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Creatine Kinase Elevation in Autosomal Dominant Polycystic Kidney Disease Patients on Tolvaptan Treatment

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Abstract

Background

Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary cause of end-stage kidney disease. Currently, tolvaptan is the only treatment that has proven to delay disease progression. The most notable side effect of this therapy is drug-induced liver injury; however, recently, there have been two reports of creatine kinase (CK) elevation in ADPKD patients on tolvaptan treatment. We set out to monitor and determine the actual incidence of CK elevation and evaluate its potential association with other clinical factors.

Methods

This is an observational retrospective multicenter study performed in rapidly progressive ADPKD patients on tolvaptan treatment from Barcelona, Spain. Laboratory tests, demographics, treatment dose, and reported symptoms were collected from October 2018 to March 2021.

Results

Ninety-five patients initiated tolvaptan treatment during follow-up. The medication had to be discontinued in 31 (32.6%) patients, primarily due to aquaretic effects (12.6%), elevated liver enzymes (8.4%), and symptomatic or persistently elevated CK levels (3.2%). Moreover, a total of 27 (28.4%) patients had elevated CK levels, with most of them being either transient (12.6%), mild and asymptomatic (4.2%), or resolved after dose reduction (3.2%) or temporary discontinuation (2.1%).

Conclusion

We present the largest cohort that has monitored CK levels in a real-life setting, finding them elevated in 28.4% of patients. More research and monitoring will help us understand the clinical implications and the pathophysiological mechanism of CK elevation in this population.

Keywords: Creatine-kinase, Tolvaptan, ADPKD, Side effect

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary kidney disease worldwide, with an incidence of 1 in every 1,000 individuals [1]. A portion of the ADPKD population progresses to end-stage kidney disease, comprising around 10% of all patients on kidney replacement therapy [2]. Despite the attempt of various therapies to slow disease progression, tolvaptan remains the only pharmacological treatment that, to date, has proven to slow down the increase of total kidney volume (TKV) and the decline of estimated glomerular filtration rate (eGFR) [3, 4].

Tolvaptan is a vasopressin-2 receptor antagonist that acts by inhibiting the vasopressin-mediated up-regulation of cyclic adenosine monophosphate (cAMP), which stimulates cyst-cell proliferation and fluid secretion [5]. As arginine-vasopressin is an antidiuretic hormone, its inhibition generates notable secondary effects from its aquaretic response, such as thirst, nocturia, and polyuria. Therefore, physicians recommend that treated patients increase their water intake [6]. In addition to this effect, during tolvaptan's pivotal clinical trials, investigators found that treated participants had a higher risk of presenting drug-induced liver injury than those on placebo [3]. Because of this finding, close monitoring of liver enzymes is indicated at tolvaptan treatment initiation and up-titration [7]. Withdrawal or dose reduction is required in those patients who elevate liver enzymes three or more times above the upper limit of normal values as this adverse effect is reversible when the drug is discontinued [8].

Notably, there has been a recent report of 2 cases of asymptomatic creatine kinase (CK) elevation in ADPKD patients on tolvaptan treatment [9]. As this phenomenon has not been widely reported, there is no information regarding the pathophysiology involved in this effect. One explanation may be related to mitochondrial respiration. The arginine-vasopressin and its second messenger, cAMP, increase fluid secretion and, hence, cyst growth and loss of functional renal tissue [5, 10]. However, cAMP and its effector protein kinase A (PKA) are stimulated when in-

tracellular nutrients and CO2 levels increase [11]. Therefore, tolvaptan-mediated inhibition of the vasopressin-2 receptor not only helps control cyst volume but may also have consequences at a mitochondrial level.

Drug-induced myopathies can lead to myositis, manifesting as CK elevation with muscle weakness, myalgia, and even myoglobinuria, potentially leading to acute rhabdomyolysis with acute kidney injury [12] or unmasking neuromuscular disorders [13]. Because of such significant associated comorbidities, a prompt diagnosis of CK alterations and tailoring tolvaptan dosing taking this into account could identify patients who refer "fatigue" while on treatment [4, 14], increase adherence, and avoid severe unwanted complications in select patients. Considering these 2 cases of CK elevation, the present study aimed to monitor, gather, and review the measured CK levels in ADPKD patients on tolvaptan treatment in a real-life multicenter environment and evaluate their potential associations with other clinical factors.

Methods

This is an observational, retrospective, single-cohort multicentric study conducted in three Spanish hospitals (Hospital Clínic, Hospital Vall d'Hebron, and Fundació Puigvert) from October 2018 to April 2021. Data were collected through institutional electronic health medical records.

Inclusion Criteria

Patients of 18 years of age or older with ADPKD that had evidence of risk for rapid progression, i.e., Mayo Clinic score of IC or greater, eGFR decline greater than 5 mL/min/1.73 m^2 in the last year or than 3.5 mL/min/1.73 m^2 in the past three, or a PROPKD score ≥6 [15], and had initiated tolvaptan treatment. Patients were excluded if they had an eGFR lower than 20 mL/min/1.73 m^2 or a past medical history of liver disease.

Tolvaptan Dosing

Before initiating treatment, patients were instructed on the drug's diuretic effects, including nocturia and the need for constant hydration. The starting dose was 60 mg in a split-dose regimen (45 mg in the morning and 15 mg in the afternoon), that could be increased progressively to a total split-dose regimen of 90 mg a day and then to 120 mg a day on each successive visit. Dosing was increased if the patient tolerated it or if urine osmolality was ≤250 mOsm/kg, which indirectly indicates an adequate ADH suppression and upon which more significant reductions in urine osmolality have not proven any further clinical benefit [16].

Variables Collected at Baseline

Demographic characteristics collected were age, sex, and ethnicity. Clinical characteristics were weight, height, body mass index (BMI), alcohol intake, smoking status, and if they practiced regular exercise (at least 30 min three times per week).

Variables Collected during Follow-Up

Every patient was followed monthly for 18 months and every 3 months after that. Changes in tolvaptan dose and laboratory tests performed before every visit were registered. The biochemical parameters collected were serum sodium, potassium, uric acid, aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, CK, calcium, lactate dehydrogenase (LDH), creatinine, and plasma and urine osmolality. eGFR was calculated by the Chronic Kidney Disease Epidemiology (CKD-EPI) formula.

Treatment Discontinuation

Tolvaptan was discontinued at the patient's request if they referred intolerance to aquaretic effects (e.g., nocturia that disturbs night rest, intolerable thirst, or polyuria that hampers work), if they were seeking pregnancy, at increased liver enzymes by tripling AST or ALT upper reference values or by fulfilling Hy's Law criteria (tripled value of AST or ALT with doubled total bilirubin levels with normal alkaline phosphatase), or if patients tripled CK upper limit reference values or continued progressive increase despite dose reduction or transitory treatment pauses. The upper limit CK reference value of all three hospitals' labs was 200 U/L based on healthy population data [17].

Statistical Analysis

Quantitative variables are described as median and interquartile ranges, while qualitative ones are reported as absolute and relative frequencies. A univariate analysis was used to estimate the associations between CK elevation and other factors. Differences in qualitative variables were analyzed with the χ^2 test or the Fisher's exact test when one or more expected values were less than five or the data were very unequally distributed among the table's cells. The normal distribution of the quantitative variables was tested with the Shapiro-Wilk test and Q-Q plots. The quantitative variables' analysis between the two groups was made with the U-Mann Whitney test, as all of them were non-normal. A two-sided p value inferior to 0.05 was considered statistically significant. Analyses were performed with IBM SPSS® Statistics 26th version.

Ethical Considerations and Disclosures

All patients gave their written informed consent to participate in this study. It was conducted following the World Medical Association Declaration of Helsinki, national and local laws, and good clinical practice standards. The Hospital Clinic Institute's Committee on Human Research approved it, register code HCB/2020/0930. The authors have no conflicts of interest to declare. This work has neither received public nor private funding for its implementation.

Results

Ninety-five patients with ADPKD initiated treatment with tolvaptan during a mean follow-up period of 21 ± 10 months (see Fig. 1). Demographic and medical baseline characteristics are shown in Table 1. No patient was on dual renin-angiotensin-aldosterone system blockade.

Treatment Discontinuation

Treatment was suspended in 27 patients (28.4%). Eight of them were due to liver enzyme elevation. All but one tripled either AST or ALT's upper reference value, with one also doubling bilirubin reference levels meeting Hy's law criteria. No cases of acute liver failure occurred. Twelve patients (12.6%) requested treatment termination due to poorly tolerated aquaretic effects. Three patients abandoned treatment to plan pregnancy, and 1 patient presented a rapid eGFR decline of 15 mL/min/1.73 m^2 in 2 months, with recovery after drug withdrawal. Moreover, treatment had to be discontinued in 3 patients due to CK elevation. Two of them presented myalgia (peak value 9,306 and 587 U/L) while the degree of persistent elevation was more than ten times their baseline value (842 and 66 U/L, respectively) that progressed after dose reduction, forcing drug suspension.

CK Elevation

Notably, there were 27 cases (28.4%) of CK elevation. Every rise either appeared within 4 months of treatment initiation or after the tolvaptan dose was increased. Tolvaptan had to be suspended in eight of them, where three corresponded to the group that presented elevated liver enzymes with only mildly elevated CK levels (409, 290, and 528 U/L). As mentioned above, one had persistently elevated CK levels and two presented myalgia. Three cases of elevated CK levels (393, 357, and 478 U/L) resolved within 2 months of tolvaptan dose reduction from 90 to 60 mg per day. Elevated CK settled in 2 patients (1,251 and 800 U/L) on 60 mg per day after a temporary treatment suspension of 3 months. Twelve patients had transient elevations that resolved without any intervention (429.5 ± 404.8 U/L). The remaining 4 patients had a persistent mild asymptomatic CK elevation without other adverse effects (261, 214, 363, and 339 U/L).

Association of CK Elevation and Other Parameters

Among baseline characteristics, there was no correlation between CK levels and age, hypertension or antihypertensive drugs, hypothyroidism, diabetes mellitus, psychiatric medication, eGFR, smoking status or alcohol habit, regular exercise, TKV, or sex. There was a non-significant tendency towards an augmented risk for elevated CK as BMI increased ($p = 0.06$), thiazide diuretics ($p = 0.06$), and statins ($p = 0.06$). Regarding other collected parameters during follow-up, serum sodium, potassium, calcium, LDH, and plasma osmolality remained unchanged while patients were on tolvaptan treatment. There was also no association between an increased risk of CK elevation and uric acid, urine osmolality, ALT, eGFR, or tolvaptan dose, which were variables that significantly changed under tolvaptan treatment. Only AST directly correlated with CK levels ($R^2 = 0.68$, $p < 0.001$). Because of an outlier that may have biased the model, we performed an analysis without it, and though when removed, the model lost fitness, it remained significant ($R^2 = 0.06$, p 0.02).

Discussion

Despite the growing use of tolvaptan as a standard of care for rapidly progressive ADPKD patients, there is still much to learn from real-life experiences. After a two-case report of CK elevation with tolvaptan use [9], some centers in our region decided to monitor and collect data from all patients initiating this drug. Our population had a larger total TKV and lower eGFR than that from the TEMPO 3:4 trial and higher than that of REPRISE [14]. Moreover, treatment

side effects that led to its discontinuation were also more frequent in our cohort. We found an overall treatment suspension in 28.4% of patients, with 12.6% due to aquaretic effects and 8.4% due to elevated liver enzymes. In contrast, the data reported in the pivotal clinical trial is 15.4%, 8.3%, and 1.2%, respectively [4]. Our findings were more in keeping with that reported from real-life experience in a Japanese cohort (11.1% of hepatotoxicity) [8].

The most notable finding in this study was the high incidence of CK elevation. More than a quarter of the population presented this laboratory abnormality, and all remained asymptomatic except for 2 patients who presented mild symptoms associated with this side effect. As mentioned above, only two cases have been reported where both patients remained asymptomatic, and like in our experience, patients' CK levels resolved 4–6 weeks after discontinuing tolvaptan [9]. The only significant predictor of CK elevation was an increased BMI; however, the association between high BMI and CK levels has been previously described [18]. Among the remaining studied variables, we found a non-significant association with statins, although the few patients on them continued to take tolvaptan; a lower eGFR that could have influenced CK renal excretion; and thiazide diuretics, possibly due to dehydration-induced muscle injury [19]; though during controls, we kept this medication and decided to observe and monitor as these patients had their hypertension well controlled. We cannot discard any of these possible associations as our study was observational and underpowered to find risk factors. Regarding statins, a post hoc analysis of the TEMPO 3:4 found no association between reported myalgias and asthenia among patients treated with both tolvaptan and statins and those on tolvaptan alone. However, it is worth noting that 5.2% of patients on tolvaptan alone reported myalgia, and 6% reported asthenia. Whether these symptoms are correlated with CK elevation cannot be determined as this parameter was not measured in that cohort [20].

We also could not find a definitive laboratory parameter that paralleled CK elevation. The closest one to follow the CK increase was AST, but the correlation coefficient was low, which could be due to the low number of subjects involved. Unlike the previously reported cases [9], we found no association between LDH and CK levels. The lack of correlation between CK elevation and tolvaptan dose or any other analyzed factor, and its occurrence in only some patients, leads us to consider this an idiosyncratic drug reaction, similar to its hepatotoxic effect. The mechanism that causes this hepatotoxic phenomenon is not well understood; however, some authors have reported that it may be secondary to inhibiting the bile acid transporter and the mitochondrial electron transport chain secondary to the reduced availablility of intracellular hepatic cAMP [21]. Thus, one hypothesis is that intracellular cAMP could also be reduced in muscle tissue, triggering a CK elevation in certain individuals. The uncertainty by which idiosyncratic reactions occur could be related to an immune-mediated process associated with each individual's HLA profile [22].

Our study has several limitations as it is an observational study with a small population and no unexposed control group; laboratory thresholds may be lower than the expected upper limit values adjusted for sex and race [13], we did not measure parathyroid hormone levels nor register the prevalence of hypothyroidism, and we did not register concomitant use of intramuscular injections during this period. Given the frequency (28%) of CK elevation seen in patients on tolvaptan treatment, and the potential clinical relevance of this biochemical parameter as it has a plausible biological explanation and that there is an “unexplained” incidence of myalgia of roughly 5% in tolvaptan's pivotal clinical trials, we propose adding CK measurement

to the other recommended safety lab values [7], every month after tolvaptan is initiated for 4 months and at any dose increment until more evidence is gathered regarding this potentially severe side effect.

In conclusion, we present the largest cohort that has monitored CK levels, showing that tolvaptan induces significant elevations of this parameter in an important number of ADPKD patients. However, further studies are needed to demonstrate the pathophysiological mechanism and clinical implications of this finding.

Statement of Ethics

All patients gave their written informed consent to participate in this study. It was conducted following the World Medical Association Declaration of Helsinki, national and local laws, and good clinical practice standards.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Research idea and study design: Miquel Blasco, Roser Torra, and Diana Rodríguez-Espinosa; data acquisition: Diana Rodríguez-Espinosa, Carla Bastida, María Isabel Alvarez, Cristina Alvarez, Carlos Nicolau, Maya Sánchez-Baya, César Ruiz, Mónica Furlano, and Irene Agraz-Pamplona; data analysis/interpretation: Diana Rodríguez-Espinosa, José Jesús Broseta, Miquel Blasco, Roser Torra, Luis Fernando Quintana, and Esteban Poch; statistical analysis: José Jesús Broseta, Diana Rodríguez-Espinosa, and Gastón Piñeiro; supervision or mentorship: Miquel Blasco and Roser Torra. Each author contributed important intellectual content during manuscript drafting or revision and agrees to be personally accountable for the individual's own contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated and resolved, including with documentation in the literature if appropriate.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

Funding Statement

This work has neither received public nor private funding for its implementation. The authors declare that they have no relevant financial interests.

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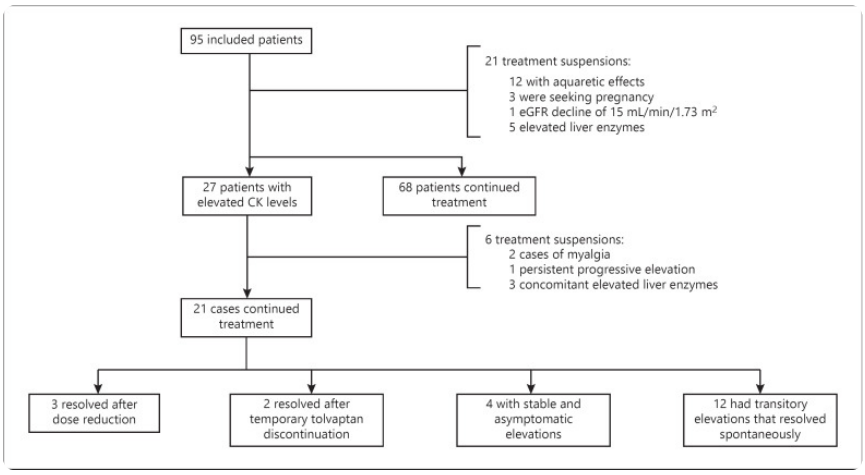
Figures and Tables

Fig. 1



Flow diagram with the number of individuals, reasons for treatment suspension, number of elevated creatine kinase levels and their management.

Table 1

Demographic and clinical characteristics of study participants according to CK levels

Characteristics	**Patients with elevated CK levels (*n* = 27)**	**Patients with normal CK levels (*n* = 68)**	***p* value**
Age, median (IQR), years	43.7 (6.5)	45.9 (8)	0.413
Male sex, *n* (%)	20 (74)	22 (32)	0.07
eGFR, mL/min/1.73 m^2, median (IQR)	59 (16.75)	60 (31)	0.358
Hypertension, mm Hg, *n* (%)	18 (67)	43 (63)	0.4
ACEi	7 (26)	35 (51)	0.1
ARBs	18 (67)	28 (41)	0.1
Thiazide diuretics	7 (26)	3 (4)	0.06
Calcium channel blockers	9 (33)	16 (24)	0.4
β-blockers	0	11 (16)	0.1
α-blockers	2 (7)	3 (4)	0.6
Statins	4 (15)	2 (3)	0.06
Smoker, *n* (%)	13 (48)	11(16)	0.1
BMI, kg/m^2, median (IQR)	27.5 (9.18)	22.4 (7.1)	0.028
Obesity, *n* (%)	12 (44)	15 (22)	0.1
Total kidney volume, mL, median (IQR)	1,586.5 (1,055.75)	1,562 (1,445.4)	0.839
Regular exercise, *n* (%)	9 (33)	20 (29)	0.5

ACEi, Angiotensin-converting-enzyme inhibitors; ARBs, Angiotensin II receptor blockers; CK, creatine kinase; eGFR, estimated glomerular filtration rate; IQR, interquartile range.