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Interaction Between Determinants Governing Urine Volume in Patients With ADPKD on Tolvaptan and its Impact on Quality of Life

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Introduction: Autosomal dominant polycystic kidney disease (ADPKD) is the most prevalent genetic cause of kidney failure. Tolvaptan, a vasopressin 2 receptor antagonist, is the first drug with proven disease-modifying activity. Long-term treatment adherence is crucial, but a considerable fraction of patients discontinue treatment, because of aquaretic side effects.

Methods: Twenty-four-hour urine was collected in 75 patients with ADPKD during up-titration of tolvaptan and, in combination with clinical characteristics, examined to identify factors influencing urine volume. Patient-reported outcomes were analyzed using the Short Form-12 (SF-12) and patient-reported outcomes questionnaires reporting micturition frequency and burden of urine volume.

Results: Initiation of therapy led to a large increase in urine volume followed by only minor further increase during up-dosing. Younger patients and patients with better kidney function experienced a larger relative rise. Twenty-four-hour urine osmolality dropped by about 50% after therapy initiation independently of dose, with a considerable proportion of patients achieving adequate suppression. Sodium and potassium intake turned out to be the only significant modifiable factors for urine volume after multivariate linear regression models, whereas age and weight could be identified as non-modifiable factors. No change in quality of life (QoL) was detected in relation to treatment or urine volume using SF-12 questionnaires, a finding that was further supported by the results of the patient-reported outcomes assessment.

Conclusion: This study provides an in-detail analysis of factors associated with the degree of polyuria on tolvaptan and puts them into the context of QoL. These findings will contribute to optimized patient counseling regarding this treatment option in ADPKD.

Kidney Int Rep (2023) **8,** 1616–1626; https://doi.org/10.1016/j.ekir.2023.05.011
KEYWORDS: ADPKD; dose; osmolality; quality of life; tolvaptan; urine volume

ADPKD is a hereditary disease characterized by cysts mainly involving the kidneys and the liver. Cyst formation in the kidney leads to kidney failure requiring kidney replacement therapy in the majority of patients.[1] For decades, the treatment of ADPKD was restricted to dialysis and transplantation, in addition to the management of symptoms and comorbidities as well as the optimization of risk factors to slow the loss of kidney function: Treatment of arterial hypertension, avoidance of obesity,[2] antibiotic treatment of urinary tract and cystic infections, salt restriction, and appropriate hydration.[3,4] Currently, the vasopressin 2 receptor antagonist, tolvaptan is the only approved drug that has demonstrated a beneficial effect on total kidney volume expansion and estimated glomerular

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Received 9 March 2023; revised 4 May 2023; accepted 15 May 2023; published online 20 May 2023

filtration rate (eGFR) decline, thereby slowing disease progression.[5] Aquaretic adverse effects (polyuria, nocturia, thirst, pollakiuria, and polydipsia) generated by the mechanism of action of tolvaptan are a common reason for treatment cessation or inadequate up-dosing.[5,6] Approximately 10% of patients discontinued treatment in Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and its Outcomes (TEMPO) 3:4 because of polyuria, nocturia, and pollakiuria.[5,7] Although one study showed osmolar excretion as a primary predictor of 24-hour urine volume during tolvaptan therapy,[8] another one demonstrated only GFR as a factor modifying 24-hour urine volume, but this also included a small number of patients.[9] Although previous data showed decrease of QoL in patients with ADPKD,[10] comparatively few data exist on this patient-relevant issue during tolvaptan therapy.[11,12] Consequently, the goal of this study was to analyze the development of 24-hour urine volumes and osmolality during tolvaptan up-dosing at all 3 dose steps, and to compare them to volumes before therapy. In addition, we aimed to investigate and identify factors that can mitigate aquaretic adverse effects to increase acceptance of the therapy and long-term adherence, as well as determine the effect of urine volume on QoL.

METHODS

Study Population and Study Design

In this cohort study, clinical data of 75 adult (≥ 18 years) patients with ADPKD enrolled in the German AD(H)PKD registry was analyzed. The AD(H)PKD study enrolls adult patients with ADPKD who present themselves for evaluation of tolvaptan therapy. Patient data were documented longitudinally and included clinical, genetic, and laboratory parameters, as well as radiological examinations, to determine renal volume. Data collection from this cohort was approved by the local institutional review board of the University of Cologne, and written informed consent was obtained from all study participants. The study is registered on clinicaltrials.gov (NCT02497521). The cohort study is conducted following the Declaration of Helsinki and the good clinical practice guidelines by the International Conference on Harmonization.

For the subcohort described here, inclusion criteria contained the diagnosis of ADPKD and indication for tolvaptan treatment, the typical renal phenotype of ADPKD (Mayo class 1)[13] and availability of 24-hour urine collection in the up-dosing phase of tolvaptan.

Patients who started treatment were asked to collect 24-hour urine volume, spontaneous urine as a first void urine (spot urine), and spontaneous urine 4 hours after tolvaptan intake (spot urine 4h). Large-volume urine collection containers (up to 16 l) were used to collect urine for 24 hours, and samples were sent to the center at room temperature after being collected once at the start of each dose.

Sodium and potassium intake were calculated from sodium and potassium excretion in 24-hour urine. Protein intake was estimated from urea excretion according to the method described by Maroni *et al.*[14] and Masud *et al.*[15] QoL was assessed using the SF-12 questionnaire[16] and an interim patient-related outcomes questionnaire containing questions about miction frequency and the tolerability of urine volume on tolvaptan therapy was used to describe burden of aquaretic side effects. Questions concerning miction frequency describe miction episodes during the day and night, and responses to the question about if the amount of urine volume is assessed as a burden have been used. Neither questionnaire was administered during the up-titration phase, and the most recent evaluation of sample asservation was utilized.

Statistical Analyses

Statistical analyses were computed with the rstatix R package version 0.7.0[17] using the R statistical software version 4.2.0 (2022-04-22 ucrt)[18] running under Windows 10 × 64 (build 19044). A P-value of <0.05 was generally regarded as significant, with the following significance levels: * (<0.05), ** (<0.01), *** (<0.001), **** (<0.0001). Missing data were excluded from the analysis. If not indicated otherwise, the normality of the data was examined using the Shapiro-Wilk test, and equality of variance was tested using Levene's test. Depending on the normality, equality of variance, and number of tested groups, the following statistical tests were performed: 2-sample paired or unpaired t-test (normally distributed, equal variance, 2 groups) or Welch's t-test (normally distributed, unequal variance, 2 groups), 2-sample Mann-Whitney or Wilcoxon rank sum test (non-normally distributed, 2 groups), Tukey Honest Significant Differences (normally distributed, equal variance, >2 groups), Games-Howell test (normally distributed, unequal variance, >2 groups) or Dunn's Test of Multiple Comparisons (non-normally distributed, >2 groups). When applicable, P-values were adjusted for multiple comparisons using the "holm" adjustment method,[19] Cohen's d and Wilcoxon r effect sizes were computed using the respective functions in rstatix. For assessing the significance of the number of patients reaching the osmolality goal, the pairwise Fisher's exact test was used. Correlation tests were performed using the Pearson (normally

distributed) or Spearman (non-normally distributed) method. All statistical output values can be found in Supplementary Table S1.

Data Presentation

Data analysis and plotting were primarily performed using tidyverse R packages.[20] The R packages used and their version numbers are indicated in Supplementary Table S2. The frequently used raincloud plots depict raw data as jittered points, statistical inference as boxplot, and probability distribution as split-half violin plots.

RESULTS

Study Population

Large-volume urine collection containers and additional materials for the specimen asservation were sent to a total of 98 patients with ADPKD who were enrolled in the German AD(H)PKD registry and who started tolvaptan between January 2016 and October 2021. Urine samples were intended to be collected at baseline (0 mg) and once for each tolvaptan dose (45/15 mg, 60/30 mg, 90/30 mg). 75 patients returned at least one 24-hour urine collection while on tolvaptan ("complete cohort"). Specifically, 11 patients returned 1 sample, 19 patients returned 2 samples, and 45 patients returned samples at all 3 dose steps. Complete data for baseline, as well as all 3 tolvaptan doses, were available for 35 patients ("longitudinal cohort"). A summary of the study population is presented in Figure 1.

The baseline characteristics of both cohorts are summarized in Table 1. The mean age of the complete cohort was 41.33 ± 10.74 (range 18–64 years) with a mean eGFR of 67.36 ± 27.29 ml/min per 1.73 m^2. Kidney magnetic resonance imaging was available for 73 patients. The longitudinal cohort showed a comparable mean age of 41.83 ± 10.15 (range 23–64 years) with a mean eGFR of 69.48 ± 27.57 ml/min per 1.73 m^2.

As expected, a significant increase in 24-hour urine volume was observed in the complete cohort between baseline (0 mg) and all tested tolvaptan doses, with a mean increase of 138% between 0 mg and 45/15 mg (Figure 2a). However, no further significant increase was observed between the different tolvaptan dosing steps for the complete cohort (Supplementary Figure S1a). As urine volume increased on tolvaptan treatment, a concomitant mean reduction of 57% in 24-hour urine osmolality was measured between 0 mg and 45/15 mg (Figure 2b), whereas the differences in osmolality between the 3 up-dosing steps were not significant. Overall, we found no significant changes in total intake of osmoles or dietary parameters such as protein and sodium intake across all dosing levels

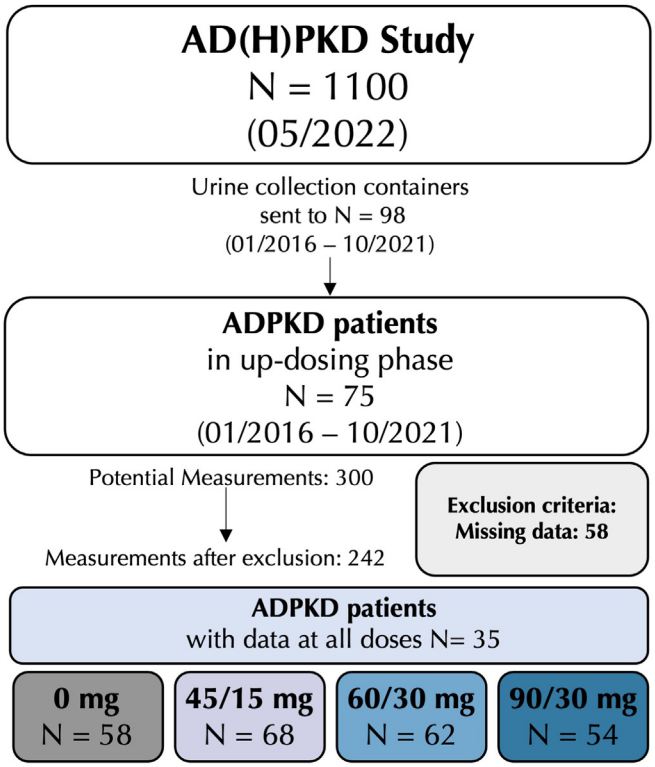

Figure 1. Study flow chart. Study flow chart depicting patient flow, exclusion criteria, and subgroup analyses. ADPKD, autosomal dominant polycystic kidney disease

(Figure 2c, and Figure 3a and b). When investigating the impact of non-modifiable factors on absolute urine volume, no significant differences were found at any dose of tolvaptan for either gender, age (<45 vs. ≥45 years), or between Mayo classes (Figures 3c–e). In

Table 1. Baseline characteristics of the ADPKD cohort

Parameter	Complete cohort	Longitudinal cohort
n, (men [%])	75, (42.67%)	35, (45.71%)
Age (yr), mean ± SD	41.33 ± 10.74	41.83 ± 10.15
Weight (kg), mean ± SD	81.08 ± 17.96	78.86 ± 17.56
eGFR (ml/min per 1.73 m^2), mean ± SD	67.36 ± 27.29	69.48 ± 27.57
TKV (ml), mean ± SD	2182 ± 2212	2655 ± 3024
htTKV (ml/m), mean ± SD	1220 ± 1196	1477 ± 1630
Mayo Classification at baseline, n	73	34
1A	-	-
1B	8	4
1C	25	7
1D	30	16
1E	10	7
CKD stage at baseline, n	75	35
1 eGFR >90 ml/min per 1.73 m^2	19	8
2 eGFR 60–89 ml/min per 1.73 m^2	18	12
3a eGFR 45–59 ml/min per 1.73 m^2	20	8
3b eGFR 30–44 ml/min per 1.73 m^2	15	7
4 eGFR 15–29 ml/min per 1.73 m^2	3	-
5 eGFR <15 ml/min per 1.73 m^2	-	-

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; htTKV, height-adjusted total kidney volume.

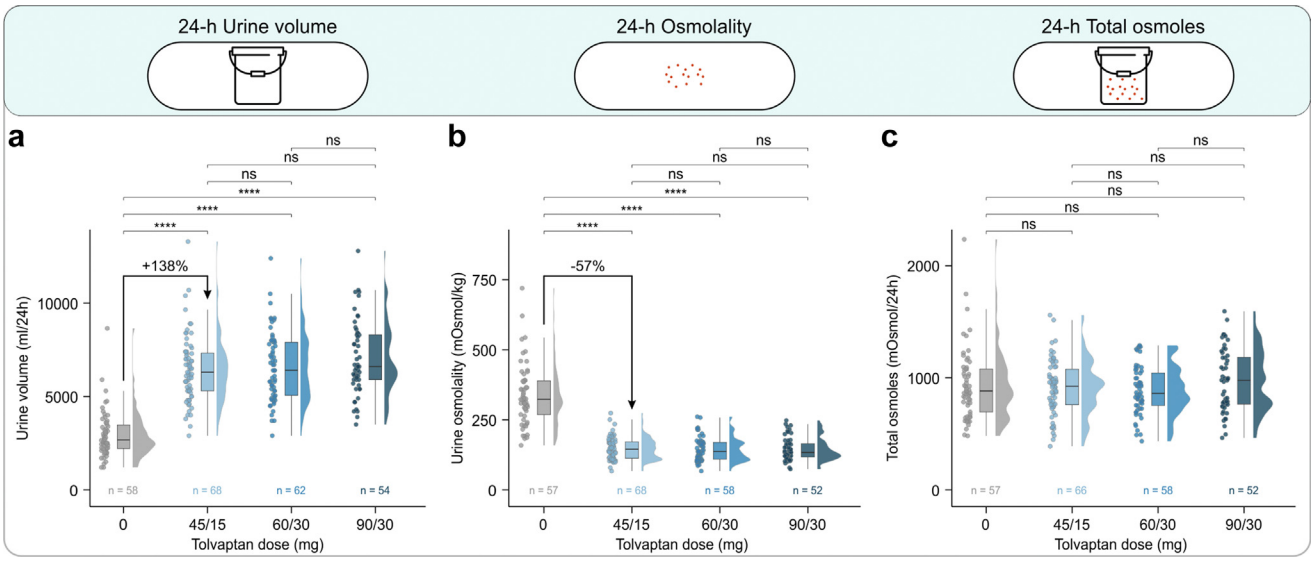

Figure 2. Urine parameters among different Tolvaptan dosing steps. 24-hour urine volume (a), urine osmolality (b) and total daily intake of osmoles (c). Details concerning the statistical tests can be found in Supplementary Table S1.

tolvaptan-naïve patients, 24-hour urine volume and eGFR did not correlate; however, a positive association was reported for all dosages, with 45/15 mg ($P = 0.013$) and 90/30 mg ($P = 0.027$) being significant (Figure 3f). When examining the relative urine volume increase between 0 mg and 45/15 mg, younger patients (<45 years) or patients with better kidney function (eGFR ≥60 ml/min per 1.73 m^2) showed a significantly higher urine volume increase, although the effect sizes were small or moderate, respectively (Supplementary Figure S1b and c). Male patients had a higher osmolality at all tested tolvaptan doses, but this difference was only statistically significant at doses 45/15 mg and 60/30 mg (Supplementary Figure S1d). In addition, a positive correlation was observed between urine osmolality and weight, as well as sodium intake and weight, at all tested tolvaptan doses (Supplementary Figure S1e and f). Furthermore, no effect of tolvaptan on blood pressure was found (Supplementary Figure S2).

All patients from the longitudinal cohort, for whom data at all dosage levels were available, were evaluated for their dose-dependent relative urine volume increase on tolvaptan treatment (Figure 4). As observed in the complete cohort, the greatest increase in urine volume occurred between 0 mg and 45/15 mg (Figure 4a), whereas higher tolvaptan doses resulted in less substantial further increases in urine volume. When examining each patient individually, the same trend was observed for total urine volume (Figure 4b), with a corresponding decrease in urine osmolality. Comparing the lowest (45/15 mg) to the highest (90/30 mg) tolvaptan dose, we set an arbitrary goal of ≥1000 ml urine volume increase and increase of ≥20% to identify individuals for whom the up-titration may have relevant consequences as well as additional factors that may influence a greater urine volume increase in a subset of patients. Of the patients, 13 of 35 showed this relevant increase in urine volume (Supplementary Figure S3a). Several significantly different parameters were found when comparing the groups with or without the relevant urine volume increase, such as sodium, total intake of osmoles, and protein intake (Supplementary Figure S4). In addition, the patients with more urine volume increase showed a higher phosphate and uric acid excretion. However, when investigating the longitudinal cohort, the relative increase in urine volume did not change significantly between tolvaptan doses (Supplementary Figure S3b). On the contrary, only 2 patients had a decrease of more than 1 l urine volume.

Using data from the longitudinal cohort, we reevaluated the effect of age and eGFR on the percent increase in urine volume on initiating tolvaptan treatment (0 mg to 45/15 mg). Whereas patients with higher eGFR still exhibited significantly more pronounced urine volume increases, the difference between age groups was not statistically significant anymore (Supplementary Figure S3c and d). Interestingly, younger patients (<45 years) appeared to be divided into 2 subgroups regarding their urine volume response. A relative urine volume increase of larger or smaller than 100% appeared to be a good cut-off to separate these groups (Supplementary Figure S3c). Those 2 subgroups were investigated in more detail to assess whether other general or urine parameters could explain the observed differential urine volume response (Supplementary Figure S5a).

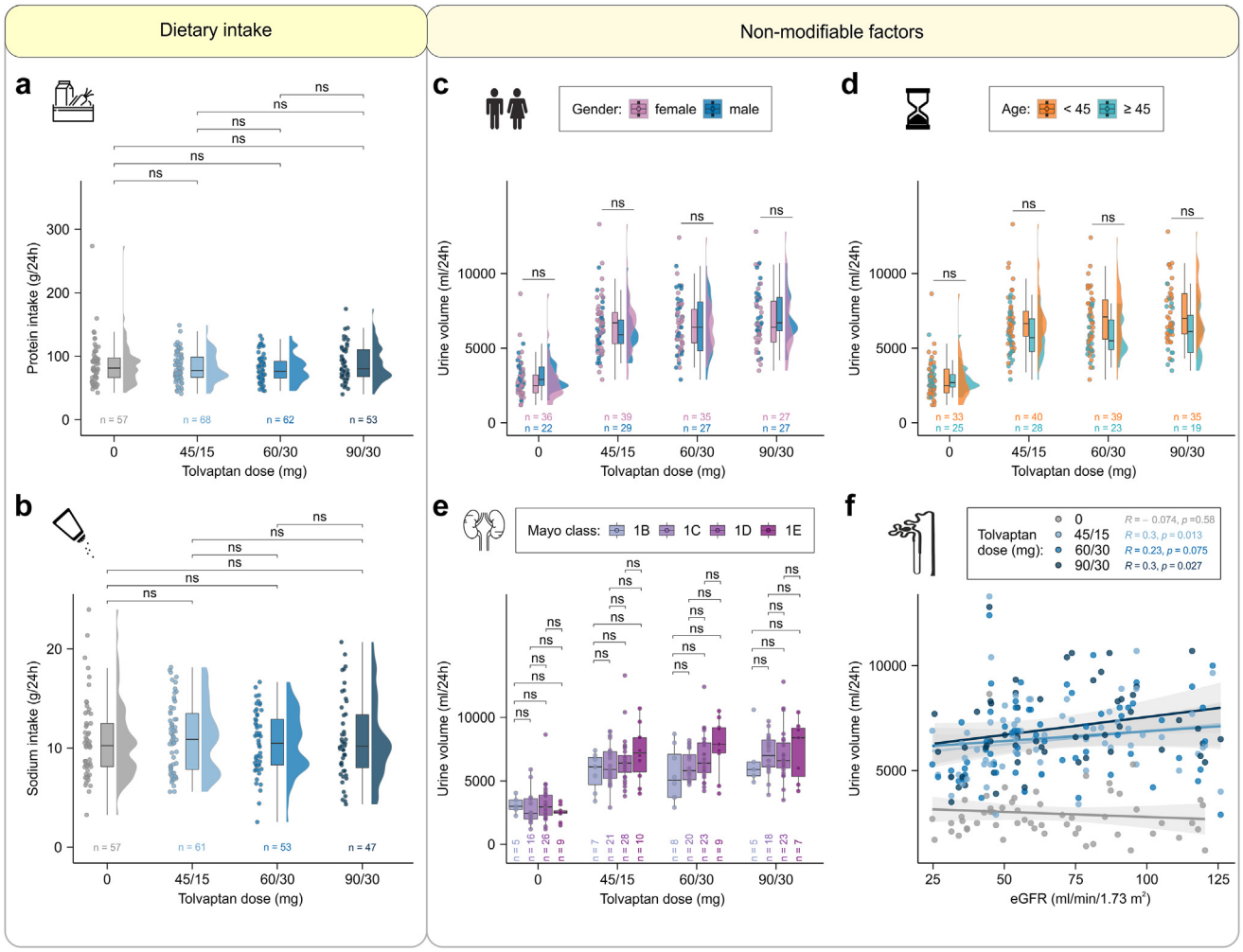

Figure 3. Dietary intake and non-modifiable factors among different tolvaptan dosing steps. (a) daily protein intake (b) daily sodium intake (c) 24-hour urine volume among genders (d) 24-hour urine volume between 2 age groups (<45 vs. ≥45 years of age) (e) 24-hour urine volume among Mayo classes (f) Spearman correlation of 24-hour urine volume with eGFR. Details concerning the statistical tests can be found in Supplementary Table S1.

Younger age, a higher eGFR, a shorter stature, or a higher sodium intake were significantly associated with a greater percentage urine volume increase (Supplementary Figure S5a–e). In light of the significant decrease in osmolality as a result of tolvaptan treatment, we asked how many patients in the longitudinal cohort achieved predefined osmolality targets with each tolvaptan dose. To this end, we set a goal of 150 mosmol/kg for 24-hour urine collection, in analogy to previous studies[8,9] and of <250 mosmol/kg in the morning spontaneous urine, values that most patients reached in TEMPO 3:4[5] (Supplementary Figure S6a–c). Whereas osmolality data was readily available for 24-hour urine collection, only fewer spot and no spot urine 4-hour collections had been examined from tolvaptan-naïve patients (0 mg). In both 24-hour and spot urine osmolality, a numerically greater number of patients met the target when the dose was increased; however, Fisher's exact test revealed no statistical significance (Supplementary Figure S6d–f, Supplementary Table S1).

To further elucidate which factors may explain the degree of increase in 24-hour urine volume we applied a series of linear regression models. To explore this question, we tested all factors using univariate analyses for the complete cohort (Supplementary Table S3). This revealed a highly significant correlation of 24-hour urine volume with urine osmolality, total intake of osmoles, sodium, and potassium intake as well as protein intake in tolvaptan-naïve patients and patients on tolvaptan. Whereas age, weight, and eGFR were identified as significant factors when examining patients on tolvaptan, gender and height-adjusted total kidney volume had no significant impact. We further performed multivariable linear regression analyses to identify independent associations of the significant factors with 24-hour urine volume (Supplementary Table S4).

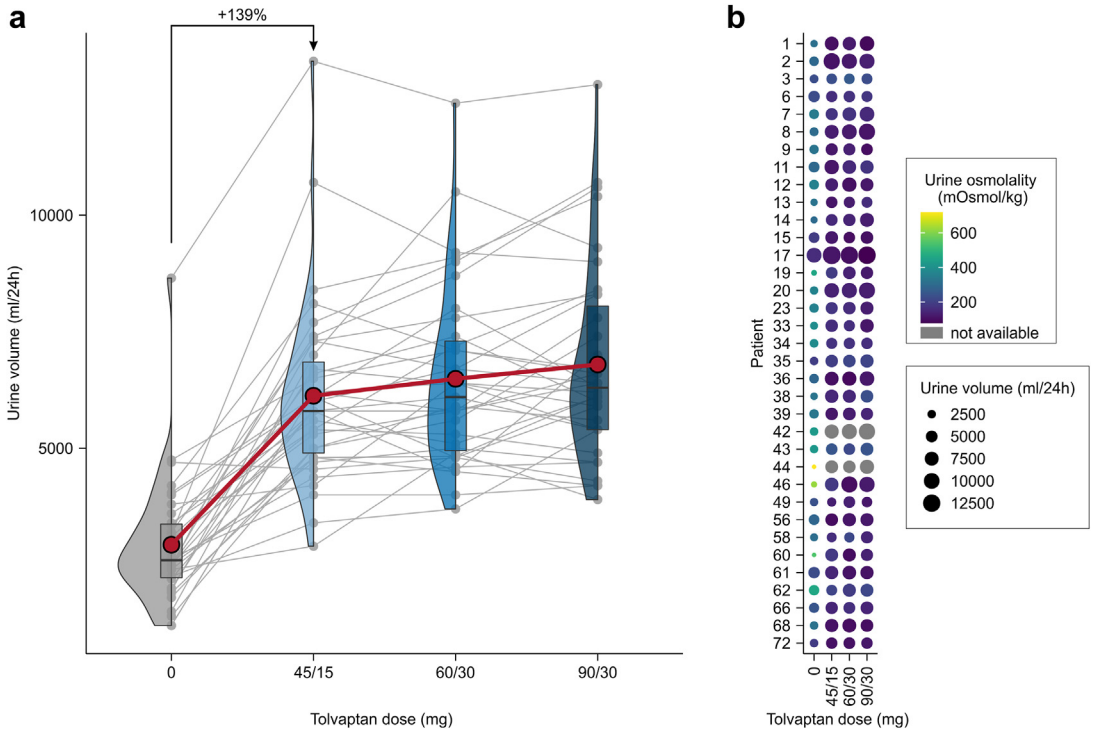

Figure 4. Longitudinal assessment of 24-hour urine collection in response to Tolvaptan dosing steps. Longitudinal development of 24-hour urine collection ($n = 35$) across different tolvaptan dosing steps (a) and per individual patient in relation to osmolality (b). The mean volume is indicated by the red line in (a). The gray color in (b) indicates that no data were available for osmolality.

Using various models, the entire cohort was further analyzed in terms of modifiable and non-modifiable factors. In model I, which contained the non-modifiable factors gender, age, kidney function, and height-adjusted total kidney volume, none of the evaluated parameters were significant. This was validated by measuring the urine volume of patients with ADPKD on 90/30 mg of tolvaptan (model II). When assessing modifiable factors in a second approach (model III), sodium intake was discovered as a significant factor in tested patients with ADPKD with ($P = 0.0097$) and without ($P = 0.0015$) tolvaptan for the estimation of 24-hour urine volume, although potassium and protein intake were not significant. In the complete model combining both non-modifiable (gender, age, eGFR, height-adjusted total kidney volume), and modifiable covariates, only sodium intake was significant for tolvaptan-naïve patients ($P = 0.0064$, model V). When the same model was applied to patients with ADPKD who were using tolvaptan (model VI), sodium intake remained significant ($P = 0.0008$) whereas age ($P = 0.0008$), weight ($P = 0.0190$), and potassium intake ($P = 0.0040$) gained significance.

Furthermore, QoL was assessed using (SF-12) questionnaires and micturition frequency on the basis of a patient-reported outcomes questionnaire (Figure 5 and Supplementary Figure S7a). No significant changes were found for either the mental or physical SF-12 score for patients with ADPKD before and on tolvaptan (Figure 5a and b). In addition, no significant correlation between 24-hour urine volume and mental or physical SF-12 score could be found (Figure 5c and d). When individually exploring self-assessment of stress because of urine volume in relation to patient micturition frequency and proportion of nocturia, the frequency of micturition did not prove to influence stress levels significantly (Supplementary Figure S7b).

DISCUSSION

Tolvaptan is a vasopressin 2 receptor antagonist that can slow the progression of kidney function loss in ADPKD.[5] However, therapy-related side effects are responsible for up to 23% of discontinuation, with aquaretic side effects being the most common (up to 10%).[22,23] Importantly, many patients do not even start the therapy because of concerns about polyuria. Consequently, optimal patient counseling on the basis of data is crucial when considering tolvaptan. Although pharmacokinetic and pharmacodynamic studies evaluated 24-hour urine output after a single dose or lower doses of tolvaptan, there was no 24-hour urine volume preservation in the most important studies.[6,7] Until now, only 2 small studies (including 27 and 18 patients respectively) have investigated the

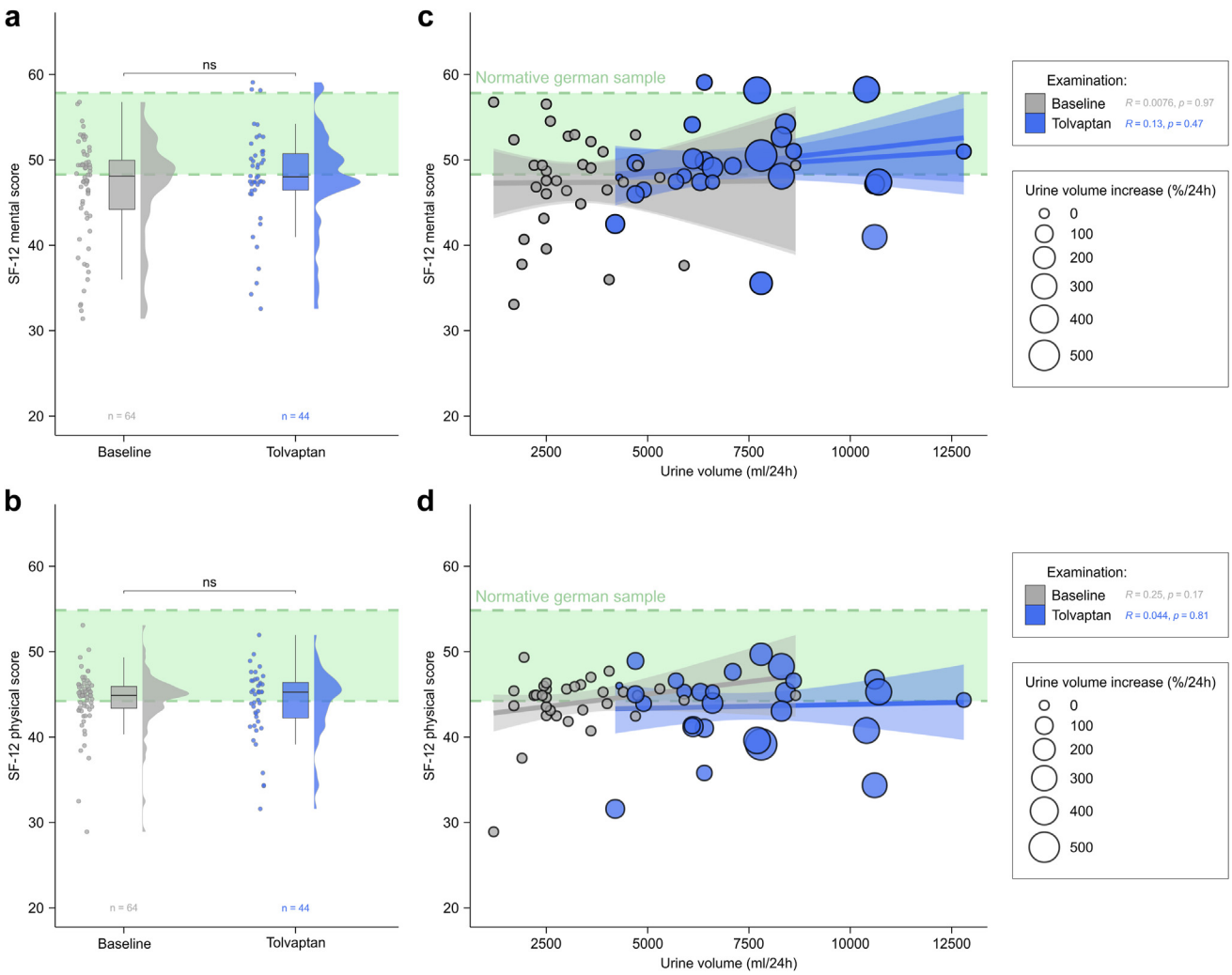

Figure 5. Quality of life assessed in patients with ADPKD. Using the SF-12 Questionnaire, mental (a) and physical (b) quality of life was assessed for 0 mg (gray) vs. 90/30 mg (blue). A similar analysis was conducted for reported 24-hour urine volume for mental (c) and physical (d) quality of life for 0 mg (gray) vs. 90/30 mg (blue). The size of the dots indicates urine volume increase (%/24h). A normative German sample (available form[21]) is indicated between the green dashed lines.

development of 24-hour urine volume in response to tolvaptan in a real-life setting, and these studies did not examine differences between dose subgroups.[8,9] Determining potential modifiable and non-modifiable factors that determine the degree of urine volume increase, and assessing the QoL during treatment and the burden of urine volume are the objectives of the present study.

We found that the most significant increase in absolute urine volume occurred after the initiation of tolvaptan therapy, and that up-dosing did not result in further significant increases, which is consistent with previous results.[9] However, some patients might experience a significant percentage increase in 24-hour urine volume following up-titration, which is crucial for long-term therapy adherence. The study identified a subset of patients in the longitudinal cohort ($n = 13$) who experienced an increase of more than 1 liter and ≥20% from 45/15 to 90/30 mg. These patients had significantly higher levels of modifiable factors, including protein intake, sodium intake, and total intake of osmoles, as well as phosphate and uric acid excretion in 24-hour urine volume. Non-modifiable factors such as GFR ($P = 0.2$) and height ($P = 0.71$) showed a non-significant upward trend. A greater proportion of these patients showed a urine osmolality <150 mOsmol/kg in 24-hour urine collections, but potential influencing factors such as water intake were not documented.

Previous studies have demonstrated that younger patients and those with a higher GFR are more likely to discontinue tolvaptan therapy because of aquaretic side effects.[22] In a small study,[9] GFR was also shown to be the sole determinant of urine volume, whereas another study confirmed the correlation between urine volume and kidney function, but did not identify GFR as a non-modifiable factor.[8] In our cohort, younger patients and those with a GFR above 60 ml/min per 1.73 m^2

indeed showed a greater percentage increase in urine volume after therapy initiation than the rest of the tested cohort, indicating that these subgroups may be more likely to discontinue therapy because of aquaretic side effects. In accordance with the findings of Kramers *et al.*,[8] GFR was not a significant non-modifiable factor in the models, indicating variation in response to tolvaptan therapy among the patient population, e.g., some patients may have had an increased urine volume before treatment initiation because of impaired urine concentrating capacity.[24] In addition, in a subset of individuals younger than 45 years (13 out of 23), a more dramatic rise in urine volume was observed, and these patients were more likely to be female and shorter in stature. In this small subset of patients, those with a higher GFR and of a younger age had more urine volume increase. Furthermore, patients with more sodium intake showed a larger increase in urine volume, which is consistent with the fact that excretion of osmoles (including sodium excretion) has been reported as the main determinant of urine volume for patients on tolvaptan.[8]

Intriguingly, heavier patients consumed more sodium, which likely explains the higher urine osmolality in heavier patients.[25] Because sodium intake was a significant predictor of urine volume before treatment initiation and on tolvaptan, this likely explains the importance of weight in our cohort's model containing modifiable and non-modifiable factors. In contrast, a recent study found that weight-adjusted doses of tolvaptan may influence its effectiveness.[26] Therefore, prospective studies with larger sample sizes are required to investigate further the effect of weight on tolvaptan urine volume.

Our study indicates that the reduction of total intake of osmoles and particularly sodium and potassium intake can be assumed to be a potential method of reducing polyuria, which should be incorporated into patient counseling, analogous to the treatment of renal diabetes insipidus, where a reduction of salt and protein intake is also recommended.[27] Smaller studies indicated that a low-protein diet may reduce vasopressin secretion[28] in patients with ADPKD. We did not find a connection between protein intake and 24-hour urine volume, in line with previous findings.[8] Previously, excretion of osmoles in 24-hour urine volume on tolvaptan has been identified as a major determinant of 24-hour urine volume on tolvaptan.[8,29] Although using a different method of assessing the association between urine volume and excretion of osmoles, the correlation between urine volume and excretion of osmoles was shown to be independent of tolvaptan in a small cohort of 18 patients.[9] Moreover, we confirmed that more potassium excretion is associated with more 24-hour urine volume on tolvaptan than in tolvaptan-naïve patients, similar to previous results.[8] During tolvaptan therapy, both total intake of osmoles, and sodium intake remained unchanged compared with before and on the tolvaptan, and this is analogous to previous results.[8,9] Exposure to tolvaptan is not related to an increase in sodium or absorption of osmoles, despite higher drinking levels. It should be noted, however, that 24-hour urine volume is included in the calculation of osmoles, potassium, and sodium intake, therefore accounting for both sides of the correlation. In the past, it has been suggested to correlate osmoles/creatinine ratio and osmolality/creatinine ratio with 24-hour urine volume.[9] Plasma samples were not collected alongside urine samples in our cohort, so we were unable to perform these calculations. In theory, this strategy seems useful for future studies as an analytical tool; however, causality cannot be demonstrated with any of these calculations, because this would require an interventional study.

After initiation of tolvaptan, urine osmolality in 24-hour urine collection decreased by 57% analogous to previous results[9] and remained unchanged after the dose increase. Most patients achieved the goals in both 24-hour urine collection and spontaneous urine, but numerically more patients achieved the goals on 90/30 mg, though not significant, similar to results from pivotal trials.[7] Consequently, whereas the urine volume shows only modest increases with increasing dose, our study does not speak against the current dosing strategy which mainly aims to efficiently reach 24-hour vasopressin 2 receptor suppression. This would mainly be reflected by morning spot urine values, but, in any case, the limitations of use of urine osmolality to measure the effect of tolvaptan need to be considered. Although urine osmolality is helpful in this regard in clinical trials across cohorts, it has limited use only in the real-life setting.

Taking gender-specific development of urine osmolality in 24-hour urine volume into account, the osmolality of 24-hour urine volume was significantly higher in male patients receiving tolvaptan at doses of 45/15 mg and 60/30 mg, but not 90/30 mg at which there was no gender difference in 24-h urine volume. However, a preliminary investigation indicates that there are gender differences in thirst and vasopressin action, which may also contribute to gender differences in osmolality.[30]

The extent to which the discussed aquaretic side effects in the context of tolvaptan therapy influence the QoL of patients is an important aspect in patient counseling. Previous data showed that tolvaptan

therapy did not have a strong impact on QoL in general.[12,31] In the present study, therapy was well-tolerated, as measured by the SF-12 questionnaire, with mental and physical scores comparable with the normative German sample. Patients with high-frequency miction did not report to feel urine volume as a burden, similar to results of other studies.[32] On the other hand, there is no evidence that assessment of QoL using SF-12 is sufficient to examine tolerability of tolvaptan treatment. The usage of more specific questionnaires such as the ADPKD urinary impact scale[32] might be more suitable to investigate this issue. In addition, patients willing to contribute 24-hour urine collection and start tolvaptan in the first place may already be pre-selected cohorts. SF-12 assessments and questionnaires were not routinely administered during the up-titration phase but at the first follow-up visit. Therefore, QoL during the first 3 months of treatment dose could not be examined. As in TEMPO 3:4, most of the patients ceased treatment during the first 3 months of treatment,[5] further studies should evaluate QoL at the start of treatment.

In conclusion, our study provides insight into the development of urine volume and osmolality during the up-dosing phase in a real-life setting, including a larger sample size of patients. Younger patients, patients with preserved kidney function as well as heavier patients had more pronounced urine volume increase. Reduction in sodium and potassium intake can help in ameliorating aquaretic side effects. On tolvaptan, no change of QoL could be identified, but it is not clear if SF-12 assessment is sufficient to clarify this issue and whether these results extrapolate to all patients considering the treatment. The results regarding urine volume increases can be helpful to reassure patients during up-dosing and together with the other findings help to provide optimal counseling. Hopefully, such data will help to improve implementation of tolvaptan and together with upcoming pharmacologic options to decrease polyuria such as comedication with hydrochlorothiazide,[33,34] contribute to having more patients benefit from this treatment option.

Limitations

The following limitations should be noted. The number of patients in the longitudinal cohort is limited. In addition, repeated measurements would be the gold standard for determining sodium intake, which was not performed in the current study. Urine osmolality measurements may be affected technically by different periods between collection and analysis. However, this is not the case for sodium. Weight was not documented at the time of urine collection; therefore, only the weight at the baseline visit was used. Change in urine osmolality from baseline in spontaneous urine was not performed because of insufficient sample size.

DISCLOSURE

R-UM was supported by the Ministry of Science North Rhine-Westphalia (Nachwuchsgruppen.NRW 2015-2021), the German Research Foundation (DFG DI 1501/9, DFG MU 3629/6-1), the Marga and Walter Boll Foundation, and the PKD Foundation. R-UM is a member of the Scientific Advisory Board of Santa Barbara Nutrients and Chair of the Working Group "Genes & Kidney" (European Renal Association). FG was supported by the Köln Fortune Program / Faculty of Medicine, University of Cologne, and the German Research Foundation (GR 3932/2-2). All the other authors declared no competing interests.

ACKNOWLEDGMENTS

We thank Cornelia Böhme for excellent technical support. Database generation was supported by "clinicalsurveys.net" (Sebastian Heimann, Jörg Janne Vehreschild). The Department II of Internal Medicine received research funding from Otsuka Pharmaceuticals and Thermo Fisher Scientific. We acknowledge support for the Article Processing Charge from the DFG (German Research Foundation, 491454339).

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. Effects of tolvaptan on 24-hour urine volume, osmolality, and sodium intake in different patient subgroups.

Figure S2. Effects of tolvaptan on blood pressure.

Figure S3. Effects of tolvaptan dosing and patient characteristics on 24-hour urine volume increase.

Figure S4. Comparison of individual factors in patients with and without relevant increase in 24-hour urine volume.

Figure S5. Patient characteristics of different groups with relevant increase in 24-hour urine volume.

Figure S6. Comparison of osmolality in 24-hour urine volume, spot urine, and spot urine 4 hours after tolvaptan administration.

Figure S7. Longitudinal data availability and patient-reported stress due to urine volume in tolvaptan treatment.

Table S1. Statistical output.

Table S2. R packages and session information.

Table S3. Univariable linear regression analysis for modifiable and non-modifiable determinants of 24-hour urine volume in relation to tolvaptan intake in patients with ADPKD. Spearman correlation was conducted for all cases.

Table S4. Multiple linear regression analysis for modifiable and non-modifiable determinants of 24-hour urine volume in patients with ADPKD. Models were conducted for tolvaptan-naïve patients (models I, III, and V) and patients on 90/30 mg tolvaptan (models II, IV, and VI).

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