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Evaluation of Kidney Function in Bipolar Patients: A Cross-Sectional Study

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ABSTRACT

Bipolar disorder is a chronic disease that represents a significant problem to the affected individual. To date, the mainstay treatment for bipolar disorder consists in mood stabilizers, mainly lithium, which have been linked to acute and chronic kidney injury. To investigate the association between Estimated Glomerular Filtration Rate (eGFR) and sociodemographic and clinical characteristics in a group of patients with bipolar disorder (BD) undergoing lithium treatment, with or without concomitant use of other psychopharmaceuticals. In this cross-sectional study data was collected using the instruments: 1 – Clinical and sociodemographic data questionnaire, developed by the Brazilian Consortium for Bipolar Disorder Research; 2 – Structured Clinical Interview for the DSM-IV Axis I Disorders; 3 – Hamilton's Rating Scale for Depression, to evaluate depressive symptoms and 4 – Young's Rating Scale for Mania to evaluate mania symptoms. Renal function was calculated through the CKD/EPI formula for eGFR. 95 patients were included in the final analysis. 26 (27.4%) patients presented reduction in eGFR, 21 (22,1%) with eGFR between 60 to 89 and 5 (5,2%) below 60. Higher serum lithium levels and age were associated with such reduction (β = -18.06 [95% CI: -34.70 to -1.42]); (β = -0.72 (95% CI: -1.10 to -0.33)), respectively. Although lithium is considered the "gold standard" in the treatment of BD, its toxicity and tolerability profile in relation to renal function still needs to be better understood. The results of this study reinforce the idea that periodic control of lithium levels is essential for preserving renal function. Long-term longitudinal studies are needed to assess the relationship between renal function and lithium therapy in BD patients.

Keywords: Lithium; Bipolar Disorder; Kidney; Renal Insufficiency

INTRODUCTION

Bipolar disorder (BD) is a chronic, recurrent mental disease that represents a significant problem to the affected individual, his family and society. According to the World Health Organization (WHO), it is one of the ten main causes of disability[1]. Furthermore, suicidal behavior is one of its most common outcomes. Around 25%-50% patients with BD attempt suicide, among which 15% are successful[2].

Amongst the pharmacological therapeutical options, the Food and Drug Administration (FDA) have approved lithium carbonate for the treatment of manic episodes since 1970[3], and it is still indicated as the first-line drug for all phases and subtypes of BD. It is also recommended as an adjuvant to the treatment of antidepressant-resistant unipolar depression[1,4,5]. Moreover, lithium's chemical properties play a key role in suicide prevention, the reason why it is considered an anti-suicide drug for people with mood disorders, regardless of its action in controlling acute manic or depressive episodes[2,4–6].

Despite countless pieces of evidence on lithium's effectiveness in controlling BD, there are still many questions to be answered concerning its safety and tolerability, especially when it comes to its adverse effects on the kidneys. Thus, its capability of causing arginine vasopressin resistance (AVP-R), formerly known as nephrogenic diabetes insipidus (NDI), is well known, but the rates vary considerably from 20% to 87% amongst studies and whose emergence can occur from two to four months since the beginning of lithium

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treatment[3,7–11]. Conversely, the ability to cause chronic kidney disease (CKD) is much more intriguing, because the literature has many studies showing both positive and negative causality[3,7–11].

The mechanism through which lithium may cause chronic kidney disease has not yet been fully elucidated, and chronic use of the medication has been associated with various types of renal injury, the main one being chronic tubulointerstitial nephropathy[12,13].

Lithium enters the principal cells of the collecting duct via sodium epithelial channels in the luminal membrane. It is believed that, during chronic use, the medication increases the resistance of principal cells to the antidiuretic hormone (ADH), thereby reducing water permeability through aquaporin-2 water channels (AQP-2)[14]. Among the proposed mechanisms to explain this phenomenon is lithium's stimulation of cyclooxygenase-2 super expression, which would lead to increased urinary excretion of prostaglandin E2 (PGE2) by medullary interstitial cells. These prostaglandins, in turn, induce degradation of AQP-2 water channels and consequently reduce the renal capacity to modulate urine concentration[15,16].

It is also proposed that lithium may reduce AQP2 gene transcription independently of PGE2 action, and cause remodeling of the collecting duct with a reduction in the relative number of principal cells compared to intercalated cells, further reducing renal function[17].

Indeed, over the years, it can be noticed that the 1980s and 1990s initial studies were more indicative of a lithium-induced nephrotoxicity[9,10]. More recent studies, however, showed lesser rates of significant kidney impairment, probably due to greater methodological refinement. But, even taking these differences into account, the weight of scientific evidence still suggests that this salt, abundantly found in various natural elements, has some potential of causing kidney disease, promoting chronic tubulointerstitial nephritis, particularly if the exposure period lasts more than 20 years. It is worth mentioning that, regarding the development of end-stage renal disease (ESRD), a greater exposure period of 27 years or more, according to some research, might be necessary[11,18].

Nevertheless, beyond the time of exposure, other factors directly related to lithium, such as the average dosage used in the recurrence prevention period, the interaction with other substances potentially nephrotoxic, lithium intoxication in higher doses and the development of AVP-R also must be taken into consideration while evaluating the nephrotoxicity risk[18]. Another relevant and unsolved point is that, even in the absence of lithium usage, mental disorders patients generally show a significant reduction in the urinary concentration, that is, the result may derive from the presence of other risk factors, such as smoking, dyslipidemia, diabetes mellitus, and hypertension, comorbidities that are frequently found in people with mental disorders[19].

Therefore, in sight of the diverging results obtained from lithium usage and kidney function studies, more research was deemed necessary. In this study, we investigated the Estimated Glomerular Filtration Rate (eGFR) of a group of patients with BD who were being treated with lithium, with or without the addition of other psychopharmaceuticals. We also evaluated the relationship between eGFR and the sociodemographic and clinical characteristics of these individuals.

METHODOLOGY

Participants

This is a cross-sectional study, in which were included patients of 18 years of age and older, diagnosed with BD of any type, evaluated in a symptomatologic remission, being treated with lithium for at least one year, in association with other psychotropics or not, regularly monitored by the Mood and Anxiety Disorders Program (CETHA), of the University Hospital Professor Edgard Santos (Complexo-HUPES), Federal University of Bahia (UFBA)'s specialized bipolar disease treatment.

This research on lithium and kidney function is part of a cohort study of the CETHA/Complexo-HUPES' Ongoing Evaluation Program, approved by the Research Ethics Committee from the Climério de Oliveira Maternity Hospital, in progress since February 23rd, 2005. The funding of this study comes from the Center's own funds, providing both human resources and physical infrastructure. After being interviewed, some patients agreed and signed the informed consent form (ICF) to be part of the project.

Exclusion criteria included the use of lithium for any condition other than BD, simultaneous use of other known nephrotoxic substances or clinical criteria for acute BD (no remisson state).

For the sociodemographic and clinic characterization of the patients the following variables were evaluated: age, sex, duration of lithium treatment in years, clinical comorbidities (diabetes mellitus, systemic hypertension and dyslipidemia), concomitant psychotropics, weight, height and lifestyle habits (alcohol drinking and tobacco smoking). For the laboratorial kidney function the following blood test results, described in the medical records, were collected: creatinine, urea, creatinine clearance and serum lithium levels.

The creatinine clearance was estimated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) group 2009 formula, which is: eGFR for women: $141 \times ([\text{creatinine}]/0.7) - 0.329 \times ([\text{creatinine}]/0.7) - 1.209 \times 0.993$ age $\times$ 1.018; for men: $141 \times ([\text{creatinine}]/0.9) - 0.411 \times ([\text{creatinine}]/0.9) - 1.209 \times 0.993$ age $\times$ 1.018[20]. The eGFR categories used are the ones proposed by the Clinical Practice Guidelines for the Evaluation and Treatment of Chronic Kidney Disease, developed by the Kidney Disease Improving Global Outcomes[21] . According

to these guidelines, there are 5 stages of kidney function: 1 – normal eGFR ($\geq$ 90 mL/min/1,73 m^2); 2 – mildly decreased eGFR (60 to 89mL/min/1,73 m^2); 3a – mildly to moderately decreased eGFR (45 to 59 mL/min/1,73 m^2); 3b – moderately to severely decreased eGFR (30 to 44mL/min/1,73 m^2) 4 – severely decreased eGFR (15 to 29mL/min/1,73); and kidney failure (eGFR < 15 or initiation of dialysis or transplant).

Data collection

The patients were recruited from March 2015 to December 2019 from a specialized outpatient clinic for BD. The interview protocol employed in this study utilized the following instruments: 1 - A clinical and sociodemographic data questionnaire, developed by the Brazilian Research Consortium on BD; 2 - The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I); 3 - The 17-item Hamilton's Rating Scale for Depression (HAM-D-17) to assess depressive symptoms; and 4 - The Young's Rating Scale for Mania (YMRS-17) to evaluate manic symptoms. Laboratory data regarding lithium levels, urea, and creatinine were obtained from the medical records at the time of the interview and corresponded to the date of the most recent collection, which was conducted within a maximum period of two months prior to the interview. Laboratory assessments in this facility are typically conducted semiannually, and the individuals included in the study were in a state of symptomatic remission.

Procedures

The procedures took place in two stages: first, after signing the ICF, the patients were initially interviewed with the application of a survey to collect sociodemographic and clinical data. Then, followed the verification of the state of symptomatologic remission (euthymia), defined as the presence of scores for depression and mania $\leq$ 7, measured by the HAM-D-17 and YMRS scales, respectively. Besides that, as part of the protocol, all patients considered in a state of euthymia underwent evaluation with the SCID to confirm the diagnosis of TB and investigate the presence of comorbidities.

In a second moment, some personal data and laboratory tests, needed for analysis in the project, were obtained via printed or online (MEDICWARE) medical records. The undertaking of periodic tests is part of the outpatient monitoring at CETHA-Complexo-HUPES.

Statistical Analysis

After being collected, the sociodemographic and clinical data were fed to the statistical program Statistical Package for Social Sciences (SPSS), version 23.0, and the statistical analyses were executed in R version 4.0.2. The numeric variables were described as average and standard deviation when normally distributed, and through median and interquartile range (IQR) when they did not have a normal distribution. The normality was evaluated based on the Shapiro-Wilk test. The categorical variables were described by absolute and relative numbers. The relation between eGFR and the baseline were compared using the Mann-Whitney-U test or the Spearman's rank correlation coefficient.

Initially, univariate analyses were made between the clinical and sociodemographic characteristics and the patients' eGFR. Then, the variables that reached values of $p < 0,1$ were included in the multivariate regression model. Were also included diabetes mellitus and systemic hypertension, regardless of their p-values in the univariate analysis, had relevant clinical plausibility. Multiple linear regression analysis was performed to investigate the association between serum lithium levels, lithium treatment duration (in years) and the eGFR, independently of the confounding factors found in the univariate analysis. In the final regression model, the values of $p \leq 0.05$ were considered significant.

Ethical aspects

This research follows the Resolution 466/2012, adopted by the 1989 Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects). It was approved by the Climério de Oliveira Maternity Hospital's Research Ethics Committee under the number 16/2005, supplemented on 14 July 2010 by the additional resolution 159/2010. After its update on the Platform Brazil, the project was once more approved by Complexo-HUPES' Research Ethics Committee, via protocol number 2.895.571 on 14 September 2018.

RESULTS

A total of 121 patients were recruited, 26 were excluded due to not being treated with lithium. The characteristics of the selected sample are presented in Table 1. The median age was 49.0 (IQR: 37.0-57.5); 80% was female, 75 (78.9%) were self-declared black/mixed race. The majority of patients (85/89,5%) were diagnosed with BD type I. The median duration of the lithium treatment was 10 years (IQR: 6 - 16) and the median serum lithium level described on the medical records was 0,70 mmol/L (IQR: 0,6 - 0,9).

Table 1: Socio demographic and clinical characteristics of patients with bipolar disorder in treatment with lithium

Variable	Values n (%)
Age (years) – median (IQR)	49.0 (37.0 to 57.5)
Females	76 (80.0)
Self-declared race	
White	20 (21.1)
Black/mixed	75 (78.9)
BMI – median (IQR)	28.4 (24.2 to 32.8)
Tobacco smoking	20 (21.1)
Hypertension	11 (11.6)
Diabetes Mellitus	14 (14.7)
Dyslipidemia	10 (10.5)
Use of antipsychotics	67 (70.5)
Use of anticonvulsants	53 (55.8)
Use of benzodiazepines	21 (22.1)
BD type	
Type I	85 (89.5)
Type II	10 (10.5)
Serum lithium level (mmol/L) – median (IQR)	0.7 (0.6 to 0.9)
Duration of lithium treatment (years)	10.0 (6.0 to 16.0)
Lithium daily dose	900.0 (900.0 to 1200.0)
Urea (mg/dL)	25.0 (21.0 to 29.5)
Creatinine (mg/dL)	0.8 (0.7 to 1.0)
eGFR (mL/min/1,73m^2)	
>90 ≥60 and <90 <60	69 (72,6) 21 (22,1) 5 (5,3)

BD – bipolar disorder; BMI – Body Mass Index; eGFR – Estimated Glomerular Filtration Rate

A total of 69 (72.5%) patients exhibits values of eGFR above 90 mL/min/1,73m^2; 21 of them (22,1%), between 60 and 90 and 5 (5,3%) patients showed values under 60 (Table 1).

In the univariate analysis, age ($p < 0.01$), smoking ($p = 0.01$), use of BZD ($p = 0.01$), and sex ($p = 0.07$) met the criteria of $p < 0.1$ (Table 2).

In the multivariate analysis, the final model was composed of serum lithium levels, duration of the lithium treatment, age, smoking, use BZD and sex. Higher serum lithium levels were associated to low eGFR levels (β = -18,06 [-34,70 to -1,42], p = 0,03); age was also associated with eGFR levels (β = -0,72 (-1,10 to -0,33), p = <0,01) (Figure 1).

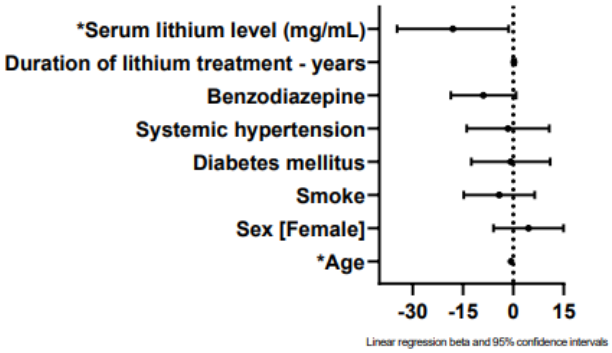

Fig. 1: Multivariate analysis

DISCUSSION

This study evaluated the renal function of patients with BD by measuring the eGFR, calculated using the CKD/EPI formula, and the results showed that higher serum lithium levels and advanced age are associated with the significant decrease of the eGFR, even though the latter has already been extensively described in the literature for both users and non-users of lithium [22]. Conversely, although factors like smoking, systemic hypertension and diabetes mellitus are classically associated with kidney dysfunction, this finding was not replicated in our sample, probably due to the small percentage of individuals with these comorbidities, or to their young age, that obviously reduced the likelihood of exposure [22,23].

A multicentric study assessed the relationship between use of lithium and eGFR and found that higher levels of lithium were linked to decreased levels of eGFR in patients with BD aged 20-89 (mean 56) and treated with lithium for 8-48 (mean 18) years. Additionally, the authors described a positive correlation between daily lower doses of lithium and higher eGFR. In this case, the lithium dosage could have been lowered to compensate for decreasing eGFR with older age and keep serum lithium levels within the recommended therapeutic range [23]. This result, as well as the one described in our study, reinforces the importance of considering the measurement of serum lithium levels during patient follow-up (maintenance phase) as an independent variable to be controlled in the prevention of damage to renal function in chronic users of lithium.

The association between higher serum lithium levels and reduced eGFR could be explained by impaired kidneys having a diminished capacity to metabolize lithium and, therefore, its serum levels increase; or higher levels of lithium could cause acute or chronic kidney damage, reducing eGFR [24]. These two hypotheses do not exclude one another. In this sense, it is extremely important to elucidate if there is any component in lithium salts that can have a direct deleterious effect on the renal parenchyma, leading to some degree of nephrotoxicity, and know when lithium should be discontinued or not [25].

Contrary to what is described in the literature, we did not find an association between time of exposure to lithium and a decrease in eGFR [24]. However, our study sample has a median duration of lithium treatment of 10 years,

Table 2: Univariate analysis and multiple linear regression

Variable	eGFR[a]	Coefficient (multivariable)[b]	Adjusted p value	Coefficient (univariable)[c]
Age (years)*	-0,58	-0,72 (-1,10 to -0,33)	<0,01	<0,01
BZD* Yes	89,3 (75,3 to 103,5)	-8,95 (-18,67 to -0,78)	0,07	0,01
Diabetes mellitus Yes	100,3 (79,4 to 108,0)	-0,78 (-12,56 to -11,00)	0,90	0,27
Duration of treatment	-0,14	0,19 (-0,31 to -0,69)	0,45	0,19
Hypertension Yes	99,4 (90,6 to 106,0)	-1,63 (-13,93 to -10,68)	0,79	0,29
Serum lithium (mmol/L)*	-0,19	-18,06 (-34,70 to -1,42)	0,03	0,09
Sex* Male Female	98,5 (81,1 to 102,0) 103,9 (91,2 to 117,3)	4,55 (-5,96 to -5,07)	0,39	0,07
Smoking* Yes	96,6 (79,8 to 103,0)	-4,21 (-14,83 to -6,40)	0,43	0,01
Anticonvulsant Yes	101,40 (95,1 to 111,4)	-	-	0,76
Antipsychotic Yes	102,6 (88,7 to 114,7)	-	-	0,70
BD type I II	101,40 (88,1 to 113,4) 103,6 (92,6 to 108,9)	-	-	0,93
BMI (kg/m^2)	-0,06	-	-	0,53
Dyslipidemia Yes	88,15 (79,4 to 106,0)	-	-	0,15
Self-declared race Black White	103,0 (96,2 to 111,0) 103,0 (85,6 to 113,0)	-	-	0,60

BD - Bipolar disorder; BZD – Benzodiazepine; BMI – Body Mass Index; eGFR– Estimated Glomerular Filtration Rate. *p < 0,1
[a]Median (IQR) or Spearman p; [b]β 95% (IC): multiple linear regression; [c]Valueof p (Mann-Whitney or Spearman correlation)

which is much shorter than that described in other studies that present values above 20 or more years of continuous therapy[23].

An Italian cohort from 1980 to 2012 evaluated 953 patients with BD and found maintenance therapy with lithium was associated with a decrease in eGFR to levels below 60mL/min/1.73m^2 in 50% of the sample, indicating some degree of impairment of renal function[26]. The same study found female sex, age and exposure time to lithium as risk factors to decrease in eGFR. One strange point is this study is that over 4 years of follow-up, it was also found that the progression of renal failure after diagnosis of eGFR reduction to < 45mL/min/1.73 m2, did not differ between 3 subgroups observed later: 1 – which continued with lithium in the same dose as before; 2 – who discontinued its use at the time of diagnosis of the renal impairment; and 3 – who maintained the blood lithium at concentrations below the therapeutic range[11,26]. These results are difficult to explain, but they bring hope, as it may be reasonable to maintain lithium in patients with BD, even when renal function is already moderately compromised. But it is important to highlight that we don't have clinical trials designed for answers these doubts. Furthermore, considering that the treatment with lithium is one of the most effective, greater efforts must be made to prevent and control the onset of kidney impairment in this population.

Therefore, although the precise details regarding the relationship between lithium usage and renal disease require further elucidation, existing literature consistently indicates a certain degree of reduction in renal function associated with long-term exposure to lithium. To address the existing uncertainties, it is imperative to conduct more methodologically rigorous longitudinal studies. Specifically, comparisons should be made between samples of bipolar disorder (BD) patients who do not use lithium and those who do, in order to shed light on this matter. These comprehensive investigations will contribute to a better understanding of the potential impact of lithium on kidney function and inform clinical decision-making regarding the management of BD.

Limitations and strengths

Naturally, our results must be interpreted carefully, as there are limitations: the sample was relatively small when compared to other studies on the subject; we did not obtain a control group composed only of non-lithium users to compare the results; this is a cross-sectional study and therefore we cannot draw cause-effect conclusions; the sample was selected from a Specialized BD Treatment Center, so we cannot generalize the results.

However, there are strengths: all patients were evaluated through a standardized diagnostic interview for BD; patients were euthymic and undergoing maintenance treatment, with no evidence of worsening symptoms that could create distortions in instrument responses or that required the use of more medications or higher doses at the time of collection of personal data and the use of CKD-EPI to measure the eGFR, which is considered the most reliable among the clinically available measure techniques[21].

CONCLUSION

This cross-sectional data extracted from an ongoing cohort at a Specialized Center for the Treatment of BD patients revealed that serum lithium levels is associated, as an independent variable, with a reduction in eGFR. This result raises the suspicion that it may be a candidate to be an early marker of nephrotoxicity. Furthermore, the duration of treatment with lithium for a period of 10 years was not associated with a reduction in eGFR, a result that reinforces the theory that longer periods of exposure to lithium are necessary for there to be significant impairment of renal function.

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REFERENCES

1. Yatham LN, Kennedy SH, Schaffer A, Parikh SV, Beaulieu S, O'donovan C, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2009. *Bipolar Disorders*. 2009;11(3):225–255. Available from: https://doi.org/10.1111/bdi.12609.
2. Miller JN, Black DW. Bipolar Disorder and Suicide: A Review. *Current Psychiatry Reports*. 2020;22(2). Available from: https://doi.org/10.1007/s11920-020-1130-0.
3. De Oliveira JL, Júnior GBDS, De Abreu KLS, Rocha NDA, Franco LFLG, Araújo SMHA, et al. Nefrotoxicidade por lítio. *Revista da Associação Médica Brasileira*. 2010;56(5):600–606. Available from: https://www.scielo.br/j/ramb/a/Lgnbk9sJbYmFCZqRShsr6Rh/.
4. Baldessarini RJ, Tondo L, Vázquez GH. Pharmacological treatment of adult bipolar disorder. *Molecular Psychiatry*. 2019;24(2):198–217. Available from: https://doi.org/10.1038/s41380-018-0044-2.
5. Takeshima M. Treating mixed mania/hypomania: a review and synthesis of the evidence. *CNS Spectrums*. 2017;22(2):177–185. Available from: https://doi.org/10.1017/S1092852916000845.
6. Lage RR, Santana CMT, Nardi AE, Cheniaux E. Mixed states and suicidal behavior: a systematic review. *Trends in Psychiatry and Psychotherapy*. 2019;41(2):191–200. Available from: https://doi.org/10.1590/2237-6089-2018-0042.
7. Bendz H, Schön S, Attman POO, Aurell M. Renal failure occurs in chronic lithium treatment but is uncommon. *Kidney International*. 2010;77(3):219–224. Available from: https://doi.org/10.1038/ki.2009.433.
8. Boton R, Gaviria M, Batlle DC. Prevalence, Pathogenesis, and Treatment of Renal Dysfunction Associated With Chronic Lithium Therapy. *American Journal of Kidney Diseases*. 1987;10(5):329–345. Available from: https://pubmed.ncbi.nlm.nih.gov/3314489/.
9. Presne C, Fakhouri F, Noël LH, Stengel B, Even C, Kreis H, et al. Lithium-induced nephropathy: Rate of progression and prognostic factors. *Kidney International*. 2003;64(2):585–592. Available from: https://doi.org/10.1046/j.1523-1755.2003.00096.x.
10. Grünfeld JP, Rossier BC. Lithium nephrotoxicity revisited. *Nat Rev Nephrol*. 2009;5(5):270–276. Available from: https://pubmed.ncbi.nlm.nih.gov/19384328/.
11. Bocchetta A, Ardau R, Carta P, Ligas F, Sardu C, Pani A, et al. Duration of lithium treatment is a risk factor for reduced glomerular function: a cross-sectional study. *BMC Medicine*. 2013;11(1):33–33. Available from: https://doi.org/10.1186/1741-7015-11-33.
12. Fmedsci GMG, Geddes JR, Geddes JR, Mcknight RF, Adida M, Budge K. Lithium toxicity profi le: a systematic review and meta-analysis. *Lancet [Internet]*. 2012;379:721–770.
13. Gitlin M. Lithium and the kidney. An updated review. *Drug Saf*. 1999;20(3):231–274. Available from: https://doi.org/10.2165/00002018-199920030-00004.
14. Grünfeld JP, Rossier BC. Lithium nephrotoxicity revisited. *Nat Rev Nephrol*. 2009;5(5):270–276. Available from: https://go.gale.com/ps/i.do?id=GALE%7CA198850501&sid=googleScholar&v=2.1&it=r&linkaccess=abs&issn=17595061&p=AONE&sw=w&userGroupName=anon%7Eccbee06a&aty=open-web-entry.
15. Christensen BM, Kim YHH, Kwon THH, Nielsen S. Lithium treatment induces a marked proliferation of primarily principal cells in rat kidney inner medullary collecting duct. *American Journal of Physiology-Renal Physiology*. 2006;291(1):F39–F48. Available from: https://doi.org/10.1152/ajprenal.00383.2005.
16. Ecelbarger CA. Lithium treatment and remodeling of the collecting duct. *American Journal of Physiology-Renal Physiology*. 2006;291(1):F37–F38. Available from: https://doi.org/10.1152/ajprenal.00046.2006.
17. Kortenoeven MLA, Schweer H, Cox R, Wetzels JFM, Deen PMT. Lithium reduces aquaporin-2 transcription independent of prostaglandins. *American Journal of Physiology-Cell Physiology*. 2012;302(1):C131–C140. Available from: https://doi.org/10.1152/ajpcell.00197.2011.
18. Volkmann C, Bschor T, Köhler S. Lithium Treatment Over the Lifespan. *Frontiers in Psychiatry Frontiers Media SA*. 2020;11. Available from: https://doi.org/10.3389/fpsyt.2020.00377.
19. Gitlin M. Lithium and the kidney. An updated review. *Drug Saf*. 1999;20(3):231–274.
20. Levey AS, Stevens LA, Schmid CH, (lucy) Zhang Y, Castro AF, Feldman HI, et al. A New Equation to Estimate Glomerular Filtration Rate. *Annals of Internal Medicine*. 2009;150(9):604–604. Available from: https://doi.org/10.7326/0003-4819-150-9-200905050-00006.
21. Stevens PE, Levin A. Evaluation and Management of Chronic Kidney Disease: Synopsis of the Kidney Disease: Improving Global Outcomes 2012 Clinical Practice Guideline. *Annals of Internal Medicine*. 2013;158(11):825–825. Available from: https://doi.org/10.7326/0003-4819-158-11-201306040-00007.
22. Hommos MS, Glassock RJ, Rule AD. Structural and Functional Changes in Human Kidneys with Healthy Aging. *Journal of the American Society of Nephrology*. 2017;28(10):2838–2844. Available from: https://doi.org/10.1681/ASN.2017040421.
23. Tondo L, Abramowicz M, Alda M, Bauer MM, Bocchetta A, Bolzani L, et al. Long-term lithium treatment in bipolar disorder: effects on glomerular filtration rate and other metabolic parameters. *International Journal of Bipolar Disorders*. 2017;5(1). Available from: https://doi.org/10.1186/s40345-017-0096-2.
24. Mcknight RF, Adida M, Budge K, Stockton S, Goodwin GM, Geddes JR. Lithium toxicity profile: a systematic review and meta-analysis. *The Lancet*. 2012;379(9817):721–728. Available from: https://doi.org/10.1016/S0140-6736(11)61516-X.
25. Davis J, Desmond M, Berk M. Lithium and nephrotoxicity: a literature review of approaches to clinical management and risk stratification. *BMC Nephrology*. 2018;19(1). Available from: https://doi.org/10.1186/s12882-018-1101-4.
26. Bocchetta A, Ardau R, Fanni T, Sardu C, Piras D, Pani A, et al. Renal function during long-term lithium treatment: a cross-sectional and longitudinal study. *BMC Medicine*. 2015;13(1):1–7. Available from: https://doi.org/10.1186/s12916-014-0249-4.