

Geographic Differences and Their Influence on Tolvaptan Treatment in Patients with ADPKD

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Abstract

Introduction:

Tolvaptan is the only approved disease-modifying treatment for autosomal dominant polycystic kidney disease (ADPKD), although its tolerability is strongly influenced by hydration status and aquaretic adverse effects. Environmental and climatic conditions may affect thirst perception and fluid loss; however, their influence on tolvaptan treatment outcomes has not been adequately investigated.

Methods:

This multicenter retrospective observational cohort study included 205 adults with ADPKD from 14 nephrology centers in Turkey who received tolvaptan therapy for at least 12 months between 2020 and 2022. Demographic, clinical, laboratory, and imaging data were collected from medical records. Meteorological parameters including temperature, humidity, sunshine duration, latitude, and longitude were obtained from the Turkish National Meteorology Institute. Correlations between climatic variables and treatment-related parameters were evaluated using Spearman correlation analysis.

Results :

Treatment interruption occurred in 27.6% of patients, mainly because of aquaretic symptoms, nephrotoxicity, or hepatotoxicity. Estimated glomerular filtration rate significantly decreased over the 2-year follow-up period ($p < 0.001$), while serum creatinine levels increased significantly ($p < 0.001$). Maximum tolerated tolvaptan dose was negatively correlated with annual maximum temperature ($r = -0.615$, $p < 0.005$). Serum sodium levels were positively associated with humidity and negatively associated with annual sunshine duration. Serum calcium levels were positively correlated with maximum temperature, whereas serum uric acid levels were inversely correlated with latitude.

Conclusion:

Geographic and climatic factors significantly influenced tolvaptan tolerability and biochemical responses in ADPKD. High temperatures and prolonged sunshine were associated with reduced tolvaptan tolerance, whereas humidity increased the risk of hypernatremia. Incorporating environmental parameters into individualized tolvaptan dose adjustments may improve safety and adherence. Larger climate-diverse studies using thermal stress indices such as the Universal Thermal Climate Index (UTCI) are warranted.

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most prevalent hereditary kidney disorder [1]. In 2018, the Food and Drug Administration approved tolvaptan as the first medication for decelerating disease progression. Recent studies on patient management and disease pathogenesis, along with the resulting guidelines, have significantly advanced ADPKD treatment[2–4]. Modifying risk factors through increased water consumption and reduced salt intake is feasible. However, advocating for high water intake and ensuring patients consume sufficient water to lower serum osmolality can be challenging and impractical. In the context of climate change and environmental nephrology, there is a pressing need for practical implications in the individualized management of ADPKD.

In individuals with ADPKD, a prescribed regimen of water consumption did not result in a decrease in copeptin levels, nor did it slow the progression of total kidney volume over three years compared to unrestricted water intake [5]. Conversely, a recent study demonstrated that consuming an adequate amount of water to reduce serum osmolality effectively decreased vasopressin levels, inhibited cyst growth, and decelerated the expansion of total kidney volume. [6]

Tolvaptan, a vasopressin receptor 2 (V2) antagonist, was the first drug approved for the treatment of ADPKD, and its clinical application began in Japan in May 2014[7]. While this medication is effective in decelerating cyst growth, a conclusive cure for ADPKD remains elusive, and halting cyst formation in the kidneys remains unattainable. In addition to its effectiveness, maintaining adherence to tolvaptan treatment is a significant challenge. The necessity for substantial water consumption and the consequent increased thirst are critical factors influencing patient compliance with their treatment regimen. Given that tolvaptan's mechanism necessitates substantial fluid intake to manage thirst and polyuria, environmental factors such as high ambient temperatures and low humidity are hypothesized to intensify patient discomfort, potentially leading to reduced adherence, increased side effects like hypernatremia, or necessitating dosage adjustments. Recent advancements in tolvaptan treatment, adjusted based on urine osmolality [8] and 24-hour urine osmolality [9], have demonstrated increased efficacy, reduced side effects, and lower dropout rates. These findings underscore the necessity of additional tools and parameters to optimize tolvaptan dosage adjustments. [8] Limited research exists on the impact of climate, geography, or other environmental factors on the effectiveness of tolvaptan treatment or the progression of ADPKD. This is the first nationwide multicenter study to evaluate the impact of climate, geography, and temperature on the treatment and clinical outcomes of patients with ADPKD nationwide. Specifically, this study hypothesized that geographical parameters (e.g., latitude, longitude), temperature, humidity, and sunshine duration would correlate with (1) maximum tolerated tolvaptan dosage, (2) treatment adherence/interruption rates, and (3) changes in specific laboratory parameters (e.g., serum sodium, calcium, uric acid) in ADPKD patients undergoing tolvaptan therapy in Turkey.

Patients and Methods

The study protocol was formulated by the Working Group on Hereditary and Cystic Kidney Diseases of the Turkish Society of Nephrology, adhering to the principles outlined in the Declaration of Helsinki. Ethical approval was obtained from the Kocaeli University Hospital Ethical Committee, as recorded in report number GOKAEK-2025/23/03. Patients were identified as having ADPKD based on the Pei criteria, which involved anamnesis, family history, and either ultrasound or magnetic resonance imaging (MRI) [10]

A total of 205 patients were enrolled from 14 separate centers located in various regions of Turkey. The study included adult participants aged 18 years or older who had been on tolvaptan therapy for a minimum of 12 months (2020-2022) and had a glomerular filtration rate (eGFR) of at least 25 ml/min/1.73 m². eGFR was determined using the CKD-EPI formula. Individuals with systemic conditions, such as diabetes mellitus, cancer, or rheumatologic disorders potentially influencing kidney function, were not included in the study. The demographic and clinical characteristics of patients are summarized in Table 1. The cohort comprised 113 men (55.1%) and 92 women (44.9%). Hypertension was prevalent, affecting 164 patients (80.8%), with ACEi/ARB being the most common medication class used (57.6%). Gene mutation analysis was available for 59 patients, showing a predominance of PKD1 mutations (37.7% of the total cohort). Treatment interruption occurred in 56 patients (27.6%), with primary reasons being patient request (60.9%), nephrotoxicity (21.7%), and hepatotoxicity (15.2%).

The study collected data on patients' ages when they started treatment, their gender, and the duration of their treatment with tolvaptan, and performed an analysis of PKD gene mutations. The Mayo classification and height-adjusted total kidney volume (HtTKV) were also recorded. Data extracted from patient records included daily tolvaptan doses, reasons and duration for treatment pauses, body mass index (BMI), blood chemistry, blood count, and protein levels in 24-hour urine samples. This information was collected at baseline, after one year, and after two years of treatment. BMI was determined by dividing the body weight in kilograms by the square of the height in meters, with the results expressed in kilograms per square meter. The 'maximum tolerated dose' was defined as the highest stable daily dose achieved by the patient for at least three months without requiring permanent reduction due to adverse effects. Treatment 'pauses' were defined as ; temporary interruption was defined as discontinuation lasting less than 3 months, whereas permanent discontinuation referred to complete cessation of therapy.

The geographical coordinates of the cities, the annual average data between 2020-2021 for daily temperature highs and lows, and humidity levels were gathered from the annual records of the National Meteorology Institute.

Statistical Analysis:

Descriptive statistics of the obtained data were calculated as the mean, standard deviation (SD), median, 25th and 75th quartiles, and numbers and percentages. The compliance of the numerical-type features obtained by measurement with a normal distribution was examined using the Shapiro-Wilk test. Other than age, the features did not show a normal distribution. Independent samples t-test, Mann-Whitney U test, or Kruskal-Wallis test were used to compare various groups. The relationships between categorical features were evaluated using the Pearson chi-square test or Fisher-Freeman-Halton exact test. The relationships between numerical-type features were examined using Spearman's rank correlation analysis. Periodic changes were evaluated using the Friedman test, and significant differences were determined using the post-hoc Conover test. In addition, factors related to HtTKV and eGFR were examined using multiple linear models. The statistical significance level was set at $P < 0.05$. SPSS (ver. 23) was used for calculations.

Results

A total of 205 patients participated in this study. Of these, 164 individuals (80.8%) were diagnosed with hypertension and had documented records of their medication usage. Demographic and baseline clinical data are presented in Table 1. Among the 205 patients receiving medications, over half (72%) were prescribed angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB). Calcium channel blockers (CCBs) and diuretics were the second most frequently used drugs.

The study included 92 women (44.9%) and 113 men (55.1%). Gene mutation analysis was available for 59 (38.3%) patients, and 58 (37.7%) had PKD1 mutations. Treatment interruption was observed in 56 patients (27.6%) (Table 1). Of the 56 patients who interrupted treatment (27.6% of the total cohort), reasons included hepatotoxicity (n=7, 12.5% of those interrupting), nephrotoxicity (n=10, 17.9%), and patient request due to side effects such as excessive thirst and frequent urination (n=28, 50%). Of the 56 patients, 7 (15.2%) stopped treatment because their liver function tests showed an increase exceeding three times the normal range. Meanwhile, 10 patients (21.7%) discontinued treatment due to a decline in renal function, indicated by an eGFR of less than 20 ml/min/1.73 m². Additionally, 28 patients (60.1%) chose to discontinue treatment at their request, citing issues such as excessive thirst, frequent urination, increased urination at night, and the need for continuous medication.

The mean age of the patients included in the study was 42.76 ± 9.95 years. Other key parameters were: follow-up period, 56.82 ± 43.55 months; HtTKV, 1718.39 ± 1302.55 mm³; BMI, 25.77 ± 4.19 kg/m²; baseline creatinine, 1.33 ± 0.52 mg/dl; baseline eGFR, 67.96 ± 29.27 ml/min/1.73 m²; and tolvaptan dose, 106.03 ± 23.38 mg/day. HtTKV demonstrated a negative correlation with basal eGFR levels (r: -0.342, p: 0.00), serum AST levels (r: -0.149, p: 0.050), serum HDL levels (r: -0.196, p: 0.050), and serum Ca levels (r: -0.147, p: 0.043). Conversely, it exhibited a positive correlation with basal creatinine levels (r: 0.216, p: 0.003), serum P levels (r: 0.174, p: 0.016), serum K levels (r: 0.171, p: 0.018), and 24-hour urinary proteinuria (r: 0.285, p: 0.00).

Changes in eGFR, creatinine, other lab parameters over time are presented in table 2. Creatinine levels significantly increased in the first and second years compared to baseline ($p<0.001$), while eGFR significantly decreased during the same periods ($p<0.001$). AST levels were significantly higher at the first month, sixth month, and first year compared to baseline ($p=0.048$). Similarly, ALT levels were significantly higher at the first and sixth months compared to baseline and first-year measurements ($p=0.004$), though no significant difference was observed between the first and sixth months or between baseline and the first year for ALT. In terms of uric acid levels, only the difference between the first year and baseline was significant ($p=0.006$). Only the difference between the first and second years and the baseline in terms of calcium and hemoglobin levels was found to be significant, and it was significantly lower in the second year ($p=0.016$ and $p=0.002$, respectively). The average systolic and diastolic blood pressure decreased significantly during the second measurement ($p<0.001$).

Changes in creatinine and eGFR levels at one and two years, compared to baseline, along with variations in demographic and biochemical parameters, were evaluated. The one-year change in creatinine was positively correlated with age, BMI, and glucose ($r=0.251$, $p=0.001$; $r=0.162$, $p=0.035$; and $r=0.164$, $p=0.031$, respectively) and negatively correlated with AST and ALT ($r=-0.249$, $p=0.001$; and $r=-0.159$, $p=0.04$, respectively). The two-year change in creatinine levels was positively correlated with age, HtTKV, and phosphorus ($r=0.286$, $p=0.001$; $r=0.182$, $p=0.042$; and $r=0.192$, $p=0.034$, respectively) and negatively correlated with hemoglobin ($r=-0.261$, $p=0.004$). Changes in demographic and biochemical parameters were evaluated using HtTKV at the time of diagnosis. Age, BMI, baseline creatinine, phosphorus, potassium, and proteinuria values were positively correlated ($r=0.316$, $p<0.001$; $r=0.181$, $p=0.016$; $r=0.216$, $p=0.03$; $r=0.174$, $p=0.016$; $r=0.0171$, $p=0.018$, and $r=0.285$, $p<0.001$, respectively), and calcium was negatively correlated ($r=-0.147$, $p=0.043$).

The geographical findings of the cities are as follows:

The geographical context, including latitude and longitude, along with the meteorological variations of the cities from which the patient data were collected, are detailed in Table 3. The average weather patterns for Turkey during 2020-2021 are illustrated in Figure 1.

Situated in Mini-Asia, Turkey's geographic coordinates are 39°00'N latitude and 35°00'E longitude. The nation's average temperature ranges between 9.6° and 18.5° C, whereas the overall humidity levels across the country fluctuate from 49.05% to 76.40%. In Turkey, the highest average temperature is recorded at 46.2°C in Diyarbakir, located in South Eastern Anatolia, while the lowest average temperature is -34.4°C in Sivas, located in Central Anatolia. (Table 3).

Table 4 presents the core findings that connect the tolvaptan dose, serum electrolytes, and uric acid with geographical and environmental parameters. When analyzing the impact of tolvaptan treatment in various geographical areas, it was found that the maximum tolerated dose of tolvaptan was inversely related to the longitude of the locations ($r=0.761$, $p<0.005$) and negatively correlated with the average highest temperature level in the city ($r=-0.615$, $p<0.005$). Furthermore, there was a direct relationship between serum sodium levels and air humidity ($r=0.783$ and 0.762 , $p<0.005$), and a negative correlation with the average yearly sunshine exposure in the region ($r=-0.733$, $p<0.005$). The correlation data are presented in Table 4. Similarly, serum calcium levels were positively associated with the highest temperature ($r=0.818$, $p<0.005$). Serum uric acid levels were negatively correlated with latitude ($r=-0.683$, $p<0.005$).

Discussion

Optimizing tolvaptan therapy is essential with practical strategies for patients and doctors. This study evaluated ADPKD patients from 11 cities. Geographical location, temperature, sunlight exposure, and humidity were key indicators for tolvaptan dosage, serum electrolytes, and uric acid levels. Our study is the first to examine these in ADPKD patients on tolvaptan. Managing water intake and thirst is challenging for patients, affecting quality of life, especially in different climates, crucial for treatment adherence.[11]

The maximum sustainable tolvaptan dose inversely correlated with longitude and city temperature. Geographical parameters are evaluated in skin cancers[12,13], autoimmune diseases[14], infectious diseases[15], vector-borne diseases[16,17], nephrolithiasis[18,19],[20] CKD progression[20–22], and vitamin D deficiencies[23,24]. No study has examined geographical variations in ADPKD progression or climate impact. More data from diverse regions are needed to understand geographical effects on tolvaptan efficacy and ADPKD progression. Turkey's narrow longitudinal range may affect result interpretation. Cultural diet and lifestyle variations between Western and Eastern cities also influence serum uric acid levels and thirst. Data on lifestyle differences, water content[25], and dietary preferences may provide more accuracy.

Higher temperatures and climate change negatively impact nephrolithiasis [26,27] and CKD in agricultural communities[28,29]. Rising temperatures increase thirst, challenging urine dilution or serum osmolality reduction.[30–32] Another study showed elevated serum osmolality and sodium levels as independent CKD progression risk factors.[33]

This study has some limitations. First, its retrospective observational design limits causal interpretation. Second, serum copeptin, urine osmolality, and fluid intake measurements were unavailable. Third, lifestyle factors, dietary habits, occupational exposure, and outdoor activity levels were not systematically assessed. Fourth, the study population consisted exclusively of patients from Turkey, which may limit generalizability to regions with different climatic characteristics. Finally, the sample size limited extensive multivariable modeling.

Environmental conditions like temperature and humidity theoretically affect medication adherence. [34] While studies on environmental impacts exist, socioeconomic factors are the main non-adherence cause. [35,36] Studies often overlook geographical differences and factors like humidity, temperature, sun exposure, climate change, and carbon emissions in drug adherence. [37] Our study found a negative correlation between serum uric acid and geographical latitude. Tolvaptan therapy, a hyperuricemia risk, and increased water loss in hot weather challenge ADPKD patients. [38] High uric acid levels correlate with hot climates, increasing nephrolithiasis risk. [39,40] Rising temperatures challenge tolvaptan users due to heat and urine supersaturation, necessitating more water intake. CKD progression heightens heat illness susceptibility, leading to treatment discontinuations and hindering maximum tolvaptan dosing. [41] For tolvaptan patients, serum sodium is positively affected by humidity but negatively by sunshine, risking hyponatremia. [42,43] Elevated humidity increases water loss and tolvaptan impact, causing hyponatremia. Prior research on dysnatremia shows humidity has little effect, while diuretics, age, children, sun, heat, and exertion significantly influence hyponatremia. [44,45]

Geographic and climatic parameters were associated with tolvaptan tolerability and biochemical changes in patients with ADPKD. Higher temperatures were associated with lower tolerated doses, whereas humidity was associated with higher serum sodium levels. Consideration of environmental conditions may contribute to more individualized and safer tolvaptan treatment strategies. Prospective multicenter studies incorporating thermal stress indices and hydration-related biomarkers are warranted.

Declarations

Informed consent:

All patients have given informed consent.

Consent for Publication:

Written informed consent for publication was obtained from all participants.

Author Contributions:

SGB, IK, KGA, EA, SB, ÖAO, DG, TY, SAE, ET, KT, FC, IB, AY, SA, NE,AD,HI, SM, ID, TK, ME, MDA, STE :data collection, interpretation and analysis. SGB, IK, SB, STV: quality control of research design and data analysis. SGB, IK, STE, KGA: wrote the first draft of the manuscript. All authors contributed to the discussion and editing of the text and approved the final version of the manuscript.

Disclosure Statement:

The authors except NE; have no conflicts of interest to disclose, and the results in this paper have not been published previously in whole or in part. The authors except NE, have declared that no competing interests exist.

Ethics Statement:

The study protocol was formulated by the Working Group on Hereditary and Cystic Kidney Diseases of the Turkish Society of Nephrology, adhering to the principles outlined in the Declaration of Helsinki. Ethical approval was obtained from the Kocaeli University Hospital Ethical Committee, as recorded in report number GOKAEK-2025/23/03.

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Availability of Data and Materials:

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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Tables

Table 1
Demographic and clinical characteristics of the patients

Sex	n	%
Male	113	55.1
Female	92	44.9
PKD Gene Mutation		
PKD1	58	37.7
PKD2	1	0.6
Unknown	95	61.7
Hypertension		
Non-Hypertensive	39	19.2
Hypertensive	164	80.8
Treatment Interruption		
Yes	56	27.6
No	147	72.4
Reason for Treatment Interruption		
Hepatotoxicity	7	12.5
Nephrotoxicity	10	17.9
Allergic Reactions	1	2.2
Unknown	28	50

Table 2
Laboratory parameters during tolvaptan treatment for two years

Serum Creatinine (mg/dl)	Bazal	First Year	Second Year	p
	1.33 ± 0.52	1.51 ± 0.84	1.59 ± 0.69	< 0.001
eGFR (ml/min)	67.96 ± 29.27	63.08 ± 29.15	56.80 ± 30.23	< 0.001
AST (U/L)	18.57 ± 5.62	21.54 ± 12.35	21.72 ± 10.35	0.048
ALT (U/L)	18.95 ± 5.62	22.07 ± 20.19	20.78 ± 11.69	0.004
Uric Acid mg/dl	5.96 ± 1.54	6.64 ± 5.38	6.27 ± 1.75	0.006
Na mmol/ L	139.98 ± 2.42	139.93 ± 2.96	140.40 ± 5.82	0.984
K mmol/L	4.39 ± 0.45	4.40 ± 5.82	4.39 ± 0.43	0.256
Ca mg/dl	9.48 ± 0.52	9.45 ± 0.50	9.39 ± 0.49	0.016
P mg/dl	3.34 ± 0.56	3.44 ± 0.57	3.43 ± 0.60	0.132
Hb gr/dl	13.87 ± 1.77	13.61 ± 1.74	13.43 ± 1.90	0.02
Systolic BP mmHg	133.49 ± 17.78		124.80 ± 16.22	< 0.001
Diastolic BP mmHg	84.17 ± 12.43		79.43 ± 9.28	< 0.001
Tolvaptan Dosage mg/day	106.03 ± 23.38	110.5 ± 9.48	98.2 ± 21.8	0.185
Values are presented as mean ± SD. Repeated-measured ANOVA was used.				
SD: Standard Deviation, HtKV: Height-adjusted total kidney volume, eGFR: Estimated Glomerular Filtration Rate, AST: Aspartate Transaminase, ALT: Alanine Transaminase, Ca: Calcium, P: Phosphorus, Hb: Hemoglobin				

Table 3

Meteorological variants (annual average data for the study period of 2020–2021 of air temperature, humidity, and sunshine) with geographical parameters (latitude and longitude) of cities

Name of City	Average Temperature	The Highest Average Temperature	The Lowest Average Temperature	The Average Sunshine Time	Maximum Temperature	Minimum Temperature	The Average Moisture	Latitude	Longitude
Ankara	12	17.9	6.4	6.7	41	-24.9	60.80	39.942928	32.860481
İstanbul	15.8	20	12.3	5	40.6	-9	76.40	41.046419	29.033115
Kocaeli	15.3	20.3	11.5	5.6	44.1	-18	76.40	40.7656	29.940659
Bursa	14.9	20.8	9.6	5.6	43.8	-20.5	68.60	40.182816	29.066148
Diyarbakir	15.9	23	8.9	7.5	46.2	-24.2	49.050	37.9137	40.224899
Sivas	9.6	16.3	3.9	6.8	40	-34.4	64.70	39.750528	37.015028
Nigde	11.3	17.6	5.1	7.5	39.7	-25.6	60.80	37.96911	34.678619
Mugla	18.5	24	13	7.1	44.6	-3.8	64.70	37.215266	28.363718
Konya	11.8	18	5.4	7.4	40.9	-28.2	60.80	37.872817	32.491991
Kayseri	10.7	18.2	3.1	7	40.7	-32.5	64.70	38.73122	35.478729
Samsun	14.7	18.4	11.1	5.3	39	-9.8	72.50	41.28157	36.33812

Table 4 - The correlation between tolvaptan maximum tolerated tolvaptan dosage and laboratory levels with meteorological and geographical parameters

Max Humidity	Daily Tolvaptan Dosage	Serum Na	Serum Ca	Serum Creatinine	Uric Acid
	-0.450	0.783*	-0.117	-0.567	-0.517
Min Humidity	-0.377	0.762*	-0.192	-0.469	-0.477
Latitude	0.009	0.617	-0.183	-0.500	-0.683*
Longitude	-0.761**	-0.483	0.183	0.117	-0.100
Yearly Average Temperature	-0.615*	0.117	0.582	-0.283	-0.233
Max Average Temperature	-0.697*	0.217	0.818**	-0.317	0.033
Min Average Temperature	-0.606*	0.533	0.327	-0.450	-0.383
Average Yearly Sunshine in Hours	0.271	-0.733*	0.096	0.467	0.600
* <0.05					
** <0.01					

Figures



Figure 1

The average weather patterns for Turkey during 2020-2021.

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