The Gut Microbiome in Autosomal Dominant Polycystic Kidney Disease

A Cross-Sectional Study

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Key Points

- Patients with autosomal polycystic kidney disease (ADPKD) display relevant alterations in gut microbiome signatures compared with a healthy control cohort.
- Gut microbiome alterations in patients with ADPKD were associated with specific markers of ADPKD disease progression.

Abstract

Background Changes in gut microbiota signatures have been associated with CKD and nephrolithiasis and may thus be a factor explaining variability of outcome in autosomal polycystic kidney disease (ADPKD). We aimed to characterize the intestinal microbiome in a cross-sectional study of patients with ADPKD and to explore the potential effect of microbiome signatures on polycystic kidney disease progression.

Methods This observational cross-sectional pilot study recruited 25 patients from the German ADPKD Tolvaptan Treatment Registry patient cohort and 12 healthy, age- and sex-matched control participants. The gut microbiome was analyzed by 16S ribosomal RNA gene profiling of stool samples. Bacteria-derived serum uremic toxins were measured using liquid chromatography coupled with tandem mass spectrometry. Microbiome data were correlated with age, kidney function, and markers of polycystic kidney disease progression like Mayo classification and arterial hypertension <35 years of age.

Results Patients with ADPKD displayed a significantly decreased abundance of Actinobacteria including probiotic Bifidobacteriaceae and significantly increased abundance of Enterobacteriaceae. Those findings were independent of kidney function. Most notably, Streptococcaceae were significantly overrepresented in patients with Mayo classes 1D and 1E compared with 1A–1C. In addition, early onset of hypertension (<35 years of age) was associated with an increased abundance of Proteobacteria and a decreased abundance of Tannerelleaceae. Furthermore, patients with ADPKD revealed an increased abundance of Peptococcaceae with increasing age and declining kidney function. Finally, serum uremic toxin levels were significantly increased in patients with ADPKD, highly correlating with eGFR.

Conclusions This pilot study suggests relevant changes in gut microbiota signatures of patients with ADPKD, which might be associated with rapid disease progression. These findings indicate that composition of the gut microbiota could potentially contribute to disease progression of ADPKD and the individual disease variability. Further investigation is warranted to assess the gut microbiota as a potential therapeutic target in ADPKD.

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Introduction

Autosomal polycystic kidney disease (ADPKD) is the most common genetic kidney disease caused by heterozygous germline mutations in the PKD1 and PKD2 genes (beside other rare forms).[1] ADPKD results in continuous cyst growth and CKD with a need for KRT in most patients.[1] Tolvaptan, which is reserved for patients with rapid disease progression, slows down but does not prevent kidney failure and comes with considerable side effects.[2,3] Because secondary effects, such as arterial hypertension, or environmental factors, such as high salt intake, are believed to accelerate disease progression, state-of-the-art polycystic kidney disease (PKD) management aims to prevent such triggers.[4,5]

More recently, next-generation DNA sequencing has led to broad characterization of the human gut microbiome, which is constantly affected by environmental factors such as diet, age, or antibiotic treatment.[6] Changes in the gut microbiota have been associated with diseases of almost every organ system, including CKD and nephrolithiasis.[7,8] Importantly, nephrolithiasis itself is a driver of disease progression in ADPKD. Several studies suggested that uremic conditions or drug treatment with phosphate-binding agents or antibiotics facilitate the emergence of significant changes in the gut microbiota in patients with CKD.[7–9] As a consequence to these changes, the intestinal barrier function can be compromised with increased permeability for bacteria-derived toxic metabolites, including serum uremic toxins (sUTs).[7–9] sUTs have been shown to accumulate during CKD, accelerate loss of kidney function, and induce systemic inflammation resulting in aggravation of CKD.[10] More recently, the gut microbiome has been implicated as a relevant cofactor in ADPKD for the first time.[11] A small uncontrolled study ($N=18$) provided a first insight into kidney function–dependent changes of gut microbiota composition in ADPKD.[11] It, however, remains unknown whether changes in the gut microbiota could be associated with ADPKD itself and be a potential modifier of disease progression. Therefore, we aimed to unravel gut microbiome alterations in patients with ADPKD in an observational cross-sectional setting including a healthy control cohort and analyze the potential association of gut microbiota signatures and ADPKD disease progression.

Methods

Study Design

This study was designed as an observational cross-sectional pilot study at the University Hospital of Cologne. The primary aim was to investigate potential differences in the gut microbiome composition and sUTs in patients with ADPKD compared with healthy individuals. The secondary aim was to elucidate associations between gut microbiota signatures and sUTs with markers of rapid disease progression according to the predicting renal outcome in PKD score algorithm,[12] *i.e.*, early onset of arterial hypertension or urologic complications (<35 years of age), kidney function, and Mayo classification. Patients with ADPKD have been recruited through the German ADPKD Tolvaptan Treatment Registry (AD(H)PKD) study cohort (NCT02497521), and biosampling was performed in the context of the Rare Kidney Disease study (DRKS00008910). Biosamples of healthy individuals were collected in parallel (DRKS00014637). All studies were approved by the local Ethics Committee (University of Cologne) and conducted according to the Declaration of Helsinki and Good Clinical Practice guidelines by the International Conference on Harmonisation.

Participants

The AD(H)PKD registry is a multicenter cohort study enrolling patients older than 18 years and a diagnosis of ADPKD (CKD G1–4) since 2015. Accordingly, patients were recruited during their regular yearly follow-up visits including empty-stomached blood work, BP measurement, and a standardized questionnaire including information about recent medication and anti-infective treatment between January 2018 and September 2019 (see the flow chart in Supplemental Figure 1). Patients were provided a stool collection kit and were asked to collect stool at home together with a Bristol Stool Scale. Stool and serum samples were collected with a median average time difference of around 10 days. In total, 80 patients have provided stool samples, of which 25 have been analyzed on the basis of equal distribution for sex, age (≤45 versus ≥50 years of age), kidney function (≤45 ml/min per 1.73 m^2 ≥60 ml/min per 1.73 m^2), and adherence to a standard diet. Patients were additionally screened for recent antibiotic use at the study visit before stool collection. Healthy controls were selected on the basis of a medical history with no internal medicine diagnoses, except arterial hypertension.

Microbiome Characterization

Stool was collected using the Fisher Scientific Commode Specimen collection kit (Fisher Scientific, 02-544-208) and stored at −80°C until analysis. DNA was extracted and purified using the FastDNA Spin Kit or Soil (MP Biomedicals 6560-200). DNA amplification was performed using the 341F (S-D-Bact-0341-b-S-17) and 805R (S-D- Bact-0785-b-A-21) primers for the V3-V4 regions of the 16S ribosomal RNA gene.[13] After sample normalization, sequencing was performed as 300-bp paired-end runs using the Illumina MiSeq System and MiSeq Reagent Kit v3 (600 cycle, Illumina MS-102-3003)[13] and processed with the DADA2 pipeline and QIIME2.[14,15] Trimmed and denoised data were rarefied at a depth of 30,000 sequences. Taxonomic classification was performed using the Naïve Bayes classifier (sklearn) trained on the SILVA rRNA gene database (Version 138).[16] α Diversity was visualized using the Shannon Index.[17] β Diversity was calculated as weighted unique fraction metric distances between samples, visualized with the principal coordinate analysis and tested with the analysis of similarity test (ANOSIM, $\alpha=0.5$).[18] Specific taxonomic groups were analyzed using linear discriminant analysis (LDA) effective size algorithm. A LDA score ≥±2 was defined as significant difference as previously described.[19]

Analysis of sUTs

The bacteria-derived sUTs trimethylamine *N*-oxide (TMAO), the protein bound and free indoxylsulfate (IS), and p-cresyl-sulfate (pCS) were quantified by liquid

Table 1. Baseline characteristics

Characteristics	ADPKD Cohort (*N*=25)	Healthy Control Cohort (*N*=12)
Sex		
Female	*n*=12 (48%)	*n*=6 (50%)
Male	*n*=13 (52%)	*n*=6 (50%)
Age in years displayed as median (IQR)	50 (14–5)	45 (25–85)
Art. hypertension	*n*=24 (96%)	*n*=1 (8%)
Early onset <35 yr of age	*n*=6 (24%)	
Medication		
Tolvaptan	*n*=3 (12%)	*n*=0 (0%)
ACE inhibitor	*n*=9 (36%)	*n*=0 (0%)
AT1 antagonists	*n*=12 (48%)	*n*=0 (0%)
Calcium antagonist	*n*=6 (24%)	*n*=1 (8.3%)
Thiazides	*n*=5 (20%)	*n*=0 (0%)
β-blocking agents	*n*=2 (8%)	*n*=1 (8.3%)
Proton pump inhibitors	*n*=3 (12%)	*n*=0 (0%)
Other medication	*n*=8 (36%)	*n*=2 (16.7%)
BMI in kg/m^2 displayed as median (IQR)	22.3 (4)	
Smoking		
Nonsmoker	*n*=9 (36%)	
Past smoker	*n*=11 (44%)	
Active smoker	*n*=5 (20%)	
Alcohol		
No alcohol	*n*=6 (24%)	
≦1 drink/wk	*n*=5 (20%)	
<1 drink/d	*n*=11 (44%)	
>1 drink/d	*n*=2 (8%)	
Not documented	*n*=1 (4%)	
Estimated salt intake in g/24 h (IQR)	9.9 (9–75)	
eGFR in ml/min per 1.73 m^2 (IQR)	62 (46)	
CKD classification		
G2	*n*=13 (52%)	
G3b	*n*=6 (24%)	
G4	*n*=6 (24%)	
Genotype		
PKD1 nontruncating	*n*=3 (12%)	
PKD1 truncating	*n*=4 (16%)	
PKD1 VUS	*n*=3 (12%)	
PKD2	*n*=7 (28%)	
Not analyzed	*n*=8 (32%)	
Early onset (<35. yr of age) of urological complications: cyst infection, flank pain, hematuria, nephrolithiasis	*n*=5 (20%)	
Mayo classification		
1A	*n*=2 (8%)	
1B	*n*=3 (12%)	
1C	*n*=9 (36%)	
1D	*n*=6 (24%)	
1E	*n*=3 (12%)	
Not analyzed	*n*=2 (8%)	

List of baseline characteristics of all patients. ACE, angiotensin-converting enzyme antagonists; ADPKD, autosomal polycystic kidney disease; AT1, angiotensin II receptor type 1 antagonists; BMI, body mass index; IQR, interquartile range; VUS, variant of unknown significance.

chromatography coupled to electron spray ionization tandem mass spectrometry using a procedure previously described with several modifications and reported in the Supplemental Methods.[20] sUTs were quantified on the basis of external calibration curves that were calculated from liquid chromatography coupled with mass spectrometry measurements of serially diluted synthetic TMAO, pCS, and IS. To each dilution, a fixed amount of the internal standards was added. The standard calibration curves were plotted on the basis of molar concentration versus peak area ratio of the endogenous uremic toxins and their respective internal standards.

Laboratory Parameters

Laboratory measurements (creatinine, eGFR [CKD Epidemiology Collaboration], Mayo classification), clinical measurements (body mass index, art. BP), and information about medical history were collected during standard-of-

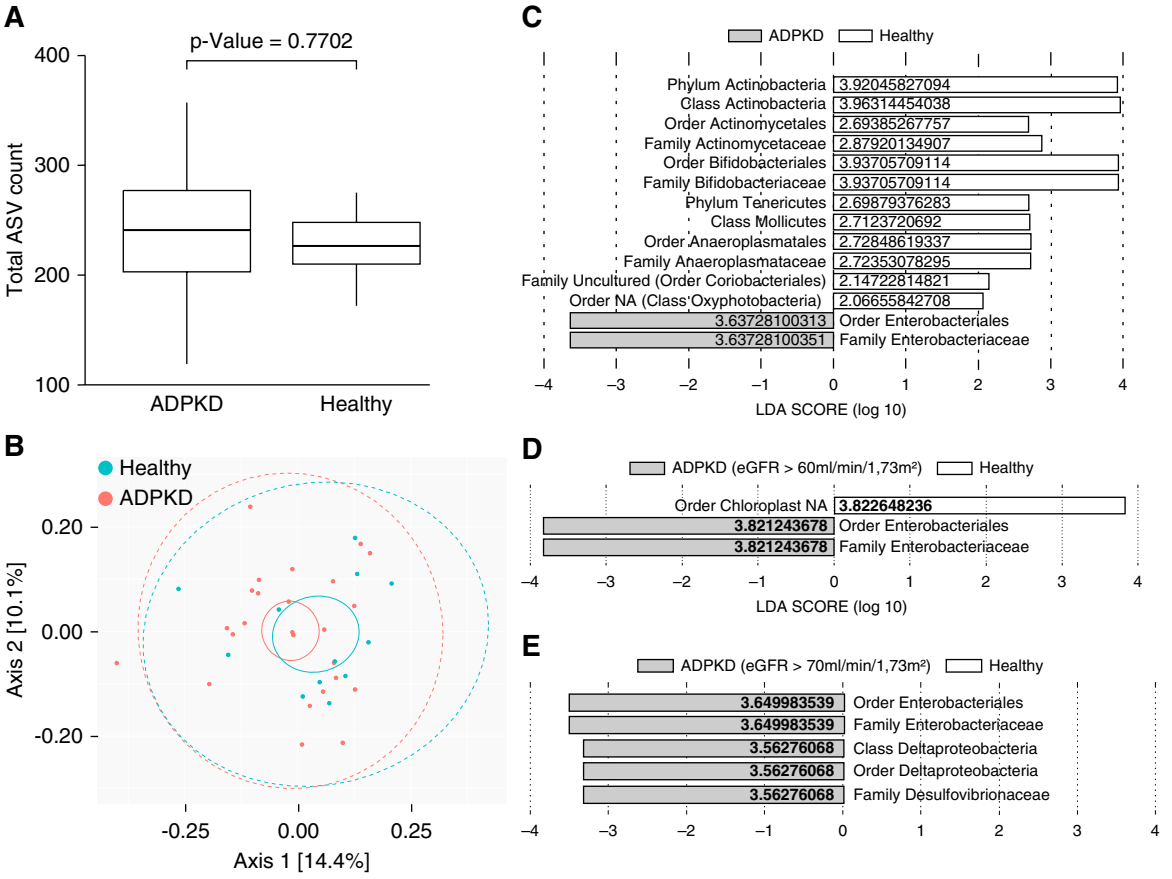

Figure 1. Microbiome characterization. (A) α-Diversity. Comparison of the total number of measured ASVs in the ADPKD and healthy cohorts using a Mann–Whitney *U* test. No significant difference could be found ($P = 0.7702$). (B) β-Diversity. β-Diversity was calculated as weighted UniFrac metric distances between samples, visualized with the PCoA and tested with the analysis of similarity test. No significant difference could be observed (PERMANOVA: $P = 0.28$; ANOSIM: $P = 0.483$; R=−0.001202). Axis 1 represents the principal coordinate that explains the largest data change, and axis 2 represents the principal coordinate that accounts for the largest proportion of the remaining data changes. 95% confidence levels assuming normal (--) distribution and 95% confidence ellipses (☐). (C–E) Analysis of ASVs. Specific ASVs were analyzed and visualized using the LEfSe. An LDA score ≥±2 was defined as significant difference as previously described.[37] Healthy control cohort was compared with the total ADPKD cohort (N=25; C), ADPKD subcohort with eGFR >60 ml/min per 1.73 m^2 (n=13; D), and ADPKD subcohort with eGFR >70 ml/min per 1.73 m^2 (n=7; E). All significantly different ASVs are displayed (white: healthy cohort; gray: ADPKD cohort). Negative LDA score defines reduction of abundance, positive LDA score increased abundance of ASVs, NA displays incomplete DNA fragments. Uncultured, displays complete DNA fragments of so-far unidentified bacteria. ADPKD, autosomal polycystic kidney disease; ANOSIM, analysis of similarities test; ASV, amplicon sequence variant; LDA, linear discriminant analysis; LEfSe, LDA effective size algorithm; NA, not applicable; PCoA, principal coordinate analysis; PERMANOVA, permutational multivariate analysis of variance; UniFrac, unique fraction.

care clinical visits. Genotype of patients with ADPKD was analyzed by a multiplex PCR-based panel established for PKD1 and PKD2.[21] Additional information about alcohol, smoking, and salt intake were collected for stratification and analysis of potential confounders.

Statistical Analyses

Statistical analysis was performed using R for Statistical Computing (incl. the phyloseq package for diversity calculation; Version 3.6.1) and SPSS (Version 28, IBM). After collection, all samples were pseudoanonymized. Researchers performing the quantification were blinded to the treatment cohorts. All datasets were tested for normal distribution and analyzed using either nonparametric Mann–Whitney *U* test or Kruskal–Wallis test. A P value < 0.05 was considered significant. Correlation analysis was performed using Spearman correlation (ordinally scaled data) or eta coefficient (nominally scaled data) followed by linear or multivariable regression analyses. Statistical testing was not adjusted for multiple comparisons because of the exploratory and focused research setting.[22] Therefore, the results should be interpreted as exploratory.

Results

Patient Characteristics

The ADPKD cohort (n=25) was slightly older than the control cohort (n=12) with an equal sex distribution (Table 1). Six patients with ADPKD (24%) experienced early onset of arterial hypertension and five (20%) early urologic complications (<35 years of age). The ADPKD cohort was

Table 2. Correlation analysis of amplicon sequence variants and potentially confounding variables

Potential Confounding Variables	Enterobacteriales	Enterobacteriaceae	Bifidobacteriales	Bifidobacteriaceae
Estimated salt intake	$r_s=-0.056$ $P = 0.814$	$r_s=-0.056$ $P = 0.814$	$r_s=0.080$ $P = 0.737$	$r_s=0.080$ $P = 0.737$
Smoking	$r_s=-0.381$ $P = 0.060$	$r_s=-0.381$ $P = 0.060$	$r_s=-0.309$ $P = 0.132$	$r_s=-0.309$ $P = 0.132$
Alcohol consumption	$r_s=0.160$ $P = 0.455$	$r_s=0.160$ $P = 0.455$	$r_s=0.296$ $P = 0.161$	$r_s=0.296$ $P = 0.161$
Mayo classification	$r_s=-0.178$ $P = 0.395$	$r_s=-0.178$ $P = 0.395$	$r_s=0.197$ $P = 0.344$	$r_s=0.197$ $P = 0.344$
Age	$P = 0.614$ F=0.262	$P = 0.614$ F=0.262	$P = 0.168$ F=2.023	$P = 0.168$ F=2.023
BMI	$P = 0.230$ F=1.521	$P = 0.230$ F=1.521	$P = 0.146$ F=2.269	$P = 0.146$ F=2.269
eGFR	$P = 0.498$ F=0.473	$P = 0.498$ F=0.473	$P = 0.119$ F=2.623	$P = 0.119$ F=2.623

Correlation analysis of significantly different abundant amplicon sequence variants with potential confounding variables using Spearman rank correlation (salt intake, nicotine, alcohol, and Mayo classification) or using simple linear regression analysis (age, BMI, and eGFR). Rank classification of salt intake: <5 g/Tag; 5 to <10 g/Tag; 10 to <15 g/Tag; and ≥15 g/Tag. Rank classification of nicotine consumption: active smoker, past smoker, nonsmoker. Rank classification of alcohol consumption: no alcohol, ≦1 drink/wk, <1 drink/d, and >1 drink/d. No significant difference could be observed. BMI, body mass index.

fairly homogenously distributed between early-stage (CKD G2, $n=13$; 52%) and later-stage (CKD G3b+G4, $n=12$; 48%) CKD. More details specifically collected in the ADPKD cohort are provided in Table 1.

Alterations of the Gut Microbiome in Patients with ADPKD

First, no significant differences in α and β diversities could be determined between the ADPKD and control cohorts (Figure 1, A and B). However, detailed analysis of the bacterial amplicon sequence variants (ASVs) using the LDA revealed a significantly increased abundance of the bacterial order Enterobacterales and the family Enterobacteriaceae in patients with ADPKD. By contrast, the abundance of the phyla Tenericutes (specifically family of Anaeroplasmataceae) and Actinobacteria, including the families Bifidobacteriaceae and Actinomycetaceae, were significantly decreased in patients with ADPKD compared with healthy controls (Figure 1C). There was no significant correlation between these ASVs with potential confounding variables (salt intake, smoking, alcohol consumption, age, and body mass index; Table 2).

Because gut microbiome alterations have been reported upon CKD, we then investigated whether those findings could be specific for ADPKD or a consequence of CKD-associated eGFR decline. Linear regression analysis of significantly altered ASVs and eGFR revealed no significant association (Table 2). Furthermore, subgroup analysis of ADPKD patients with preserved kidney function (eGFR >60 ml/min per 1.73 m^2; eGFR >70 ml/min per 1.73 m^2) confirmed the increased abundance of the bacterial order of Enterobacterales and the family of Enterobacteriaceae compared with the healthy control cohort while no differences were detected for Tenericutes and Actinobacteria (Figure 1, D and E). Taken together, these data suggest specific alterations of the gut microbiome in patients with ADPKD.

Changes of Bacterial Abundance in Relation to Mayo Classification

Next, we analyzed bacterial ASVs in relation to determinants of disease progression in patients with ADPKD. Regarding the Mayo classification, the key imaging-based biomarker for disease progression in ADPKD, we grouped patients with ADPKD with Mayo 1A–1C as slow progressors and patients with Mayo 1D-1E as fast progressors. Most notably, patients with a predicted fast PKD disease progression showed significantly increased abundance of bacteria of the class Bacilli, with its order of Lactobacillales and family Streptococcaceae (Figure 2, A and B). These taxa did not correlate with kidney function (Supplemental Figure 2A). Further analyses of those ASVs in each separate Mayo class revealed a trend not reaching statistical significance with positive correlation of these ASVs with increasing Mayo class (Bacilli $P = 0.085$; Lactobacillales $P = 0.089$; Streptococcaceae $P = 0.070$; Figure 2C).

Early Onset of Arterial Hypertension is Associated with Microbiome Alterations

On the basis of these findings, we analyzed the association of microbiome alterations with additional markers of rapid disease progression such as early onset of arterial hypertension (<35 years of age).[12] Patients with ADPKD and early onset of arterial hypertension showed an increased abundance of the phylum Proteobacteria, specifically the α-proteobacteria with its order Rhodospirillales, as well as β-proteobacteriales with its family Burkholderiaceae (Figure 3, A and B). These findings were independent of kidney function (Supplemental Figure 2B). No significant differences in the gut microbiome signature could be detected between patients with and without early onset of urologic complications (data not shown).

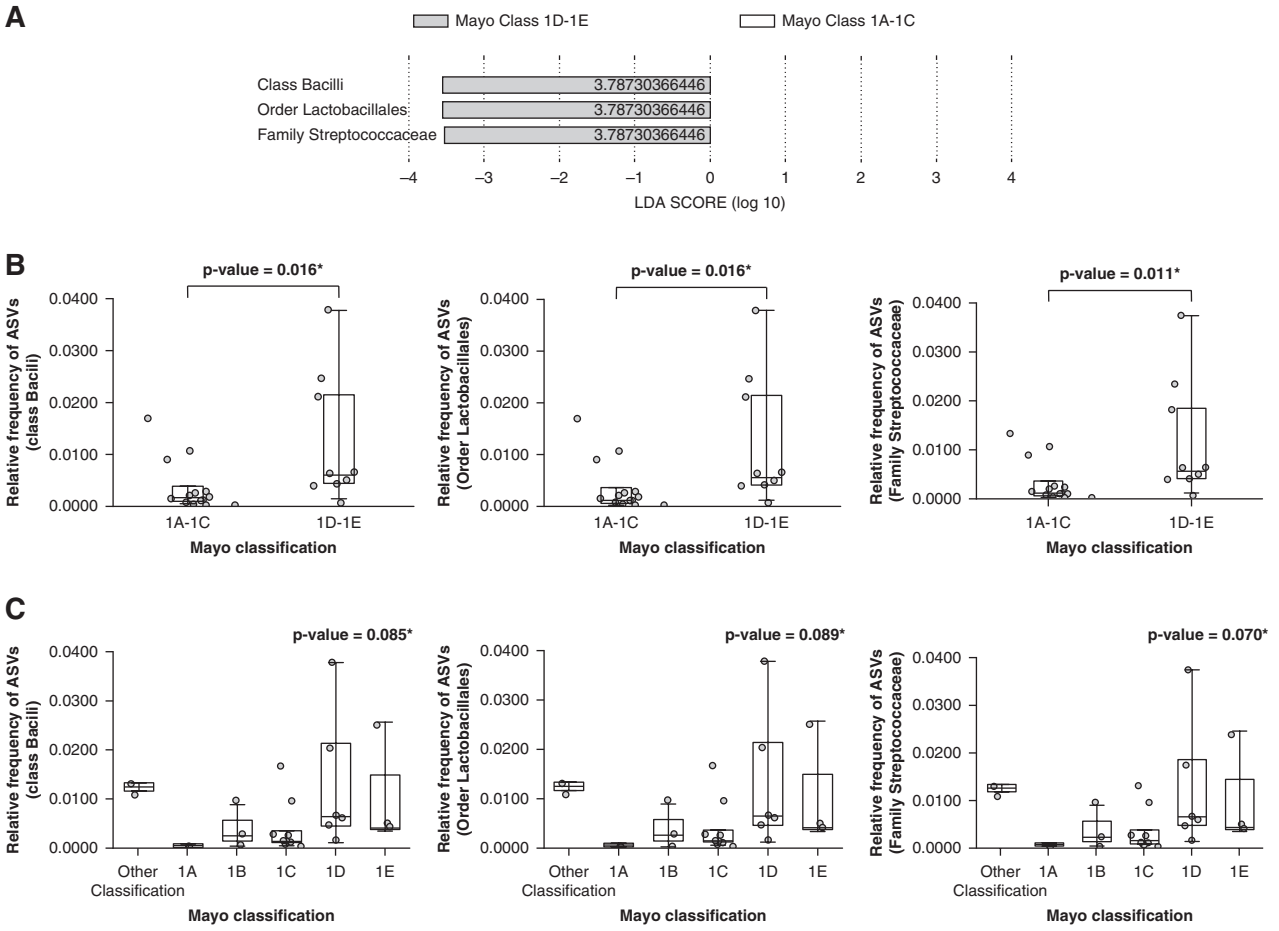

Figure 2. Correlation of ASVs with Mayo classification. (A and B) Patients with ADPKD were divided on the basis of Mayo class as a marker of ADPKD disease progression: Mayo class 1A–1C (n=14) versus 1D+1E (n=9). The ASV abundance was analyzed using the LEfSe algorithm and LDA score. Significant differences in abundance were observed for the class of Bacilii with its order of Lactobacillales and its family Streptococacceae. (C) Analysis of the ASV abundance of the class Bacilii, order Lactobacillales and family Streptococacceae upon separate Mayo Classes using a Kruskal-Wallis test. *P values refer to the entire test-model. "Other classification" displays patients with ADPKD where the Mayo classification could not be determined.

Abundance of Peptococcaceae Depends on Age and Kidney Function

Because ADPKD is characterized by a continuous loss of kidney function with increasing age, we analyzed potential changes of the gut microbiome in relation to age and kidney function.[1,5] Therefore, we divided the ADPKD cohort into two even subgroups by age (≤45 years of age, ≥50 years of age) and kidney function (≥60 ml/min per 1.73 m^2, ≤45 ml/min per 1.73 m^2). The analysis revealed an increased abundance of the bacterial families Peptococcaceae and Coriobacteriales in patients aged 50 years and older (Figure 4A). By contrast, in the control cohort, the abundance of Peptococcaceae was increased in the group of younger individuals (≤45 years; Supplemental Figure 2C).

No significant differences were found upon the separation by kidney function (data not shown). However, separating patients with ADPKD aged 50 years and older additionally by kidney function (≥60 ml/min per 1.73 m^2, ≤45 ml/min per 1.73 m^2), the LDA showed an increased abundance of Peptococcaceae exclusively for decreased kidney function ≤45 ml/min per 1.73 m^2 (Figure 4B), indicating a combined impact of age and declining kidney function on the abundance of Peptococcaceae. Performing a multiple linear regression analysis, we could confirm an increasing abundance of Peptococcaceae with increasing age and declining kidney function (Figure 4, C and D). Although having reached a significant result on the whole regression model (F=5343; P value 0.013, additional testing using robust structural equation modeling of the heteroskedasticity-consistent standard error 3), it has to be noted that the regression coefficient for eGFR did not reach significance (P value 0.057; Supplemental Tables 1 and 2).

sUTs in Patients with ADPKD

sUTs are generally cleared by the kidney but can accumulate upon decline of kidney function.[23] A distinctive

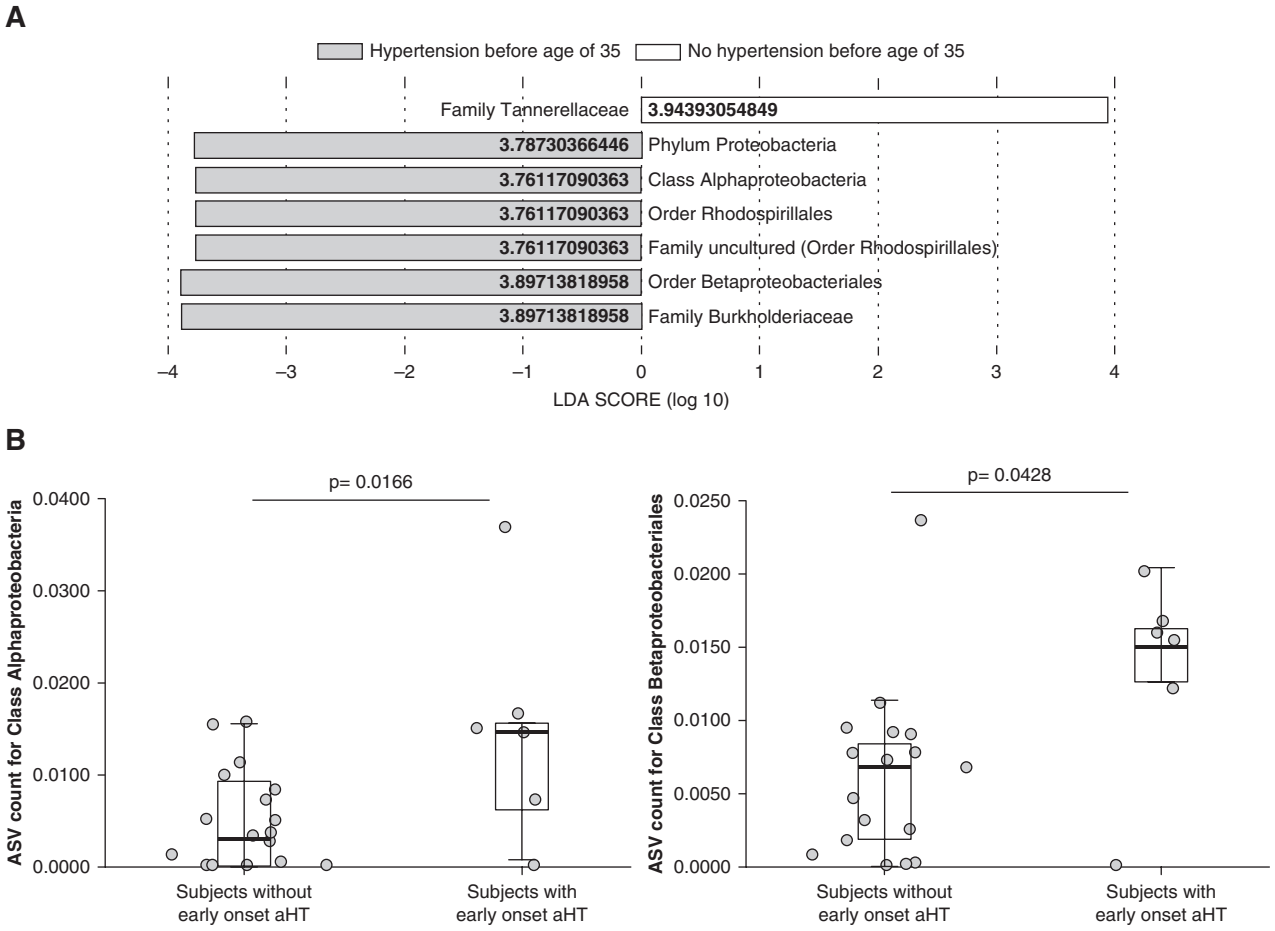

Figure 3. Correlation of ASVs with early onset of art. hypertension. (A) Analysis of ASV abundance in patients with ADPKD with and without early onset of art. hypertension (<35 years of age) using the LEfSe algorithm and LDA score. (B) Significant differences in abundance were observed for phylum α-proteobacteria and β-proteobacteria and analyzed by Mann–Whitney *U* test. aHT, arterial hypertension.

fraction of sUTs originates from the gut microbiota. This gut microbiota–derived fraction of sUT is predominantly found to be protein bound. These metabolites include IS, pCS, and TMAO.[10,24] Because we have found significant gut microbiome alteration upon ADPKD, we hypothesized that sUT could be altered in patients with ADPKD independent of kidney function. In this study, patients with ADPKD revealed significantly increased serum concentrations of total and free IS, pCS, and TMAO compared with the control cohort, indicating a significant increase in the protein-bound gut bacteria-derived fraction of sUTs (Figure 4E and Table 3). As expected, all sUTs positively correlated with eGFR decline (Table 4), but did not correlate with age, except for free pCS, which is probably due to the small cohort sizes (Table 4). In addition, sUTs did not correlate with markers of rapid PKD disease progression, including arterial hypertension, urologic complications, or Mayo classification (Table 4). However, analyzing the association of bacterial ASV signatures in ADPKD from our previous analyses with sUTs, we found a not-yet-significant tendency of positive correlation between the bacteria family Peptococcaceae with increased total serum IS and pCS levels (Supplemental Table 3).

Discussion

ADPKD represents a genetic kidney disease leading to CKD that requires frequent antibiotic treatment due to cyst infections.[1] Dietary modifications represent a cornerstone of disease management, which could in turn result in microbiome alterations.[5] However, so far there was just one uncontrolled pilot study indicating microbiome alterations in patients with ADPKD.[11]

In this study, we investigated the gut microbiome of patients with ADPKD compared with a control cohort. Although we did not find significant differences in α and β diversities—probably because of the small cohort size—patients with ADPKD showed a significantly higher abundance of bacteria from the Enterobacteriaceae family. Enterobacteriaceae include an array of potentially pathogenic species that directly affect the intestinal epithelial barrier and increase the permeability for uremic toxins, which can affect systemic inflammation and kidney function decline.[8,25–27] While Yacoub *et al.* did not detect changes in the abundance of Enterobacteriaceae,[11] a more recent study in patients with ADPKD reports increasing Enterobacteriaceae abundance upon kidney function decline as reported for CKD.[28,29] In our study, this finding appeared

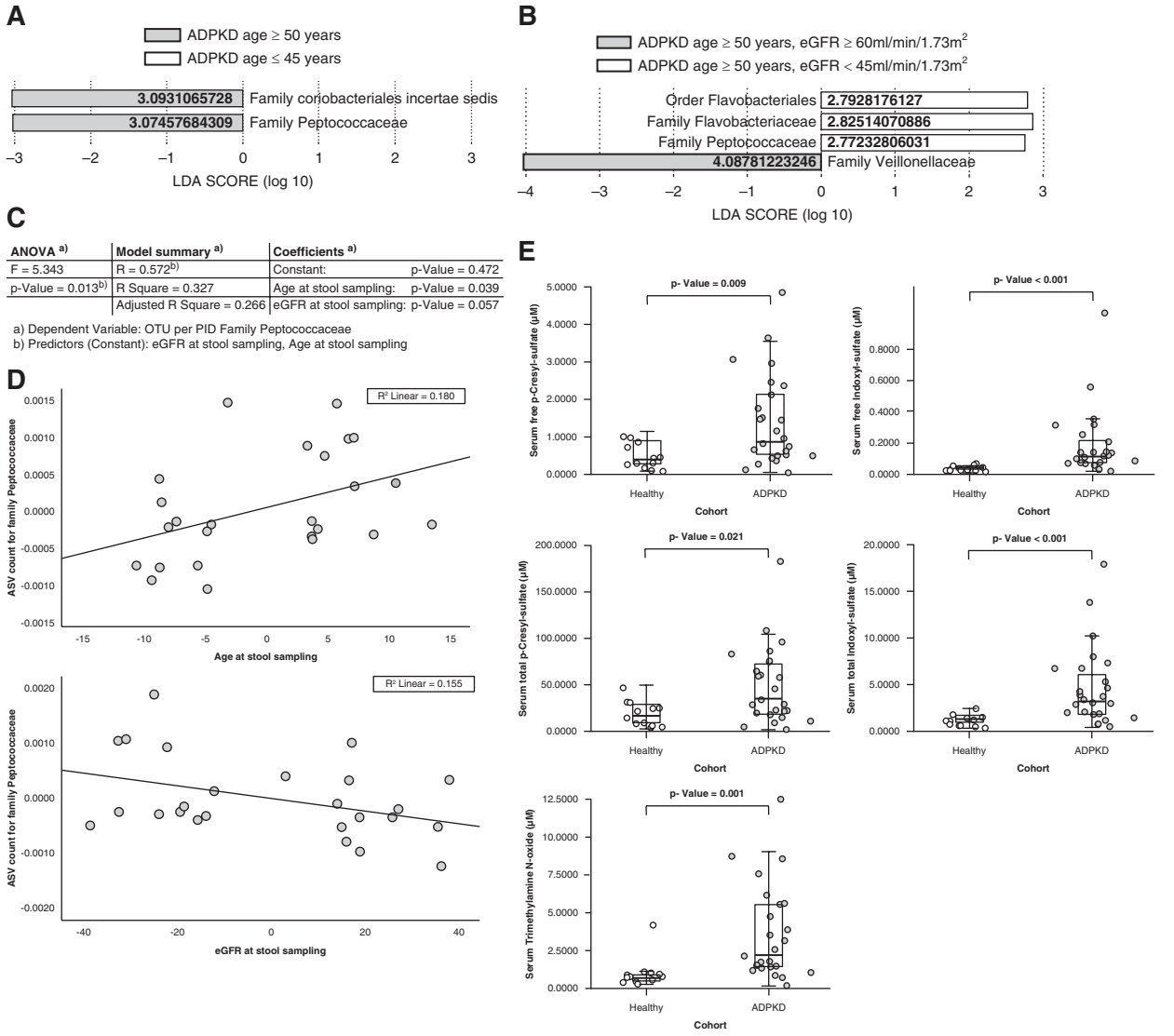

Figure 4. Correlation of ASVs with age and eGFR and analysis of sUT. (A) Patients with ADPKD were divided into two subgroups by age (≤45 years of age, ≥50 years of age) and ASV abundance were analyzed using the LEfSe algorithm and LDA score. (B) Patients with ADPKD were divided into subgroups by age (≤45 years of age, ≥50 years of age) and kidney function (≥60 ml/min per 1.73 m^2, ≤45 ml/min per 1.73 m^2) and ASV abundance were analyzed using the LEfSe algorithm and LDA score. (C) Key figures of the multiple linear regression analysis showing the relationship between the ASV count of the family Peptococcaceae in the gut microbiome of patients with ADPKD and the kidney function (eGFR) as well as the age at the time of stool sampling. The ANOVA states that the regression model as a whole is of significance (*P* value 0.013). The adjusted R^2 indicates that 26.6% of the total spread of ASV counts (Peptococcaceae) can be explained by the independent variables age and kidney function at the time of stool sampling. *t* Tests for the regression coefficients show that the constant and independent variable eGFR at stool sampling do not reach significance at the 95th confidence interval. (D) Partial regression plots depicting the linearity between the dependent variable ASV count of the family Peptococcaceae and the independent variables age at stool sampling and kidney function (eGFR) at stool sampling. The *y* axis provides the residues for the dependent variable ASV count of the family. The *x* axis provides the residues for the independent variables age at stool sampling or eGFR at stool sampling regressed to all other independent variables. (E) Analysis of sUT. Analyses of total and free sUT of healthy control and ADPKD cohort using mass spectrometry. pCS, IS and TMAO were measured as replicates and medians in micrometer were analyzed using a Mann–Whitney *U* test. IS, indoxylsulfate; pCS, p-cresyl-sulfate; sUT, serum uremic toxin; TMAO, trimethylamine *N*-oxide.

not to be associated with kidney function but potentially driven by ADPKD itself. Interestingly, patients with ADPKD display an increased prevalence for diverticulosis while polycystins are expressed in intestinal epithelial cells potentially affecting the intestinal epithelial barrier.[30–32] In line with this, it was recently reported that the intestinal barrier function declines with PKD disease progression in animal models.[33] Thus, a dysfunction of polycystins could directly affect the host–microbiome interaction and affect microbiome composition. Furthermore, patients with ADPKD revealed a significantly lower abundance of the phyla Actinobacteria, including the Bifidobacteriaceae family, which have been previously used as probiotics because of beneficial immunomodulatory and protective effects on

Table 3. Analysis of serum uremic toxins

sUTs as Median in μM (IQR)	Healthy Control Cohort	ADPKD Cohort	*P* Value
Total IS	1.181 (0.869)	3.251 (4.398)	<0.001
Free IS	0.037 (0.023)	0.108 (0.156)	<0.001
Total pCS	15.930 (22.190)	34.157 (57.426)	0.021
Free pCS	0.332 (0.668)	0.833 (1.746)	0.009
TMAO	0.834 (0.450)	2.186 (4.326)	0.001

Analyses of total and free serum uremic toxins of the healthy control and ADPKD cohorts using mass spectrometry. p-Cresyl-sulfate, indoxylsulfate, and trimethylamine *N*-oxide were measured as replicates, and the medians in micrometer were analyzed using a Mann–Whitney *U* test. ADPKD, autosomal polycystic kidney disease; IQR, interquartile range; IS, indoxylsulfate; pCS, p-cresyl-sulfate; sUT, serum uremic toxin; TMAO, trimethylamine *N*-oxide.

the epithelial intestinal barrier.[34–36] Although there was no association with eGFR in the linear regression model, subgroup analysis of patients with ADPKD with preserved kidney function indicated that this alteration in Actinobacteria could be driven by kidney function decline, and, thus, CKD.[37] Nonetheless, considering the limited size of the cohort, further studies will be needed to fully dissect eGFR dependency of this finding.

Furthermore, we also observed an increased abundance of the family Peptococcaceae associated with increasing age, which is in line with previous reports.[38] However, our findings are limited to patients with ADPKD with ≤45 ml/min per 1.73 m^2, suggesting a potentially combined impact of age and kidney function on the abundance of Peptococcaceae. Further investigations in larger cohorts will need to elucidate this colinear association. Although Yacoub *et al.* described changes in the abundance of ten ASVs upon eGFR decline in patients with ADPKD, no changes in the abundance of Peptococcaceae were reported. These differences could be explained by the significantly different study design. While our ADPKD patient cohort was equally distributed for age, eGFR, and Mayo classification and was compared with an age- and sex-matched control group, the study cohort of Yacoub *et al.* was uncontrolled and the unmatched subcohorts displayed highly advanced CKD, with one third being on hemodialysis and one third displaying a median eGFR of around 33 ml/min per 1.73 m^2. Thus, the lack of a control cohort and the effect of hemodialysis and highly variable serum urea concentrations could have affected their findings.[7,9]

Most notably, our study investigated the potential association of gut microbiota signatures with markers of ADPKD disease progression, an analysis which is lacking in previous approaches.[11,28] We observed a significant increased abundance of the bacterial class Bacilli, specifically from the order Lactobacillales and Streptococcaceae family in patients categorized into Mayo classes 1D and 1E (compared with Mayo classes 1A–C), which characterizes rapid

Table 4. Correlation analysis of serum uremic toxins with eGFR, age, and marker rapid ADPKD disease progression

Serum Uremic Toxins	eGFR	Age		Art. Hypertension <35 yr of Age	Urologic Complications <35 yr of Age	Mayo Classification
	ADPKD	Healthy	ADPKD	ADPKD	ADPKD	ADPKD
Total IS	F=35.304	r_s=0.021	r_s=0.191	U=73,000	U=41,000	U=61,000
	P = >0.001	*P* = 0.948	*P* = 0.361	*P* = 0.333	*P* = 0.575	*P* = 0.926
Free IS	F=18.266	r_s=0.21	r_s=0.354	U=67,000	U=41,000	U=61,000
	P = <0.05	*P* = 0.948	*P* = 0.082	*P* = 0.555	*P* = 0.575	*P* = 0.926
Total pCS	F=18.694	r_s=0.503	r_s=0.312	U=72,000	U=40,000	U=53,000
	P = <0.01	*P* = 0.095	*P* = 0.129	*P* = 0.366	*P* = 0.530	*P* = 0.557
Free pCS	F=17.679	r_s=0.566	r_s=0.445	U=68,000	U=39,000	U=52,000
	P = <0.01	*P* = 0.055	*P* = 0.026	*P* = 0.514	*P* = 0.488	*P* = 0.516
TMAO	F=26.436	r_s=0.308	r_s=0.136	U=75,000	U=54,000	U=67,000
	P = <0.001	*P* = 0.331	*P* = 0.517	*P* = 0.274	*P* = 0.818	*P* = 0.829

eGFR: simple linear regression analysis of eGFR and serum uremic toxins in the ADPKD cohort.
Age: two-tailed Spearman correlation analysis of age and serum uremic toxins in the healthy control and ADPKD cohort.
Art. hypertension <35 years of age: analysis of serum uremic toxins in patients with ADPKD with and without early onset of art. hypertension using the Mann–Whitney *U* test.
Urologic complications <35 years of age: analysis of serum uremic toxins in patients ADPKD with and without early onset of urologic complications using the Mann–Whitney *U* test. Mayo classification: analysis of serum uremic toxins in patients with ADPKD with Mayo class 1D+E compared with patients with Mayo class 1A–C using the Mann–Whitney *U* test. Art. hypertension, arterial hypertension; ADPKD, autosomal polycystic kidney disease; IS, indoxylsulfate; pCS, p-cresylsulfate; TMAO, trimethylamine N-oxide.

progression of ADPKD.[39] Taken together, our data indicate a clear correlative trend of specific ASVs upon Mayo classes but further investigation in larger patient cohorts is warranted.

In addition, we investigated further risk factors that have been previously used to predict the individual risk of rapid disease progression (predicting renal outcome in PKD-Score), including early onset of arterial hypertension or urologic complications.[12] We observed a significant increase of the phylum Proteobacteria in ADPKD patients with early onset of arterial hypertension, while the family Tannerelleaceae was decreased. This is consistent with previous microbiome studies of patients with arterial hypertension.[40,41] It, however, remains to be elucidated whether those microbial alterations cause early onset of arterial hypertension or are the consequence of it. By contrast, no association between gut microbiota composition and urologic complications has been found, which might be due to the underrepresentation of patients with urologic complications ($N=5$). However, changes in gut microbiota signatures seems to be associated with recurrent urinary tract infections and nephrolithiasis.[42–44] Several studies have recently identified a network of gut bacteria that metabolize oxalate (including *Oxalobacter formigenes* and *Bifidobacterium lacti*) and uric acid (*Clostridium cylindrosporum* and *Faecalibacterium spp.*) facilitating kidney stone formation.[42,45,46] Nephrolithiasis is more prevalent in patients with ADPKD, but the reason for this still remains unknown.[47] It seems reasonable that changes in the gut microbiota signature, *e.g.*, by changes in oxalate metabolism,[42,45,46] affect nephrolithiasis in ADPKD, which in turn drives ADPKD disease progression. This needs to be investigated in larger cohorts in the future. Taken together, our data suggest a shift toward an unfavorable intestinal colonization in patients with ADPKD that seems to be associated with markers of rapid ADPKD disease progression.

Finally, we investigated sUTs in patients with ADPKD and could identify significantly increased concentrations of protein-bound IS, pCS, and TMAO, which predominantly originate from gut bacteria.[10] sUT levels were correlated with eGFR decline, as expected, but not with markers of rapid ADPKD disease progression, suggesting that sUT accumulation in ADPKD is mainly driven by eGFR decline. A first trend of positive correlation between the abundance of Peptococcaceae with total IS and pCS serum levels, however, suggests an association of gut microbiota signatures with increasing sUT levels. Because sUT is associated with cardiovascular events and overall mortality,[10,24,48,49] sUTs could also be involved in the increased risk of cardiovascular disease in patients with ADPKD. Prospective analyses are warranted to elucidate the potential impact of sUTs on extrarenal cardiovascular events and PKD disease progression.

Our study has several limitations. Beside the small cohort size, stool and serum samples were analyzed just at one time point and were collected with a median average time difference of around 10 days facilitating the chance of discrepancies between the results. Data on anti-infective treatment, diets, drugs, or other preexisting diseases were limited in this study but could have affected our results. This study did not include a CKD control cohort. However, the results of the linear regression model as well as a subgroup analysis of ADPKD patients with well-preserved kidney function indicate gut microbiome alterations, which may indeed be independent from kidney function and thus specific to ADPKD.

In conclusion, and taking these limitations into account, our study reveals for the first time a shift in the gut microbiome composition in patients with ADPKD compared with a healthy control cohort, which could affect ADPKD disease progression. This represents a significant advancement in elucidating the potential impact of microbiome composition in ADPKD. ADPKD is characterized by a high inter- and intrafamiliar variability of disease progression that is not explained by genotype, but considered to be mediated by environmental effects.[4] Our findings suggest that gut microbiome signatures might be a previously unrecognized disease-modifying factor. It remains unknown whether changes in the gut microbiota composition are primarily associated with ADPKD because of potential polycystin-1/polycystin-2 mutations in intestinal epithelial cells or are the consequence of other risk factors associated with or treatments prescribed to improve ADPKD.[30] Especially antibiotics are frequently prescribed to patients with ADPKD because of frequent urinary tract and cyst infections. Further investigations in larger ADPKD patient cohorts will be necessary to untangle these associations. If proven correct, these results could lead to new, feasible, and cost-effective treatment options in ADPKD through well-established probiotic or dietary interventions.

Disclosures

Disclosure forms, as provided by each author, are available with the online version of the article at http://links.lww.com/KN9/B86.

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Data Sharing Statement

Partial restrictions to the data and/or materials apply. The data that support the findings of this study are available on request from the corresponding author.

Supplemental Material

This article contains the following supplemental material online at http://links.lww.com/KN9/B87, http://links.lww.com/KN9/B88.

Supplemental Figure 1. Study flow chart.

Supplemental Figure 2. Correlation analysis of kidney function and ASVs.

Supplemental Table 1. Multiple regression statistics for the effect of age and kidney function on the abundance of Peptococcaceae in patients with ADPKD.

Supplemental Table 2. Multiple regression statistics for the effect of age and kidney function on the abundance of Peptococcaceae in patients with ADPKD.

Supplemental Table 3. Correlation analysis of sUTs with ASVs.

Supplemental Methods

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