ORIGINAL ARTICLE

Does lower urine-specific gravity predict decline in renal function and hypernatremia in older adults exposed to psychotropic medications? An exploratory analysis

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Abstract

Background: Exposure to psychotropic agents, including lithium, antipsychotics and antidepressants, has been associated with nephrogenic diabetes insipidus (NDI). This is especially concerning in older adults already at risk of developing chronic kidney disease (CKD) and hypernatremia with advanced aging. This study investigates whether commonly performed random urine-specific gravity (USG) tests can predict adverse NDI outcomes (CKD and hypernatremia) in psychotropic-exposed older adults.

Methods: This was a retrospective longitudinal study of 173 geriatric psychiatry patients (age ≥65 years) exposed to psychotropic medications. Our main continuous outcome was 'decrease in estimated glomerular filtration rate (eGFR) >10 mL/min/1.73 m²' over 5-year follow-up. Hypernatremia and acute kidney injury (AKI) were secondary outcomes. Whether baseline USG <1.010 predicted outcomes was assessed in bivariate and multivariate analyses.

Results: USG <1.010 predicted hypernatremia episodes (sodium concentration ≥150 mmol/L—28.1 versus 12%, χ^2 = 4.7, P = 0.03). USG <1.010 [odds ratio 2.36 (95% confidence interval 0.93–6.0), P = 0.07], baseline eGFR and typical antipsychotic use independently predicted decrease in eGFR >10 mL/min/1.73 m². Patients with a single baseline sodium concentration of ≥140 mmol/L and USG <1.010 have a 26.3% incidence of AKI and a 57.9% incidence of hypernatremia over the ensuing 5 years.

Conclusions: In psychotropic-exposed older adults, there appears to be a clinically important association between low USG and developing both hypernatremia and CKD. USG may be a useful surrogate measure for NDI-related outcomes in large administrative database studies, where ideal measures such as 24-h urine volume may not be available.

Key words: hypernatremia, nephrogenic diabetes insipidus, older adults, renal disease, urine specific gravity

Introduction

Nephrogenic diabetes insipidus (NDI) is characterized by the kidney's inability to respond to antidiuretic hormone, leading to excessive dilute urine and thirst [1, 2]. Lithium is the psychotropic agent most associated with NDI. However, exposure to other psychiatric medications [3], including antidepressants [4] and

antipsychotics [2, 5–7] as well as normal aging [8, 9], can increase the risk of NDI. This is concerning for older adults with psychotropic exposure, since NDI is a risk factor for chronic kidney disease (CKD) [8–10], acute kidney injury (AKI) [11] and hypernatremia [12], all of which are associated with hospitalization and elevated mortality [12]. Despite these significant risks, the long-term consequences of NDI have not yet been evaluated in older psychiatric patients exposed to psychotropic medications.

It remains unknown whether randomly ascertained low urine-specific gravity (USG), with or without water restriction, may be a helpful predictor of future NDI-related medical outcomes in psychiatric patients. NDI is often measured using urine osmolality following 10–24 h of water restriction. However, USG <1.010 appears to correspond very closely to urine osmolality <300 mOsm/kg (r = 0.84) [13]. Random USG is often routinely performed in geriatric psychiatry clinical practice [14]. If random USG could predict adverse NDI outcomes in psychiatric patients, this would be highly translatable into clinical practice.

In this study, we hypothesized that in older psychiatric patients exposed to psychotropics, randomly ascertained low USG would be associated with serious NDI-related conditions such as CKD, AKI and hypernatremia in long-term follow-up.

Materials and methods

This was a retrospective study performed at the Jewish General Hospital (JGH) in Montreal, Canada. Between 2003 and 2008, 226 geriatric psychiatry patients were admitted in the inpatient psychiatric unit. Of these, 173 patients had USG test results available at baseline and were therefore included in our analyses. All patients included in the analysis were followed for the entire 5 years (e.g. 2007–2012 if hospitalized in 2007). Our data included both outpatient and inpatient laboratory records from the JGH, where patients were followed in geriatric psychiatry and obtained blood tests at least once annually. Patients also often obtained blood tests from other medical specialists or family physicians at the JGH. Ethical approval was obtained at the JGH.

Exposures

The main continuous and dichotomous exposure variables were USG and decreased USG (defined as USG <1.010), respectively. USGs had been randomly ascertained as part of clinical practice, not necessarily following a period of water restriction. These were usually routinely performed in the emergency room immediately prior to patients' baseline psychiatric admission. USG was measured using reagent strips at the JGH Diagnostic Medicine laboratory (http://jgh.ca/en/DiagnosticMedicine).

Outcome measures

The main outcome was having a clinically important decrease in estimated glomerular filtration rate (eGFR) ≥10 mL/min/1.73 m^2, over 5-year follow-up based on the National Institutes for Health and Clinical Excellence (NICE) guidelines [15]. Baseline eGFR was measured at the same time as USG in the emergency room immediately prior to patients' baseline psychiatric admission. Both baseline and 5-year eGFR values were calculated from serum creatinine using the Modification of Diet in Renal Disease (MDRD) formula [15]. All blood for serum creatinine measurements was processed at the JGH Diagnostic Medicine laboratory (http://jgh.ca/en/DiagnosticMedicine).

Secondary outcomes included hypernatremia defined as either at least one serum sodium concentration ≥147 mmol/L or ≥150 mmol/L during the 5-year study period follow-up [16] and

AKI (at least one event involving an acute 50% reduction in eGFR compared with baseline) [17]. Two thresholds were used to assess hypernatremia: although concentrations ≥147 mmol/L have been associated with hospitalization and even mortality [12], many clinicians have considered ≥150 mmol/L as a more clinically important cutoff [16].

Statistical analysis

Baseline demographic characteristics were described. USG <1.010 and USG ≥1.010 groups were compared using bivariate correlations, χ^2 and Fisher's exact tests, as appropriate for factors previously associated with NDI such as age, sex, lithium exposure and use of other certain psychiatric medications at baseline (e.g. atypical and typical antipsychotics, as well as antidepressants) [3, 8, 9, 13].

Additionally, logistic regression tests were then conducted to assess whether USG independently predicted 'change in eGFR >10 mL/min/1.73 m^2' [12]. Potential confounding variables were assessed with bivariate correlations, χ^2 or t-tests with 'change in eGFR >10 mL/min/1.73 m^2', and were included in the multivariate model if P < 0.10. The variables tested were age, hypertension, diabetes mellitus and use of medications such as angiotensin converting enzyme inhibitors (ACEIs), angiotensin-2 receptor blockers (ARBs), non-steroidal anti-inflammatory drugs (NSAIDs), hydrochlorothiazide, loop diuretics, typical and atypical antipsychotics [7, 18].

Theoretically, a baseline USG of <1.010 and sodium concentration ≥140 mmol/L (both measured at the same time as other baseline tests) in combination would have similar or higher predictive value for NDI outcomes than USG alone: we performed additional exploratory analyses to assess whether this was the case.

Results

Sample characteristics

Patients had a mean age of 76.6 years, and 64% of them were female. USG <1.010 trended towards being associated with advanced age [77.5 versus 75.1 years, t(169) = 1.7, P = 0.09] and less ACEI use (20.9 versus 37.2%, χ^2 = 4.56, P = 0.033), while other factors previously associated with NDI, such as lithium use (n = 13) or antipsychotic use (n = 110), were not significantly correlated with USG (Table 1).

USG and outcomes

In bivariate analyses (Table 2), USG <1.010 was associated with several NDI-related outcomes in 5-year follow-up. This was the case for events of hypernatremia at both thresholds—sodium concentration ≥150 mmol/L (28.1 versus 12%, χ^2 = 4.7, P = 0.03) and ≥147 mmol/L (50 versus 32%, χ^2 = 3.4, P = 0.06). In the hypernatremic patients, sodium concentration ranged from 147 to 163 mmol/L. Although it did not predict AKI, USG <1.010 predicted having long-term renal decline: having a lower eGFR after 5-year follow-up [66.5 versus 78.1 mL/min/1.73 m^2, t(129) = 2.03, P = 0.04] and having a decrease in eGFR by >10 mL/min/1.73 m^2 (40.6 versus 25%, χ^2 = 2.88, P = 0.09).

For the multivariate analysis, USG <1.010, lithium use, typical antipsychotic use and baseline eGFR had bivariate associations/trends with decrease in eGFR >10 mL/min/1.73 m^2 (P < 0.10) and were included in the regression model (Table 3). USG <1.010 [odds ratio 2.36 (95% confidence interval 0.93–6.0), P = 0.07], baseline eGFR and typical antipsychotic use independently predicted decrease in eGFR >10 mL/min/1.73 m^2. These results remained significant when including only non-lithium patients.

Table 1. Baseline demographic and clinical characteristics

	USG <1.010 (*n* = 43) [% (*n*) or mean (±SD)]	USG >1.010 (*n* = 130) [% (*n*) or mean (±SD)]	Statistics
Demographics			
Age (years)	75.1 (±7.2)	77.5 (±7.9)	$t(169) = 1.70$, P = 0.09
Female gender	69.8% (*n* = 30)	63.1% (*n* = 82)	$\chi^2 = 0.63$, P = 0.43
Medication variables (*n* = 169)			
Number of psychotropics	2.19 (±1.02)	2.27 (±1.14)	$t(168) = 0.42$, P = 0.67
Lithium use	11.9% (*n* = 5)	6.3% (*n* = 8)	Fisher's exact P = 0.31
Antidepressant use	48.8% (*n* = 21)	51.5% (*n* = 67)	$\chi^2 = 0.09$, P = 0.76
Atypical antipsychotic use	58.1% (*n* = 25)	70.5% (*n* = 91)	$\chi^2 = 2.26$, P = 0.13
Typical antipsychotic use	7.0% (*n* = 3)	6.2% (*n* = 8)	Fisher's exact P = 1.0
Hydrochlorothiazide use	16.3% (*n* = 7)	16.3% (*n* = 21)	$\chi^2 = 0.00$, P = 1.0
Loop diuretic use	12.2% (*n* = 5)	10.2% (*n* = 13)	$\chi^2 = 0.12$, P = 0.72
ACEIs/ARBs	20.9% (*n* = 5)	37.2% (*n* = 13)	$\chi^2 = 4.56$, P = 0.033
NSAID/COX-2 inhibitor use	37.2% (*n* = 16)	31.0% (*n* = 40)	$\chi^2 = 0.56$, P = 0.45
Medical history			
Hypertension	53.5% (*n* = 23)	55.0% (*n* = 71)	$\chi^2 = 0.03$, P = 0.86
Diabetes mellitus	16.3% (*n* = 7)	22.5% (*n* = 29)	$\chi^2 = 0.75$, P = 0.39
Baseline eGFR (mL/min/1.73 m^2) (*n* = 169)	67.1 (±17.6)	73.8 (±25.2)	$t(167) = 1.57$, P = 0.12
Baseline sodium concentration (*n* = 136)	140.5 (±4.4)	140.8 (±3.5)	$t(134) = 0.49$, P = 0.63

SD, standard deviation; ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin-2 receptor blockers; NSAID, non-steroidal anti-inflammatory drug; COX-2, cyclooxygenase-2; eGFR, estimated glomerular filtration rate.

Table 2. USG <1.010 and NDI outcomes during 5-year follow-up

	USG <1.010 (*n* = 43) [% (*n*) or mean (±SD)]	USG ≥1.010 (*n* = 130) [% (*n*) or mean (±SD)]	Statistics
eGFR after 5-year follow-up (mL/min/1.73 m^2) (*n* = 132)[a]	66.5 (±29.1)	78.1 (±27.6)	$t(129) = 2.03$, P = 0.04
Change in eGFR (mL/min/1.73 m^2) (*n* = 132)	0.20 (±24.8)	4.6 (±22.9)	$t(129) = 0.93$, P = 0.35
eGFR decrease >10 mL/min/1.73 m^2 (*n* = 132)	40.6% (*n* = 13)	25.0% (*n* = 25)	$\chi^2 = 2.89$, P = 0.09
Largest % decrease in eGFR from baseline during follow-up	27.7% (±28.5%)	20.5% (±29.6%)	$t(131) = 1.21$, P = 0.23
At least one event of AKI (>50% decrease in eGFR from baseline) (*n* = 131)	18.8% (*n* = 6)	11.1% (*n* = 11)	$\chi^2 = 1.25$, P = 0.26
Highest sodium concentration during 5-year follow-up (mmol/L)	147.7 (±7.6)	145.8 (±4.9)	$t(131) = 1.65$, P = 0.10
At least one event of serum sodium concentration ≥147 mmol/L (*n* = 132)	50.0% (*n* = 16)	32.0% (*n* = 32)	$\chi^2 = 3.40$, P = 0.06
At least one event of serum sodium concentration ≥150 mmol/L (*n* = 132)	28.1% (*n* = 9)	12.0% (*n* = 12)	$\chi^2 = 4.71$, P = 0.03

SD, standard deviation; eGFR, estimated glomerular filtration rate; AKI, acute kidney injury.
[a]Baseline eGFR and eGFR after 5-year follow-up were available in *n* = 169 and *n* = 132 patients, respectively.

Table 3. Logistic regression: independent predictors of decrease in eGFR >10 mL/min/1.73 m^2

	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Wald χ^2 (adjusted OR)	P-value (adjusted OR)
Lithium	3.22 (1.01, 10.2)	1.62 (0.41, 6.5)	0.47	0.50
Typical antipsychotics	4.42 (1.01, 19.3)	4.71 (0.81, 27.3)	2.99	0.08
Baseline eGFR (mL/min/1.73 m^2)	1.03 (1.01, 1.05)	1.03 (1.01, 1.05)	8.96	0.003
USG <1.010	2.05 (0.89, 4.75)	2.36 (0.93, 6.0)	3.27	0.07

OR, odds ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate.

A total of 19 people (11.0% of the sample) had both USG <1.010 and a baseline sodium concentration ≥140 mmol/L. Compared with other patients, these patients (*n* = 19) had higher rates of decrease in eGFR >10 mL/min/1.73 m^2 (52.6 versus 25.9%, χ^2 = 5.74, P = 0.017), hypernatremia ≥147 mmol/L (57.9 versus 35.3%, χ^2 = 3.64, P = 0.056) and even AKI (26.3 versus 11.2%, Fisher's exact P = 0.078), as well as higher peak sodium concentration during 5-year follow-up [149.7 versus 145.7 mmol/L, *t*(132), P = 0.028].

Discussion

We found that USG <1.010 was associated with lower eGFR at 5-year follow-up, higher rates of eGFR decreases >10 mL/min/ 1.73 m^2 and hypernatremic events. Patients with a single baseline sodium concentration of ≥140 mmol/l and USG <1.010 had a 26.3% incidence of AKI and a 57.9% incidence of hypernatremia over the ensuing 5 years. This supports the possible role of NDI as a mechanism responsible for hypernatremia [12] and eGFR decline in geriatric psychiatry patients exposed to psychotropic medications [10, 12, 18]. We found that even non-lithium psychotropic exposure may contribute to hypernatremia and renal dysfunction in older adults, consistent with some early findings in the literature [10, 18].

Interestingly, random USG, which is not as specific for NDI as 24-h urine volume or urine osmolality following 10–24 h water restriction, was able to predict these hypothesized NDI outcomes in

psychiatric patients. This suggests that random USG could be used as a proxy measure for NDI in large administrative database analyses or other retrospective studies where more specific NDI measures are unavailable. This also suggests that when more specific NDI measures are used in future prospective studies of psychotropic-exposed populations, NDI will likely predict future events of hypernatremia and renal decline.

It is possible that baseline AKI in some patients may explain in part the improvement in eGFR and high rates of eGFR decreases >10 mL/min/1.73 m^2 [10] in both USG <1.010 and USG ≥1.010 groups over 5-year follow-up (40.6 and 25%). However, this may require further investigation, since the course of eGFR decline can be highly variable in older adults—although patients generally decline 0.8 mL/min/1.73 m^2, some patients' eGFR dramatically decreases while other patients' eGFR increases [15]. Other possibilities explaining why USG <1.010 and ≥1.010 groups had an overall mean eGFR increase include that some patients had AKI at presentation or that there had been weight loss with decreased creatinine production.

Limitations

Our study had some notable limitations. It was not possible to obtain USG values under uniform conditions of water restriction, so there are other possible explanations for a low USG. Some patients may have a dilute urine because psychotropic drugs can make them thirsty and therefore drink excessively. Other patients may have low urinary solute excretion because they are not eating much. Nonetheless, USG <1.010 predicted 5-year renal and hypernatremia outcomes and the data in our study are similar to those available in routine clinical practice and administrative databases. Secondly, it would have been useful to have a non-psychiatric control group to verify whether USG was lower in psychotropic-exposed patients. Additionally, lithium use was not statistically associated with USG <1.010 (11.9 versus 6.3%, P = 0.31), which may have been primarily related to power (n = 13 lithium users, Table 1). Although patients with lower USG had lower baseline eGFR, we controlled for this in our logistic regression. If anything, the association between low USG and subsequent decline may be larger than our results show, since patients with low baseline eGFR are less likely to have subsequent eGFR reductions [13]. During the time period of our study, many laboratories worldwide changed their creatinine assay, which would have affected eGFR measurements; however, this was not the case at the JGH in our study. Many nephrologists consider eGFR unreliable in acutely ill patients and would perhaps prefer serum creatinine in our study's baseline renal function blood tests from the psychiatric emergency room. We used eGFR since this is often the preferred measure for our main outcome, change in renal function over 5-year follow-up [15]. Lastly, we did not have access to data regarding the duration and dosage of medications used during the 5-year follow-up, although psychotropic medication use patterns tend to stay relatively unchanged in 80% of older adults over 5-year follow-up [10]. Future prospective studies could confirm our findings by subjecting participants to both random USG and more specific NDI measures (e.g. urine osmolality following water restriction).

Conclusion

Our results suggest that lower USG may predict an increased 5-year risk of eGFR decline and hypernatremia among elderly psychiatric patients. This may imply that NDI is present in a subset of older adults exposed to psychotropic medications, including non-lithium users. Additionally, random USG could be useful as a surrogate for NDI when examining NDI-related outcomes in large administrative health data studies (including CKD, hypernatremia and even mortality), where more detailed data are unavailable.

Conflict of interest statement

None declared.

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