease section for UpToDate. T. Watnick has a patent to Athena Diagnostics issued, is on the scientific advisory committee of the PKD Foundation (no financial relationship), serves in an advisory capacity as chair of the advisory committee to the PKD Foundation's ADPKD registry (no financial relationship). All remaining authors have nothing to disclose.

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Author Contributions

K. Abebe and A. Althouse were responsible for data curation and formal analysis; K. Abebe, K. Bae, K. Hallows, R. Perrone, S. Seliger, and T. Watnick conceptualized the study; K. Abebe, K. Bae, R. Perrone, S. Seliger, and T. Watnick were responsible for project administration; K. Bae was responsible for funding acquisition; K. Bae, K. Hallows, D. Miskulin, R. Perrone, S. Seliger, and T. Watnick were responsible for investigation; K. Bae, K. Hallows, R. Perrone, S. Seliger, and T. Watnick were responsible for methodology; S. Seliger and T. Watnick wrote the original draft; and all authors reviewed and edited the manuscript.

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