Urine Osmolarity and Risk of Dialysis Initiation in a Chronic Kidney Disease Cohort – a Possible Titration Target?

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Abstract

Background: Increasing evidence is linking fluid intake, vasopressin suppression and osmotic control with chronic kidney disease progression. Interestingly, the association between urine volume, urine osmolarity and risk of dialysis initiation has not been studied in chronic kidney disease patients before.

Objective: To study the relationship between urine volume, urine osmolarity and the risk of initiating dialysis in chronic kidney disease.

Design: In a retrospective cohort analysis of 273 patients with chronic kidney disease stage 1–4 we assessed the association between urine volume, urine osmolarity and the risk of dialysis by a multivariate proportional sub-distribution hazards model for competing risk data according to Fine and Gray. Co-variables were selected via the purposeful selection algorithm.

Results: Dialysis was reached in 105 patients over a median follow-up period of 92 months. After adjustment for age, baseline creatinine clearance, other risk factors and diuretics, a higher risk for initiation of dialysis was found in patients with higher urine osmolarity. The adjusted sub-distribution hazard ratio for initiation of dialysis was 2.04 (95% confidence interval, 1.06 to 3.92) for each doubling of urine osmolarity. After 72 months, the estimated adjusted cumulative incidence probabilities of dialysis were 15%, 24%, and 34% in patients with a baseline urine osmolarity of 315, 510, and 775 mosm/L, respectively.

Conclusions: We conclude that higher urine osmolarity is associated with a higher risk of initiating dialysis. As urine osmolarity is a potentially modifiable risk factor, it thus deserves further, prospective research as a potential target in chronic kidney disease progression.

Introduction

Medicinal use of water in chronic kidney disease (CKD) has gained research interest lately [1], as established efforts to retard CKD progression remain far from satisfactory [2]. Epidemiological data associating fluid intake or urine volume with GFR decline in humans have not been fully conclusive [3–7]. Nonetheless, there is increasing evidence linking fluid intake, vasopressin suppression and osmotic control with CKD and ADPKD progression [8–12]. Kidney excretion is adjusted according to water and dietary solute intake, as well as water and solute losses by lungs, skin, and the gastrointestinal tract. The required urine volume can be determined by dividing the daily osmolar excretion, to maintain the body’s solute content at steady state, by the maximal urinary osmolality, with failing kidneys losing capacity to concentrate urine maximally. As such, water intake required to achieve comparable urinary solute dilution varies considerably between individuals. [1]

Interestingly, median 24-hour urine osmolality is greater than that of plasma in humans, suggesting continuous antidiuretic action [13], which has been associated with renal function decline [10]. Consequently, Wang et al. recently devised a quantitative method to determine the amount of water needed on a case-by-
case basis to achieve a mean urine osmolality equivalent to that of plasma [13]. Relationships between urine osmolality (given as mosm/L compared to mosm/kg H₂O for osmolality) and GFR decline have been described in two studies [3,7] with contrasting results. We were interested in studying urine volume and urine osmolality in terms of harder endpoints in chronic kidney disease. Thus we set out to study these variables in terms of risk of initiating dialysis, with death as a competing event.

**Subjects and Methods**

**Patients**

All patients attending our nephrology outpatient department between 1 January 2000 and 31 December 2002 were included in a single-centre cohort study. The study baseline was defined as one year after the first visit, while the time period between the first visit and baseline was defined as the run-in phase. Baseline demographic data for each patient were collected from outpatient files including medication, co-morbidities, and the nature of renal disease. A minimum of two visits, with 24-hour urine samples taken before and after baseline, were defined as inclusion criteria. Exclusion criteria were a reported urine volume less than 500 ml/d or a creatinine clearance below 15 ml/min (CKD 5). The mean of all measurements taken during the run-in phase (median: 5 [25th-75th percentiles: 3–8]) was used as the baseline value for each parameter.

The primary endpoint of the study was time to dialysis, with death as the competing event. Mortality data and data on the initiation of dialysis until 31 December 2008 were obtained from Statistics Austria (the national statistics institution) and the Austrian Dialysis and Transplantation Registry (ODTR), respectively. Patients starting dialysis had no loss of follow-up according to ODTR. Because of a possible relocation of a patient to a country other than Austria, a minor loss of follow-up for mortality data from Statistics Austria cannot be excluded.

**Ethics Statement**

This was a retrospective study making use of data already collected during routine patient care at our outpatient department. The processing and analysis of data was done after anonymization. Therefore no informed consent was requested from patients. This approach was reviewed and approved by the local ethics committee (Ethikkomission Medizinische Universität Wien).

**Laboratory data**

Standard 24-hour urine samples of the patients were analysed in regard of proteinuria, creatinine, sodium, urea nitrogen, and potassium levels, in accordance with routinely used methods at our central laboratory (Clinical Institute of Medical and Chemical Laboratory Diagnostics, Medical University of Vienna). On the day of each visit, serum samples were analysed for creatinine, sodium, potassium, glucose and urea nitrogen levels in accordance with routine methods.

After conversion of glucose and urea nitrogen from mg/dl in mmol/L, the estimated urine osmolality ($U_{\text{osm}}$) (mosm/L) was calculated as follows:

$$U_{\text{osm}} = 2 \times (U_{\text{Na}} + U_{\text{K}}) + U_{\text{urea}}$$

Estimated plasma osmolality ($P_{\text{osm}}$) (mosm/L) was calculated as follows:

$$P_{\text{osm}} = 2 \times (P_{\text{Na}} + P_{\text{K}}) + P_{\text{urea}} + P_{\text{glucose}}$$

$U_{\text{Na}}, U_{\text{K}},$ and $U_{\text{urea}}$ are the concentrations of sodium, potassium and urea in the urine (all in mmol/L), and $P_{\text{Na}}, P_{\text{K}}, P_{\text{urea}}$ and $P_{\text{glucose}}$ are the concentrations of sodium, potassium, urea and glucose in plasma (in mmol/L).

**Statistical analysis**

Continuous variables were described by medians (25th to 75th percentiles), and compared between groups using Wilcoxon’s rank sum tests. Correlations between continuous variables were assessed by Spearman’s rank correlation coefficient. For further analysis, osmolality, proteinuria and creatinine clearance were log-base-2 transformed because of the skewed distributions of these variables. To describe intra- versus inter-individual variance of urine osmolality, we conducted a variance component analysis including all run-in urine osmolality values that were available for each patient using a mixed model with patients as levels of a random factor. The outcome variable was time to dialysis, with death as the competing event. Patients who were alive without dialysis at the time of their last visit were censored. Absolute event rates were computed as the number of events divided by the total follow-up time for all patients. Observations with missing values were not used in the calculated models. We described the distribution of time to dialysis using cumulative incidence functions, and compared groups using Gray’s test [14].

Due to the established relationship between baseline creatinine clearance and risk of initiating dialysis/ESRD, and the known progressive loss in urine concentration ability with decreasing renal function [1], it seemed important to introduce creatinine clearance as an adjustment factor in all further analyses.

We fitted two multivariate proportional sub-distribution hazards models for competing risk data according to Fine and Gray [15] in order to assess the effect of urine osmolality or volume on the risk for initiating dialysis. In these models, we considered osmolality or urine volume and included those variables that either proved significant in a multivariate model ($P<0.10$) or changed the log hazard ratio of osmolality or urine volume by more than 15% when those variables were excluded from the analyses (purposeful selection algorithm) [16]. We assumed that any variable not selected would have no relevant impact on our conclusions. All variables listed in Table 1 (except 24-hour proteinuria, 24-hour osmolar excretion and 24-hour sodium excretion) were considered as potential confounders. Results from multivariate competing risk regression were described by means of sub-distribution hazard ratios (SHR) and 95% confidence intervals (95% CI), and by computing and visualising estimated cumulative incidence curves at specific covariate values. As urine osmolality and creatinine clearance were log-base-2 transformed, their SHR correspond to each doubling of these variables. We checked for significant pairwise interactions of variables and for time-dependent effects by including interactions with follow-up time. Non-linear effects were assessed by the method of fractional polynomials [17]. For sensitivity analysis, we also estimated a cause-specific (death-censored) Cox regression model. The R-software, version 2.12 (www.r-project.org), was used for statistical analysis.

**Results**

**Baseline data**

Three hundred and seventy-two patients were examined for eligibility. After applying all inclusion and exclusion criteria, a total of 273 patients (56% male) with CKD class 1-4 and a median age of 56 years (42 to 67 years) were confirmed eligible and included in the study (Table 1). Median creatinine clearance was 48 (30 to 79) ml/min. Kidney disease was unknown in 46% of the patients; the
remaining patients had mainly polycystic kidney disease, different forms of glomerulonephritis, or diabetic nephropathy (Table 1). Nearly all patients received antihypertensive drugs with an effect on protein excretion, such as inhibitors of the renin angiotensin aldosterone system, non-dihydropyridine calcium channel blockers, or beta-blockers.

There was a significant inverse correlation between average run-in 24-hour urine volume and average run-in urine osmolarity (R = -0.45; P < 0.001). Urine osmolarity was significantly higher in men than in women (522 [446 to 629] vs. 458 [385 to 596] mosm/L; P = 0.05). Urine osmolarity and creatinine clearance were positively correlated (R = 0.6, p < 0.01). The total variance for run-in urine osmolarity was 45253; the intra-individual variance was about one fourth (\( s^2 = 11349 \)), i.e., random fluctuation within a patient explained 25% of the total variance, while the inter-individual variance component explained about 75% of the total variance. One patient was missing data for proteinuria, and 20 patients each were missing data for diuretics and beta-blocker therapy.

**Follow-up**
Median follow-up until death or censoring was 92 (76 to 95) months. End-stage renal disease developed in 105 patients (39%).
Thirty-eight patients (14%) died on dialysis and 35 patients (13%) died with functioning kidneys. The absolute event rate for ESRD was 0.07/year. Event rates were 0.05/year for patients with mild to moderate chronic kidney disease (CKD stage 1–3, creatinine clearance ≥30 ml/min), and 0.22/year for those with severe CKD (stage 4, creatinine clearance 15–29 ml/min).

**Urine osmolarity and risk of initiating dialysis**

Univariate analysis, without adjustment for baseline creatinine clearance (see correlation above), suggested a higher cumulative incidence of dialysis in patients with lower-than-median urine osmolalities (p<0.01). Multivariate competing risk regression analysis, with death as the competing risk, adjusted for age, creatinine clearance, proteinuria, type of underlying renal disease, beta-blocker and diuretic therapies, showed that a higher urine osmolarity was associated with a higher risk of initiating dialysis (Table 2).

Based on this model, we estimated the adjusted cumulative incidence probabilities of dialysis for patients with three different urine osmolalities (10th, 50th and 90th percentile), assuming average values for all other covariates. A constant and stepwise significant increase was seen in patients with low (315 mosm/L), intermediate (510 mosm/L), and high (775 mosm/L) baseline urine osmolarity (Figure 1; p<0.05). At 72 months, the estimated cumulative incidence probabilities of dialysis in these patients were 13%, 24% and 34%, respectively. Lower baseline creatinine clearance, higher baseline protein excretion, the type of underlying renal disease, and treatment with diuretics were also independently associated with a higher risk of dialysis (Table 2). No significant interactions of urine osmolarity with other variables in the model were found. There was no evidence of time-dependent effects or a non-linear effect of urine osmolarity or any other metric covariate. The cause-specific Cox model yielded a similar result for the adjusted effect of urine osmolarity (cause-specific hazard ratio 2.19, 95% CI 1.21 to 3.95).

**Urine volume and risk of initiating dialysis**

There was a significant inverse association between average 24-hour urine volume and average urine osmolarity (R = −0.46; P<0.01). Therefore, we did not adjust for urine osmolarity in the multivariate regression analysis for urine volume. In this model, higher protein excretion, lower creatinine clearance, and the underlying renal disease but not urine volume were associated with a higher risk of dialysis (Table 3).

| Table 2. The independent effect of urine osmolarity, age, protein excretion, kidney function, renal disease and different drugs, on the risk of initiating dialysis in the competing risk regression analysis. |
|---|---|---|---|
| **Urine osmolarity (per doubling)** | **SH Ratio** | **95% confidence interval** | **p-value** |
| | 2.04 | 1.06 | 3.92 | 0.03 |
| **Age (per decade)** | 0.87 | 0.74 | 1.02 | 0.08 |
| **Proteinuria (per doubling)** | 1.85 | 1.60 | 2.13 | <0.001 |
| **Creatinine clearance (per doubling)** | 0.15 | 0.09 | 0.23 | <0.001 |
| **Renal disease (PKD vs. other renal diseases)** | 3.44 | 1.73 | 6.81 | <0.001 |
| **Beta-blocker therapy (yes vs. no)** | 1.54 | 0.97 | 2.43 | 0.07 |
| **Diuretic therapy (yes vs. no)** | 1.62 | 1.03 | 2.55 | 0.04 |

Abbreviations: SH Ratio, subdistribution hazard ratio; PKD, polycystic kidney disease doi:10.1371/journal.pone.0093226.t002

**Discussion**

The present study demonstrates an independent, positive relationship between urine osmolarity and risk of initiating dialysis in a cohort of CKD patients stage 1 through 4. Competing risk models were adjusted for age, creatinine clearance, proteinuria, type of underlying renal disease, beta-blocker and diuretic therapies. Two published studies have described relationships between 24-hr urine osmolarity and GFR change over time. Hebert et al. reported a significant inverse relationship between baseline urine osmolarity and GFR decline in non-polycystic kidney disease patients (subgroup of full cohort), adjusted for diet, blood pressure and body surface area. Adjusting for additional covariates such as baseline GFR or diuretics use failed to result in statistically
Opposed to the prevailing view that water is beneficial in CKD, osmolarity in several studies. [3,19] Other authors have used estimated urine osmolarity (collected after the study baseline; thus, not fully comparable) and did stay significant after further adjustments. [3] In support of Hebert et al., Wang et al. found a weak, but significant association between higher urine volume and GFR decline. [4] A large study by Clark et al. showed a relationship between higher urine volume and lower rate of eGFR decline, which stayed significant after multivariable adjustment. [5] Another large study reported worse kidney function in individuals with a lower self-reported fluid intake [6]; however, neither urine volume nor urine osmolarity were evaluated. It has been suggested that lower mean baseline GFR in cohorts of Hebert et al. and Wang et al., which is associated with alterations in water metabolism, might explain these paradoxical findings. With falling GFR, the ability to concentrate urine to osmolalities greater than that of plasma is progressively lost. [1] As such, in contrast to the general population, solute excretion and urine osmolality are closely interrelated in severe chronic kidney disease [20,21]. In our study we did not find a significant relationship between urine volume and a higher risk of dialysis. The rather weak association between urine volume and 24-hour urine osmolality in the present study suggests that, in contrast to patients with severe kidney failure, urine concentration by vasopressin was still effective in the vast majority of the patients.

Stimulation of vasopressin secretion is supposed to be the cause of the more rapid decline of kidney function in patients with a high urine osmolarity. Vasopressin exerts a range of different effects and interacts through the three receptors V1a, V2 and V1b [22]. The antidiuretic effect is mainly mediated by the V2 receptor and includes increased tubular permeability for water and urea, and stimulation of ENaC-mediated sodium reabsorption [22]. Chronic administration of vasopressin in rats was shown to increase renal blood flow, glomerular filtration rate, and renal mass [23–25]. Vice versa, prevention of hyperfiltration in 5/6 nephrectomised rats by chronic inhibition of vasopressin secretion led to less glomerular sclerosis, less interstitial fibrosis and slower progression of renal failure [8,9,26]. However, precise plasma levels of vasopressin are difficult to obtain. Furthermore, non-detectable changes of vasopressin lead to a broad range of different urine osmolalities [22].

The optimal range of urine osmolality is difficult to define. Studies in normal rats and healthy humans have shown that urine concentration above an osmolality of about 300 mosm/L induces a significant hyperfiltration [22,27]. In accordance with these findings we registered the lowest risk of initiating dialysis in patients with a urine osmolarity of a similar range. On the other hand we cannot rule out that urine osmolarity values below those

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**Table 3.** The independent effect of urine volume, age, protein excretion, kidney function, renal disease and different drugs, on the risk of of initiating dialysis in the competing risk regression analysis.

|                      | SH Ratio | 95% confidence interval | p-value |
|----------------------|----------|-------------------------|---------|
| Urine volume (per 0.5 L/d) | 1.05     | 0.92                    | 1.20    | 0.49    |
| Age (per decade)     | 0.90     | 0.77                    | 1.05    | 0.18    |
| Proteinuria (per doubling) | 1.79     | 1.54                    | 2.07    | <0.001  |
| Creatinine clearance (per doubling) | 0.20     | 0.13                    | 0.30    | <0.001  |
| Renal disease (PKD vs. other renal diseases) | 3.76     | 1.92                    | 7.34    | <0.001  |
| Beta-blocker therapy (yes vs. no) | 1.58     | 0.98                    | 2.54    | 0.06    |
| Diuretic therapy (yes vs. no) | 1.59     | 0.99                    | 2.54    | 0.05    |

Abbreviations: SH Ratio, subdistribution hazard ratio; PKD, polycystic kidney disease
in our cohort range might worsen the risk of renal function decline as suggested by the cohort of Hebert et al. (see above).

Either increasing fluid intake or decreasing the intake of osmolytes could achieve a reduction of urine osmolality. A recently published formula could be used to estimate the quantity of fluid needed to achieve a urine osmolality equivalent to that of plasma [15]. An automatic approach might be the use of vaptans, which suppress vasopressin activity by antagonistic binding to the VP receptors. Recently a protective effect of dual V1α/V2 blockade on the progression of CKD has been reported in rats [28]. A similar effect has been shown in diabetic rats, where the rise in albuminuria was prevented by a V2 antagonist [29].

Our study is limited by its design. As an observational cohort study can only prove associations and not causality, it remains to be proven in a prospective trial that changing urine osmolality indeed has a positive effect on rate of renal function decline in CKD, before any therapeutic recommendation can be made. Furthermore, our study cohort showed a high event rate for ESRD, which might be explained by the cohort’s relatively high baseline proteinuria. Thus, it is not clear if the study results are applicable to CKD populations with different demographics. Nonetheless, our study further strengthens the link between urine osmolality and renal function decline by establishing a relationship with risk of dialysis initiation. In addition to the hard end-point of ESRD, a long follow-up period, the use of baseline variables issued from several measurements over a 1 year run-in phase reducing the impact of possible occasional sampling errors, and the application of competing risk analysis techniques strengthen the conclusions of this study.

With it is indisputable that, in the presence of a competing risk such as death, cumulative incidence curves are the method of choice rather than conventional Kaplan-Meier estimates, there is some controversy as to whether the standard cause-specific (death-censored) Cox regression analysis or the proportional sub-distribution hazards (Fine-Gray) model should be used to obtain adjusted hazard ratios. We decided to use the latter because it directly models differences in cumulative incidences and permits the investigator to predict the cumulative incidence of ESRD based on the covariate values of a patient. This would not have been possible when using the cause-specific Cox model. Our competing risk analysis using the Fine-Gray model mirrors more precisely the association between a covariate and the cumulative incidence of ESRD in patients at high risk of death during the observation period. Our observation that urine osmolality might be positively associated with the risk for ESRD is robust as regards the type of analysis used, as results of the cause-specific Cox model were very similar.

In conclusion, we demonstrate that higher urine osmolality is independently associated with a higher risk of initiating dialysis in a cohort of patients with CKD stage 1 to 4. Modifying urine osmolality by dietary counselling or pharmaceutical interventions might evolve into a further treatment option in ESRD.

Author Contributions
Conceived and designed the experiments: MP MK LB GH MH. Performed the experiments: SS AH. Analyzed the data: MP MK LB GH MH. Contributed reagents/materials/analysis tools: MP MK GH. Wrote the paper: MP MK LB GH MH.

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