Received: 20 September 2022 | Revised: 13 December 2022 | Accepted: 28 December 2022

DOI: 10.1111/acps.13531

ORIGINAL ARTICLE

Acta Psychiatrica Scandinavica WILEY

Acute effects of lithium augmentation on the kidney in geriatric compared with non-geriatric patients with treatment-resistant depression

Sarah Luise Osterland[1] | **Mazda Adli**[1,2] | **Turgay Saritas**[3,4] | **Peter Schlattmann**[5] | **Joachim Behr**[6,7,8] | **Ronja Müller-Mertel**[9] | **Kai Hoffmann**[1] | **Thomas J. Stamm**[1,9] | **Tom Bschor**[10] | **Christoph Richter**[1,11] | **Bruno Steinacher**[12,13] | **Maria-Christiane Jockers-Scherübl**[14] | **Stephan Köhler**[1] | **Andreas Heinz**[1] | **Roland Ricken**[1] | **Pichit Buspavanich**[6,7,15]

[1]Department of Psychiatry and Psychotherapy, Charité - Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany

[2]Department of Psychiatry and Psychotherapy, Fliedner Klinik Berlin, Berlin, Germany

[3]Division of Nephrology and Clinical Immunology, University Hospital RWTH Aachen, Aachen, Germany

[4]University Hospital RWTH Aachen, Institute of Experimental Medicine and Systems Biology, Aachen, Germany

[5]Department of Statistics, Informatics and Data Sciences, Jena University Hospital, Jena, Germany

[6]Department of Psychiatry, Psychotherapy and Psychosomatics, Brandenburg Medical School Theodor Fontane, Neuruppin, Germany

[7]Faculty of Health Sciences Brandenburg, Joint Faculty of the University of Potsdam, Brandenburg University of Technology Cottbus-Senftenberg and Brandenburg Medical School, Potsdam, Germany

[8]Research Department of Experimental and Molecular Psychiatry, Department of Psychiatry and Psychotherapy, Charité - Universitätsmedizin Berlin, Berlin, Germany

[9]Department of Psychology - Clinical Psychology and Psychotherapy, Brandenburg Medical School Theodor Fontane, Neuruppin, Germany

[10]Department of Psychiatry and Psychotherapy, Technical University of Dresden Medical School, Dresden, Germany

[11]Department of Psychiatry and Psychotherapy, Vivantes Klinikum Kaulsdorf, Berlin, Germany

[12]Department of Psychiatry and Psychotherapy, Vivantes Wenckebach-Klinikum, Berlin, Germany

[13]Department of Psychiatry and Psychotherapy, Vivantes Auguste-Viktoria-Klinikum, Berlin, Germany

[14]Department of Psychiatry, Oberhavel Kliniken, Hennigsdorf, Germany

[15]Research Unit Gender in Medicine, Department of Psychiatry and Psychotherapy, Institute of Sexology and Sexual Medicine, Charité - Universitätsmedizin Berlin, Berlin, Germany

Correspondence
Pichit Buspavanich, Department of Psychiatry and Psychotherapy, Charité Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany.
Email: pichit.buspavanich@charite.de

Funding information
Mood Disorders Research Unit of Charité -

Abstract

Introduction: Lithium augmentation (LA) of antidepressants is a first-line therapy option for treatment-resistant depression (TRD). Nevertheless, it is rarely used in geriatric patients mostly because of the fear of kidney toxicity. The purpose of this study is to investigate estimated glomerular filtration rate

Roland Ricken and Pichit Buspavanich contributed equally to this work.

Universitätsmedizin Berlin, Department of Psychiatry and Psychotherapy, Campus Charité Mitte (CCM). We acknowledge financial support from the Open Access Publication Fund of Charité – Universitätsmedizin Berlin and the German Research Foundation (DFG).

(eGFR) changes and number of acute kidney injuries (AKI) using LA in geriatric compared with non-geriatric patients.

Methods: In a prospective multicenter cohort study, eGFR changes were measured in 201 patients with unipolar depression ($n_{age\geq65years} = 29$; $n_{age<65years} = 172$) at baseline and over 2–6 weeks of LA. We used linear mixed models to investigate changes in eGFR upon LA and assessed the number of AKIs, according to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.

Results: Both age groups showed a significant eGFR decline over the course of treatment with lower eGFR in geriatric patients. The lithium serum level (interpretable as "effect of LA") had a significant effect on eGFR decline. Both effects (age group and lithium serum level) on eGFR decline did not influence each other, meaning the effect of LA on eGFR decline did not differ between age groups. Two AKIs were observed in the geriatric age group when serum lithium levels exceeded the therapeutic range of >0.8 mmol/L.

Conclusion: This is the first study investigating eGFR change and AKI upon LA for TRD in geriatric compared with non-geriatric patients. Our data suggest that LA, as an effective treatment option in geriatric patients, should be closely monitored to avoid AKIs.

KEYWORDS

acute kidney injury, geriatric patients, glomerular filtration rate, lithium augmentation, treatment-resistant depression

1 | INTRODUCTION

Lithium augmentation (LA) is the first line therapy in treatment-resistant depression (TRD) for non-geriatric as well as geriatric patients.[3,24,35] Previous studies have shown a high efficacy of LA in geriatric patients with TRD.[4] Lithium is almost entirely excreted through the kidneys and therefore its toxicity depends on kidney function.[14] Due to the narrow therapeutic range, it is necessary to monitor the lithium serum level regularly to avoid severe lithium intoxication with possible life-threatening consequences such as acute kidney injuries (AKI).[13,20]

Especially in geriatric patients, safety concerns exist regarding lithium, for example, because of a natural age-related decline in glomerular filtration rate (GFR) and a higher occurrence of somatic comorbidities leading to polypharmacy.[6,24,40] The risk of lithium intoxication can be lowered by awareness of potentially interacting drugs, frequent laboratory controls, adequate patient instructions and education on side effects.[11]

There are several studies that have investigated the kidney toxicity of lithium. Most of these studies have focused on patients with bipolar disorders.[21,30,35] McKnight et al. concluded in their meta-analysis that there is little evidence for a clinically significant reduction in kidney function except of reduced kidney

Significant outcomes

- Both age groups showed a significant eGFR decline over the course of treatment with lower eGFR in geriatric patients. The lithium serum level had a significant effect on eGFR decline.
- Both effects (age group and lithium serum level) on eGFR decline did not influence each other, meaning the effect of LA on eGFR decline did not differ between age groups.
- Two acute kidney injuries were observed in the geriatric age group when lithium levels exceeded the therapeutic range during acute therapy.

Limitations

- Main limitation of our study is the lack of a control group for age-matched subjects not exposed to lithium.
- Considering that we focused on the acute phase of LA to capture AKIs, we therefore cannot predict any long-term effects of LA on kidney functions.

TABLE 1 Comparison of characteristics: Geriatric versus non-geriatric patients; *n* (%), mean [standard deviation]

	All participants $N = 201$	Geriatric patients $n = 29$	Non-geriatric patients $n = 172$	*p*-Value*
Age (years)	50.23 [13.6]	72.14 [5.4]	46.53 [10.7]	
Sex				0.99
Male	76 (37.8)	11 (37.9)	65 (37.8)	
Female	125 (62.2)	18 (62.1)	107 (62.2)	
BMI at baseline (kg/m^2)	26.23 [5.59]	26.19 [6.1]	26.23 [5.5]	0.86
Co-medication affecting lithium level at baseline[a,b]	36 (17.9)	13 (44.8)	23 (13.4)	**<0.01**
Nephrotoxic co-medication at baseline[a,c]	8 (4.0)	2 (6.9)	6 (3.5)	0.33
Comorbidities				
Hypertension	35 (17.4)	12 (41.4)	23 (13.4)	**<0.01**
Diabetes mellitus	9 (4.5)	3 (10.3)	6 (3.5)	0.12
Charlson comorbidity index[d]	0.25 [0.8]	0.55 [1.2]	0.20 [0.7]	**0.02**
Last measured lithium serum level (mmol/L)	0.67 [0.19]	0.71 [0.18]	0.66 [0.19]	0.13
Sufficient lithium level	185 (92.0)	28 (96.6)	157 (91.3)	0.33
Toxic lithium serum level[e]	4 (2.0)**	4 (13.8)	0 (0.0)	**<0.01**
Number of creatinine values per patient	3.99 [1.19]	3.76 [1.12]	4.02 [1.19]	0.63
Creatinine at baseline (mg/dl)	0.84 [0.15]	0.86 [0.18]	0.84 [0.14]	0.57
Last creatinine measurement (mg/dl)	0.89 [0.19]	0.97 [0.35]	0.88 [0.15]	0.23
eGFR at baseline (ml/min/1.73 m^2)	94.75 [15.4]	80.67 [12.1]	97.12 [14.6]	**<0.01**
eGFR categories at baseline[f]				**<0.01**
≥90 ml/min/1.73 m^2	122 (60.7)	7 (24.1)	115 (66.9)	
60–89 mL/min/1.73 m^2	78 (38.8)	22 (75.9)	56 (32.6)	
30–59 ml/min/1.73 m^2	1 (0.5)	0	1 (0.6)	
15–29 ml/min/1.73 m^2	0	0	0	
≤15 mL/min/1.73 m^2	0	0	0	
Last eGFR measurement (ml/min/1.73 m^2)	89.82 [17.29]	74.78 [16.98]	92.36 [16.05]	**<0.01**
Outcome for severe nephrotoxicity: AKI[f]				
AKI1 (≥1.5 fold creatinine increase over baseline)	1 (0.5)**	1 (3.4)	0	0.14
AKI2 (≥2 fold creatinine increase over baseline)	0	0	0	
AKI3 (≥3 fold creatinine increase over baseline)	1 (0.5)**	1 (3.4)	0	0.14

[a]Stable during LA (defined as no new medication or change of dosage after start of LA).
[b]In our sample loop diuretics, thiazides, methylxanthine, angiotensin receptor blockers, angiotensin converting enzyme inhibitors, non-steroidal anti-inflammatory drugs except low dose 100 mg/day acetylsalicylic acid.
[c]In our sample ibuprofen, enalapril, topiramate, mesalazine.
[d]Severity of somatic comorbidity assessed from the updated Charlson comorbidity index.
[e]Toxic lithium serum level = >1.2 mmol/L for geriatric and >1.5 mmol/L for non-geriatric patients.
[f]AKI = acute kidney injury; classification based on Kidney Disease: Improving Global Outcomes guidelines (KDIGO).
*Result of *t* test or Mann–Whitney *U* test for metric parameters; chi-square-test or Fisher's exact test for categorical parameters.
**Clinical signs of lithium intoxication (e.g., tremor, nausea, dizziness) occurred in two cases; see Table S1 for details.
Bold indicates significant *p*-value.

concentration capacity.[21] In contrast, a recent meta-analysis by Schoretsanitis et al. found the risk for kidney impairment to be up to two-fold higher under lithium treatment with increasing risk with old age and duration of treatment.[35]

Despite the known benefit of LA in geriatric patients,[4,24] only few studies have investigated the kidney toxicity of lithium in this age group. Up to date, only two randomized controlled trials,[2,16] and four observational studies[17,27,28,41] investigated the adverse effects of lithium on kidney function in geriatric patients. They found either a decline in eGFR,[27,28,41] an improvement in kidney function after lithium discontinuation[16] or no significant kidney impairment.[2,17] There are a few retrospective studies that investigated acute effects of lithium on eGFR and separated their findings by age group but only in the context of acute lithium intoxication.[9,18]

To the best of our knowledge, there is no study comparing eGFR changes of LA in geriatric versus non-geriatric patients. The purpose of this study was to investigate eGFR changes and number of AKIs upon LA in geriatric compared with non-geriatric patients in the acute therapy of TRD in a prospective multi-center cohort study.

2 | MATERIALS AND METHODS

2.1 | Patients

The study is a prospective observational multicenter cohort study within the Berlin Research Network on Depression. Inclusion criteria were: patients with unipolar depression (ICD-10F32.1-3 and F33.1-3), at least 18 years of age, indication for an antidepressant pharmacotherapy, insufficient response to an antidepressant over at least 4 weeks and clinical indication for LA, Hamilton Depression Rating Scale (HDRS-17) score ≥12[15] and written informed consent. If patients received co-medication known to be potentially nephrotoxic[12] or potentially affecting lithium serum levels,[8] the medication had to be stable during the course of treatment (defined as no new medication or change of dosage after start of LA). For potentially nephrotoxic medication or with an effect on lithium levels at baseline see Table 1.

Exclusion criteria were: contraindication for LA (e.g., severe kidney insufficiency; chronic kidney disease [CKD] category G4 [<30 ml/min/1.73 m^2] or G5 [<15 ml/min/1.73 m^2] as defined by Kidney Disease: Improving Global Outcomes [KDIGO] 2012), depressive syndrome because of another somatic or psychiatric diagnosis, diagnosis of dementia, substance abuse disorders with abstinence of less than 6 months, and antisocial personality disorders. Patients were recruited between February 2008 and February 2020 in 12 psychiatric departments of the Berlin Research Network on Depression, Berlin, Germany. We defined geriatric patients as age ≥65 years.[38] Diagnosis of unipolar depression was confirmed by the Mini-International Neuropsychiatric Interview.[36] The majority of patients were inpatients. The local ethics committee approved the study. Severity of somatic comorbidity was assessed according to the updated version of the Charlson comorbidity index (CCI),[25] with diagnoses according to the patients´ records. The comorbidities hypertension and diabetes mellitus were assessed with the codes of the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) from the patients' records as potential risk factors for kidney function decline.

2.2 | Exposure

Patients were monitored for up to 6 weeks under LA, which is the time span during which the patients usually remained hospitalized for their initial treatment. All patients received a titration of a personalized dosage of lithium carbonate approximately over the first 2 weeks of treatment which was adapted based on individual lithium serum levels in order to reach a therapeutic concentration of 0.5–0.8 mmol/L for non-geriatric patients and 0.4–0.8 mmol/L for geriatric patients.[42,43]

A sufficient lithium level was defined as at least 0.4 mmol/L for the geriatric group[43] and at least 0.5 mmol/L for the non-geriatric group[3] for a minimum of 2 weeks. We set the cut-off for toxic lithium serum levels at 1.5 mmol/L for non-geriatric patients and 1.2 mmol/L for geriatric patients as recommended in international guidelines.[22,42] The variable "lithium serum level" describes the weekly measured lithium levels over time and as trough level, that is, immediately before the next intake.

2.3 | Outcome

Laboratory assessment was obtained from the patients´ medical records, including weekly data of serum creatinine (mg/dl), which was measured according to standard laboratory methods. The time between two measurements was approximately 1 week (range: 5–9 days) according to the weekly study visits. Included patients had to have at least one laboratory value before their first lithium dose and at least one during the treatment with LA. The last available creatinine value in the observation period of a maximum of 6 weeks set the endpoint. The Chronic Kidney Disease (CKD) Epidemiology Collaboration (CKD-EPI) 2021 equation was used to calculate the eGFR.[7,19] CKD was determined on the basis of the five stages for CKD adapted to KDIGO 2012. Stage G3 (GFR

<60 ml/min/1.73 m^2) was the cut off for the definition of "decreased" eGFR.[39] We included outcomes of a deterioration in kidney function, which was the number of AKIs upon LA, a ≥1.5 fold (AKI1), ≥2 fold (AKI2) or ≥3 fold (AKI3) serum level creatinine increase over baseline during LA adapted to KDIGO 2012.

2.4 | Statistics

To investigate eGFR changes upon LA we used a random-intercept linear mixed-effects model for repeated measurements with eGFR as the dependent and age group ("age ≥ 65 years" = geriatric patients versus "age <65 years" = non-geriatric patients) as the independent variable. We analyzed the interaction of age group and lithium serum level on eGFR to investigate if changes in eGFR over the course of treatment differ between age groups. Lithium serum level is interpretable as "effect of LA" because all participants started lithium treatment at the beginning of the study and baseline eGFR was measured before the beginning of lithium intake.

Linear mixed-effects models allow the investigation of variability between patients (heterogeneity) and the simultaneous adjustment for the within-subject correlation. We included the covariates lithium serum level sex, Charlson comorbidity index, hypertension, and co-medication affecting the lithium serum level as fixed effects into the model. Model regression coefficients are reported together with their standard error estimates (SE) and a 95% confidence interval (CI) (Table 2). For exploratory purposes, we show the result of a linear mixed model based on the covariates time, geriatric versus non-geriatric and the interaction thereof in Figure 1.

The Kolmogorov–Smirnov test was used to verify the normal distribution of the sample. For descriptive statistics *T*-test, Mann–Whitney *U* test, Chi-square test, and Fisher's exact test were applied when appropriate. A significance level of $p < 0.05$ (two-sided) was set for all analyses. We used the Statistical Analysis System (SAS) software (version 9.4) for the linear mixed models and SPSS (version 27) for descriptive statistics.

TABLE 2 The effect of LA in geriatric versus non-geriatric patients on estimated glomerular filtration rate (eGFR) (ml/min/1.73 m^2); number of observations = 783

	Parameter estimates	Standard error	95%- Confidence-interval		*t*-Value	*p*-Value
			Lower	Upper		
Age						
1 = non-geriatric (<65 years)	15.26	3.09	9.17	21.35	4.93	**<0.01**
0 = geriatric (≥65 years) (Ref)	-	-	-	-	-	-
Lithium serum level	−8.66	1.76	−12.12	−5.19	−4.91	**<0.01**
Interaction						
age group × lithium serum level						
1 = non-geriatic × lithium serum level	1.28	1.96	−2.57	5.13	0.65	0.51
0 = geriatric × lithium serum level (Ref)	-	-	-	-	-	-
Sex						
1 = Female (Ref)	-	-	-	-	-	-
0 = Male	7.08	2.03	3.09	11.08	3.49	**<0.01**
Diagnosis of hypertension (ICD-10)						
1 = yes	3.15	3.53	−3.82	10.11	0.89	0.37
0 = no (Ref)	-	-	-	-	-	-
Charlson Comorbidity Index	−3.16	1.30	−5.72	−0.60	−2.44	**0.02**
Co-medication affecting the lithium serum level						
1 = yes	−3.69	3.51	−10.62	3.23	−1.05	0.29
0 = no (Ref)	-	-	-	-	-	-

Note: Ref, Reference. ICD, International Statistical Classification of Diseases and Related Health Problems. Medication affecting the lithium serum level, Diuretics (Thiazides, Loops, Osmotics, Methylxanthine); angiotensin converting enzyme inhibitors; angiotensin receptor blockers, non-steroidal anti-inflammatory drugs (except low dose (100 mg) acetylsalicylic acid).
Bold indicates significant *p*-value.

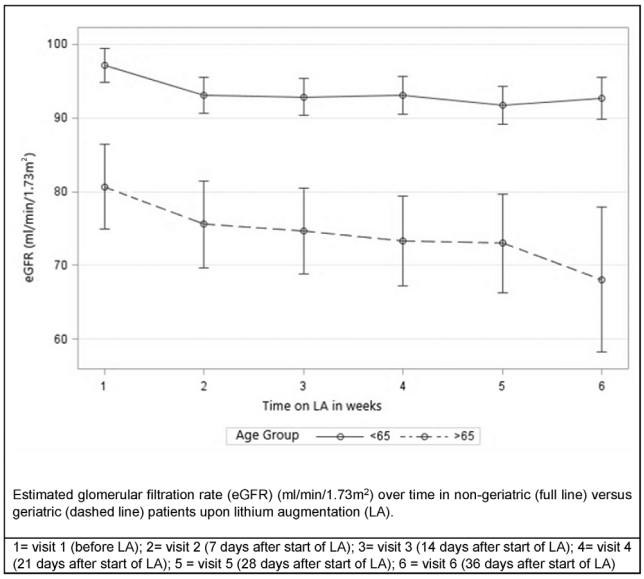

FIGURE 1 Result of a linear mixed model based on the covariates time, geriatric versus non-geriatric and the interaction thereof estimated glomerular filtration rate (eGFR) (ml/min/1.73 m^2) over time in non-geriatric (full line) versus geriatric (dashed line) patients upon lithium augmentation (LA). 1 = visit 1 (before LA); 2 = visit 2 (7 days after start of LA); 3 = visit 3 (14 days after start of LA); 4 = visit 4 (21 days after start of LA); 5 = visit 5 (28 days after start of LA); 6 = visit 6 (36 days after start of LA)

3 | RESULTS

Two hundred and one (201) patients entered the cohort according to the inclusion criteria as mentioned above. Twenty-nine (29) were geriatric (mean age [SD]: 72.1 [5.4]) and 172 were non-geriatric patients (46.5 [10.7]). For descriptive statistics, see Table 1.

The effects of LA in geriatric versus non-geriatric patients on eGFR are displayed in Table 2. Both age groups showed a significant eGFR decline over the course of treatment with lower eGFR in geriatric patients ($p < 0.01$). The lithium serum level, that can be interpreted as the "effect of LA," had a significant effect on eGFR decline ($p < 0.01$). Notably, we found no statistically significant interaction between lithium serum level and age on eGFR decline ($p = 0.51$). Both effects (age group and lithium serum level) on eGFR decline did not influence each other, meaning the effect of LA on eGFR decline did not differ between age groups. The mean eGFR decline from baseline to last measured eGFR on LA was 5.89 ml/min/1.73 m^2 for geriatric and 4.76 ml/min/1.73 m^2 for non-geriatric patients. Females and patients with a higher somatic severity index had a more pronounced decline of eGFR than males (sex: $p < 0.01$) and patients with a lower somatic severity index (CCI: $p = 0.02$). The covariates "co-medication affecting lithium level" and "arterial hypertension" had no significant effect on eGFR ($p > 0.05$).

Two geriatric patients and none of the non-geriatric patients developed AKIs. Both events occurred under toxic lithium levels and clinically relevant lithium intoxication (Table S1). One patient, aged 83 years, developed an AKI stage 1 with creatinine increasing from 0.82 mg/dl before LA versus 1.28 mg/dl after the first week of treatment under the toxic lithium serum level of 1.52 mmol/L. eGFR declined from 70.93 ml/min/1.73 m^2 before LA to 41.57 ml/min/1.73 m^2. The lithium dosage was 12.2 mmol/day. The other patient, aged 82 years, developed an AKI stage 3 with a creatinine increase from 0.90 mg/dl before LA to 2.93 mg/dl after 2 weeks upon LA. eGFR declined from 63.83 ml/min/1.73 m^2 before the start of LA to 15.48 ml/min/1.73 m^2 within 2 weeks. This occurred under the toxic lithium serum level of 2.0 mmol/L. The initial lithium dosage was 6.1 mmol/day and was increased to 24.4 mmol/day after only 5 days of treatment. Both patients presented clinical signs of lithium intoxication (e.g., tremor, nausea, dizziness) and were treated with intravenous fluid substitution with complete recovery. There was no need for acute dialysis (for details see Table S1). Two more cases of toxic lithium serum levels occurred in the geriatric group with no clinical symptoms of lithium intoxication or AKI, while we did not observe any cases of toxic lithium serum levels in the non-geriatric group, which makes this a highly significant result ($p < 0.01$).

4 | DISCUSSION

This is the first study investigating the change of eGFR as a marker of kidney function upon LA for TRD in geriatric compared with non-geriatric patients. Despite several studies on lithium monotherapy, there are only limited studies on LA in geriatric patients investigating the acute effects on the kidney.[16,21,28,30,35] In our study, both groups showed a significant decline of eGFR under LA. While age ≥65 years and serum lithium level had a significant negative effect on eGFR, the interaction of age group and serum lithium level had no significant effect on eGFR, meaning that eGFR decline over the course of treatment did not differ in both groups.

Most previous prospective studies monitored for long-term lithium use over years, sometimes decades, but missed to report the acute effects of LA on the kidney. We chose a short follow-up time of maximally 6 weeks to capture the acute effects of LA on the kidney. We found a significant decline in eGFR over the course of treatment (approximately 5 ml/min/1.73 m^2) independently in both age groups. The average loss in adults is approx. 1 ml/

min/1.73 m^2 per year, which is mainly because of the loss of functioning nephrons.[33] A decline of eGFR of more than 3 ml/min/1.73 m^2 per year indicates a rapid decline of the kidney function. For the acute therapy with LA the decline in our study can be interpreted as rapid decline in both groups.

Especially earlier studies found the risk for a progression of CKD to be low and without clear association to time on lithium.[10] A recent systematic review on kidney side effects of lithium in geriatric patient conclude that there was no clear association between lithium treatment and acute kidney injury or chronic kidney disease.[29] Contrary to this, a recent meta-analysis investigated the prevalence of CKD and found the risk for kidney impairment to be twice as as high in patients with lithium treatment with significant association to time on lithium. The prevalence was higher with older age.[35] Most long-term studies found a decline in kidney function after years of treatment. The average time to progression of CKD after the start of lithium usage is 16.5–31 years.[34] These results demonstrate the necessity of long-term monitoring of kidney function in clinical practice and future studies. Comparing our findings with those of previous studies is difficult because of the different observation periods. Even studies with an observation period of one to 2 years are considered short-term studies.[37] Since we did not include a long-term follow-up, we cannot answer if our findings of eGFR decline are temporary and whether kidney function might recover.

As expected, in this study the geriatric group started with a lower eGFR before they received the first lithium dosage compared with the non-geriatric group (see Figure 1). The eGFR naturally declines with age because of the loss of functioning nephrons.[33] Although there is a steady decline in both groups, a greater decline may be seen in geriatric patients because of the lower number of functioning nephrons later along the long-term course of treatment. Elevated serum levels of lithium are an important risk factor for adverse effects of lithium. At the same time, toxic lithium serum levels can also be the consequence of a rapid kidney function decline.[34] Target lithium serum levels usually range in between 0.5/0.6 and 1.1/1.2 mmol/L.[42] The recommended target lithium serum level for geriatric patients ranges from 0.4 to 0.8 in different guidelines.[29,42,43] Elevated serum lithium levels can critically affect the kidney function and are associated with AKI. The study by Kirkham et al. found, for example, that one incident of a serum lithium level exceeding 1.0 mmol/L is enough to cause a significant eGFR decline for 3 months after the incident.[18] A recent cohort study did not find an association of long-term lithium treatment and nephrotoxicity but only as long as no episodes of acute intoxication occurred.[5] In line with this, severe AKI (AKI stage three) occurred in one patient who had the toxic lithium serum level of 2.0 mmol/L in our study. One moderate AKI (AKI stage one) occurred at a lithium serum level of 1.52 mmol. These findings emphasize that keeping lithium serum levels low but sufficient is crucial for a safe treatment. In general, the lowest sufficient lithium levels should be targeted to avoid intoxication.[34] As lithium has a narrow therapeutic window, there is always the risk that the first dose will cause toxicity. The importance of a slow adjustment of lithium dosage is underlined by four cases in the geriatric age group with lithium levels above the therapeutic range (compared with none in the non-geriatric group). In one of these cases the eGFR declined rapidly resulting in a severe AKI. The eGFR improved slowly after discontinuation of treatment after a couple of days and administration of intravenous fluid. Due to narrow monitoring, all cases of intoxication were detected rapidly and treated immediately. We did not observe cases with need for acute dialysis. Especially in geriatric patients, who often start with a lower eGFR as in our study, close monitoring is very important and may prevent severe kidney damage. In our study, the geriatric age group had a higher rate of comorbidities and important determinants of kidney function. Being aware of and monitoring for interaction with other medications is essential.[34] As stated above, it should be aimed for the lowest sufficient lithium level. Adjustment of dosage or pausing in case of declining kidney function, dehydration, or acute illness should be considered.[34]

In this study, we found a significant negative effect of female sex on the eGFR during LA. Our results are partially in line with former studies. A comprehensive study found women to be more "sensitive" to lithium damage on kidney function as "generally accepted"[14] but literature on this is controversial.[1,31,32]

Our study has several strengths and limitations. The most important strength of our study is the longitudinal design with eGFR values for every participant with at least two measurements during the course of treatment. We also assessed for comorbidities with impact on kidney function such as arterial hypertension and other severe chronic comorbidities summarized by the CCI.[25] In contrast, the lack of a control group for age-matched subjects not exposed to lithium is the main limitation of our study. Furthermore, we focused on the acute phase of LA to capture AKIs. Thus, we cannot predict any long-term effects of LA on the kidney function from our study. Serum creatinine is not an ideal marker for detecting reduced GFR since it is increased only after a decline in GFR of at least 50%[23] and can be subject to fluctuation, for example, due to varying fluid or protein intake.[26] However, with an average of almost four creatinine measurements per patient (see Table 1) and the beginning of LA in all patients it is unlikely that the observed eGFR

changes were caused by another cause than lithium. Most formulas that are established to estimate the GFR from serum creatinine might be lacking accuracy and there is no one formula equally suitable for all age groups, sex, and race. We used the CKD-EPI 2021 equation, which is the currently recommended formula for adults to estimate the GFR by KDIGO.[7,19]

To conclude, our data suggest that geriatric patients might be at higher risk for AKI during LA because of their reduced ability to compensate the treatment-related decline in eGFR. The significantly higher occurrence of lithium intoxication in the geriatric patients were detected and treated acutely due to weekly laboratory tests and assessment of adverse effects in our study. If close monitoring is taken into consideration, clinicians might consider LA more frequently and earlier on in the course of treatment for TRD in geriatric patients.

AUTHOR CONTRIBUTIONS

Sarah Luise Osterland recruited study subjects, undertook the statistical analysis, managed literature searches, and wrote the first draft of the manuscript. Joachim Behr, Ronja Müller-Mertel, Kai Hoffmann, Thomas J. Stamm, Tom Bschor, Christoph Richter, Bruno Steinacher, Maria-Christiane Jockers-Scherübl, Andreas Heinz and Stephan Köhler recruited study subjects and provided critical feedback. Peter Schlattmann undertook the statistical analysis. Turgay Saritas provided literature search and provided critical feedback. Mazda Adli designed the study, wrote the protocol and recruited study subjects, supervised the project and provided critical feedback. Roland Ricken designed the study, wrote the protocol, recruited study subjects, supervised the project, undertook the statistical analysis, and managed the literature searches. Pichit Buspavanich recruited study subjects, supervised the statistical analysis, managed literature searches, and wrote the first draft of the manuscript. Authors Roland Ricken and Pichit Buspavanich contributed equally to this work. All authors contributed to and have approved the final manuscript.

FUNDING INFORMATION

The study was funded by sources of the Mood Disorders Research Unit of Charité -Universitätsmedizin Berlin, Department of Psychiatry and Psychotherapy, Campus Charité Mitte (CCM). We acknowledge financial support from the Open Access Publication Fund of Charité – Universitätsmedizin Berlin and the German Research Foundation (DFG).

CONFLICT OF INTEREST

Mazda Adli received research grants from Servier, Lundbeck, and Gilead; speaker honoraria from Aristo Pharma, Deutsche Bank, HRMForum, Merz Pharma, Gilead, ViiV, MSD, Berlin Chemie, BMS, myTomorrows, Servier, and Lundbeck; and reimbursement of fees and of travel expenses from Lundbeck, Aristo Pharma, and Servier. Pichit Buspavanich received a research grant from Gilead. Roland Ricken received a research grant and speaker honoraria from Aristo Pharma. The other authors declare no conflicts of interest.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/acps.13531.

DATA AVAILABILITY STATEMENT

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

ORCID

Stephan Köhler https://orcid.org/0000-0002-2978-0982
Pichit Buspavanich https://orcid.org/0000-0002-4545-2575

REFERENCES

1. Aiff H, Attman PO, Aurell M, et al. Effects of 10 to 30 years of lithium treatment on kidney function. *J Psychopharmacol*. 2015;29:608-614.
2. Aprahamian I, Santos FS, dos Santos B, et al. Long-term, low-dose lithium treatment does not impair renal function in the elderly: a 2-year randomized, placebo-controlled trial followed by single-blind extension. *J Clin Psychiatry*. 2014;75:e672-e678.
3. Bauer M, Adli M, Ricken R, Severus E, Pilhatsch M. Role of lithium augmentation in the management of major depressive disorder. *CNS Drugs*. 2014;28:331-342.
4. Buspavanich P, Behr J, Stamm T, et al. Treatment response of lithium augmentation in geriatric compared to non-geriatric patients with treatment-resistant depression. *J Affect Disord*. 2019;251:136-140.
5. Clos S, Rauchhaus P, Severn A, Cochrane L, Donnan PT. Long-term effect of lithium maintenance therapy on estimated glomerular filtration rate in patients with affective disorders: a population-based cohort study. *Lancet Psychiatry*. 2015;2:1075-1083.
6. Cooper C, Katona C, Lyketsos K, et al. A systematic review of treatments for refractory depression in older people. *Am J Psychiatry*. 2011;168:681-688.
7. Delgado C, Baweja M, Crews DC, et al. A unifying approach for GFR estimation: recommendations of the NKF-ASN task force on reassessing the inclusion of race in diagnosing kidney disease. *J Am Soc Nephrol*. 2021;32:2994-3015.
8. Finley PR. Drug interactions with lithium: an update. *Clin Pharmacokinet*. 2016;55:925-941.
9. Ganter NM, Tong K, McDonald C, Doherty AM. The clinical characteristics and correlates of lithium toxicity in a tertiary referral Centre. *Ir J Med Sci*. 2019;188:1103-1109.
10. Gitlin M. Lithium and the kidney: an updated review. *Drug Saf*. 1999;20:231-243.
11. Gitlin M. Lithium side effects and toxicity: prevalence and management strategies. *Int J Bipolar Disord*. 2016;4:27.
12. Goldstein SL, Mottes T, Simpson K, et al. A sustained quality improvement program reduces nephrotoxic medication-associated acute kidney injury. *Kidney Int*. 2016;90:212-221.

13. Grandjean EM, Aubry JM. Lithium: updated human knowledge using an evidence-based approach: part III: clinical safety. *CNS Drugs*. 2009a;23:397-418.
14. Grandjean EM, Aubry JM. Lithium: updated human knowledge using an evidence-based approach. Part II: clinical pharmacology and therapeutic monitoring. *CNS Drugs*. 2009b;23: 331-349.
15. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23:56-62.
16. Hardy BG, Shulman KI, Zucchero C. Gradual discontinuation of lithium augmentation in elderly patients with unipolar depression. *J Clin Psychopharmacol*. 1997;17:22-26.
17. Head L, Dening T. Lithium in the over-65 s: who is taking it and who is monitoring it? A survey of older adults on lithium in the Cambridge Mental Health Services catchment area. *Int J Geriatr Psychiatry*. 1998;13:164-171.
18. Kirkham E, Skinner J, Anderson T, Bazire S, Twigg MJ, Desborough JA. One lithium level >1.0 mmol/L causes an acute decline in eGFR: findings from a retrospective analysis of a monitoring database. *BMJ Open*. 2014;4:e006020.
19. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150: 604-612.
20. Markowitz GS, Radhakrishnan J, Kambham N, Valeri AM, Hines WH, D'Agati VD. Lithium nephrotoxicity: a progressive combined glomerular and tubulointerstitial nephropathy. *J Am Soc Nephrol*. 2000;11:1439-1448.
21. McKnight RF, Adida M, Budge K, Stockton S, Goodwin GM, Geddes JR. Lithium toxicity profile: a systematic review and meta-analysis. *Lancet*. 2012;379:721-728.
22. Ott M, Stegmayr B, Salander Renberg E, Werneke U. Lithium intoxication: incidence, clinical course and renal function - a population-based retrospective cohort study. *J Psychopharmacol*. 2016;30:1008-1019.
23. Priem F, Althaus H, Birnbaum M, Sinha P, Conradt HS, Jung K. Beta-trace protein in serum: a new marker of glomerular filtration rate in the creatinine-blind range. *Clin Chem*. 1999;45:567-568.
24. Pruckner N, Holthoff-Detto V. Antidepressant pharmacotherapy in old-age depression-a review and clinical approach. *Eur J Clin Pharmacol*. 2017;73:661-667.
25. Quan H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol*. 2011;173:676-682.
26. Raman M, Middleton RJ, Kalra PA, Green D. Estimating renal function in old people: an in-depth review. *Int Urol Nephrol*. 2017;49:1979-1988.
27. Rej S, Abitbol R, Looper K, Segal M. Chronic renal failure in lithium-using geriatric patients: effects of lithium continuation versus discontinuation-a 60-month retrospective study. *Int J Geriatr Psychiatry*. 2013;28:450-453.
28. Rej S, Herrmann N, Gruneir A, et al. Association of lithium use and a higher serum concentration of lithium with the risk of declining renal function in older adults: a population-based cohort study. *J Clin Psychiatry*. 2020;81:19m13045.
29. Rej S, Herrmann N, Shulman K. The effects of lithium on renal function in older adults—a systematic review. *J Geriatr Psychiatry Neurol*. 2012;25:51-61.
30. Rodrigo C, de Silva NL, Gunaratne R, Rajapakse S, De Silva VA, Hanwella R. Lower estimated glomerular filtration rates in patients on long term lithium: a comparative study and a meta-analysis of literature. *BMC Psychiatry*. 2014;14:4.
31. Rybakowski JK, Abramowicz M, Chłopocka-Wozniak M, Czekalski S. Novel markers of kidney injury in bipolar patients on long-term lithium treatment. *Hum Psychopharmacol*. 2013;28: 615-618.
32. Rybakowski JK, Abramowicz M, Drogowska J, Chłopocka-Woźniak M, Michalak M, Czekalski S. Screening for the markers of kidney damage in men and women on long-term lithium treatment. *Med Sci Monit*. 2012;18:Cr656-660.
33. Schmitt R, Melk A. Molecular mechanisms of renal aging. *Kidney Int*. 2017;92:569-579.
34. Schoot TS, Molmans THJ, Grootens KP, Kerckhoffs APM. Systematic review and practical guideline for the prevention and management of the renal side effects of lithium therapy. *Eur Neuropsychopharmacol*. 2020;31:16-32.
35. Schoretsanitis G, de Filippis R, Brady BM, Homan P, Suppes T, Kane JM. Prevalence of impaired kidney function in patients with long-term lithium treatment: a systematic review and meta-analysis. *Bipolar Disord*. 2021;24(3):264-274.
36. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The mini-international neuropsychiatric interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry*. 1998;59-(suppl 20):22-33. quiz 34-57.
37. Shine B, McKnight RF, Leaver L, Geddes JR. Long-term effects of lithium on renal, thyroid, and parathyroid function: a retrospective analysis of laboratory data. *Lancet*. 2015;386:461-468.
38. Singh S, Bajorek B. Defining 'elderly' in clinical practice guidelines for pharmacotherapy. *Pharm Pract (Granada)*. 2014;12:489.
39. Stevens PE, Levin A. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. *Ann Intern Med*. 2013;158:825-830.
40. Sun M, Herrmann N, Shulman KI. Lithium toxicity in older adults: a systematic review of case reports. *Clin Drug Investig*. 2018;38:201-209.
41. van Melick EJ, Meinders AE, Hoffman TO, Egberts TC. Renal effects of long-term lithium therapy in the elderly: a cross-sectional study. *Int J Geriatr Psychiatry*. 2008;23:685-692.
42. Wijeratne C, Draper B. Reformulation of current recommendations for target serum lithium concentration according to clinical indication, age and physical comorbidity. *Aust N Z J Psychiatry*. 2011;45:1026-1032.
43. Young RC, Gyulai L, Mulsant BH, et al. Pharmacotherapy of bipolar disorder in old age: review and recommendations. *Am J Geriatr Psychiatry*. 2004;12:342-357.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Osterland SL, Adli M, Saritas T, et al. Acute effects of lithium augmentation on the kidney in geriatric compared with non-geriatric patients with treatment-resistant depression. *Acta Psychiatr Scand*. 2023;147(3): 267-275. doi:10.1111/acps.13531