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The Effect of Long-Term Lithium Use on Renal Functions in Patients with Bipolar Disorder

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Abstract: It is known that especially glomerular side effects of lithium lead to serious consequences such as end-stage renal disease. Therefore, it is critical to evaluate patients on long-term lithium therapy for glomerular pathologies. The present study investigated the changes in renal functions, prevalence of renal failure and progress in patients have been followed up for at least six years with bipolar disorders (BD) and on regular lithium treatment. 51 patients with BD and 38 age and sex matched healthy controls were enrolled for the study. The serum blood urea nitrogen (BUN), creatinine, uric acid, electrolytes, calcium (Ca), phosphorus (P), vitamin D (25-OH D3), parathyroid hormone (PTH) and eGFR levels were measured to compare the kidney functions of patients and control group. The relation between the renal functions and mean serum lithium levels and duration of lithium treatment were also investigated. Mean eGFR level, 25-OH D3 and urine density of patients with were significantly lower whereas creatinine, uric acid, Ca and PTH were significantly higher than that of controls. The duration of lithium treatment and mean lithium levels were negatively correlated with eGFR level. Eight of 51 patients have critical eGFR level as lover than 60ml/minute thus further nephrological investigation was needed. The study revealed that the renal functions of the patient group was significantly lower than controls. The findings suggested that both duration of lithium treatment and high serum lithium levels may have a negative impact on renal functions. These findings suggest that it is important to clarify the response type to lithium in patients who are on long term treatment with lithium and maintain the treatment with the lowest possible therapeutic serum levels and carefully monitoring the renal functions in patients with good response to lithium. © 2023 NTMS.

Keywords: Lithium; Chronic Kidney Disease; Bipolar Disorder; Glomerular Filtration rate.

1. Introduction

Lithium, which has been in the treatment of bipolar disorder for more than 70 years, has been proven to be effective in the treatment of both depressive and manic episodes at the present time [1]. Lithium, which is

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known to reduce the suicide rate significantly and has superiority over other mood-stabilizing drugs in this aspect, is also accepted as the first choice in the maintenance treatment of bipolar disorder (BD) [2].

Despite its effectiveness in the treatment, the side effects of lithium on the thyroid gland and kidneys are feared of. Side effects on kidney functions are divided into two groups as effects on tubular functions and effects on glomerular functions. Lithium is the most common cause of drug-induced nephrogenic diabetes insipidus (NDI), and studies on this subject report an incidence between 20 % and 87 % [3]. The first publications on whether lithium causes chronic renal failure (CRF) are based on case reports [4]. As a result of kidney biopsies performed on patients using lithium, drug-induced chronic tubulointerstitial nephritis (CTIN) was defined. In a study published in 2000, in all 24 patients who received lithium treatment for an average of 13.6 years and underwent renal biopsy due to renal failure, CTIN characterized by tubular atrophy and interstitial fibrosis was detected; It has been reported that end-stage renal failure (ESRD) developed in 8 of 19 patients followed up despite stopping lithium treatment, and initial serum creatinine levels were important in the development of ESRD [5]. Tubular cyst formation detected by imaging methods is thought to be an indicator of lithium-induced nephropathy [6].

The incidence of lithium-induced ESRD is estimated to be as low as 0.2% to 0.7% [7]. However, these rates are approximately eight times higher compared to the general population and cause controversy regarding lithium use [8].

Glomerular functions are evaluated by calculating serum creatinine level, creatinine clearance and glomerular filtration rate (GFR). Early studies reported that long-term lithium use did not cause a significant change in GFR [9]. The prevalence of decreased GFR was found to be 15 % in a meta-analysis of 14 studies published before 1987 [10]. However, in subsequent studies, between 21 % and 55 % of patients treated with lithium were found to have GFR levels <60 ml/min/1.73 m^2 (stage 3 renal failure cut-off point) [11]. A decrease in GFR was detected in 21 % of patients using lithium for at least 15 years [12], and in another study, 21 % of patients using lithium for a long time had serum creatinine levels of 1.5 mg/dl and above in two consecutive measurements, and it has been emphasized that the risk of renal failure is increased after the 15th year of treatment [13]. On the other hand, in a recent study conducted with participants matched for age, gender, and baseline GFR, it was reported that lithium and control groups did not differ in terms of reductions in GFR levels, and it was thought that methodological differences in studies reporting the opposite opinion might have affected the result [14]. Also, in a recently done meta-analysis, it was reported that the decrease in GFR levels due to lithium treatment was not clinically significant in most patients and that medical comorbidities frequently found in BD patients may be effective in the development of renal failure [15]. Despite different results, it is a dominant view in the literature and a serious clinical problem that lithium leads to the development of CRF by causing CTIN [16].

Based on the current data we have, it does not seem possible to predict ESRD that may develop in patients using lithium other than knowing some risk factors such as taking lithium treatment for a long time, advanced age, low initial GFR, history of lithium intoxication, presence of nephrogenic diabetes insipidus, presence of additional medical diseases that increase the risk of CRF such as hypertension and diabetes mellitus, use of nephrotoxic drugs. Current guidelines on monitoring and managing kidney functions in clinical follow-up are insufficient.

Although the renal tubular side effects of lithium have been clearly demonstrated, there are uncertainties regarding glomerular side effects with more serious consequences. Therefore, it seems important to determine the development of chronic renal failure and the factors that predispose it, especially in patients under long-term lithium treatment

In this study, it is aimed to identify the effects of long-term lithium treatment on kidney functions in BD patients, whether other metabolic and endocrine system parameters such as parathormone (PTH), serum calcium, 25-hydroxyvitamin D3 (25-OH D3) levels have predictive effects on lithium use and kidney functions, and associated factors.

2. Material and Methods

2.1. Sample

This cross-sectional study was conducted with 51 patients diagnosed with BD according to DSM-V diagnostic criteria, and 38 healthy volunteer participants without a psychiatric diagnosis who were matched for age and gender. In the power analysis performed with 80 % power and 0.05 alpha level based on the creatinine clearance loss per year in the reference study [17], the minimum and the maximum number of samples to be included in the study were determined as 56 and 94 respectively. Patients who were followed up in Istanbul University Faculty of Medicine, Department of Psychiatry, using lithium regularly for at least 6 years and whose retrospective information such as medical data and mood graphs were well recorded, and those who gave voluntary consent to the study were included in the study. A detailed history about internal diseases was taken from the patients and healthy controls, and the patients who used lithium irregularly, had a known kidney disease and were on dialysis as a result of lithium intoxication, and participants from the control group with known psychiatric disorders, severe internal or kidney diseases were excluded. All bipolar patients on long-term lithium therapy were included in the study, and a second analysis was performed by excluding participants with confounding factors such as DM and antihypertensive drug use that may affect glomerular functions. The protocol of the study was approved by Istanbul University Non-Interventional Clinical Research Ethics Committee (File no:

2015/1999) and written informed consent was obtained from all participants.

2.2. Data Collection Tools

The participants' sociodemographic and clinical characteristics, medications, responses to lithium, alcohol and substance use, and psychiatric histories were recorded in the semi-structured interview form.

The treatment response of the patients to lithium was determined by the mirror model method. By using the lifelong mood monitoring charts in the patients' files, the pre-lithium period and the lithium treatment period were compared and the type of response to lithium was examined in three categories. Accordingly, good response of lithium response; no mood episodes during treatment, moderate response of lithium response; when compared to the pre-lithium period, a decrease in the frequency, duration and severity of mood episodes was observed in the lithium-using period, and a poor lithium response was defined as no decrease in the frequency, duration and severity of mood episodes. In order to calculate the mean lithium blood level of the patients, the arithmetic mean of the lithium blood levels, which were checked regularly during the follow-up period, was taken.

In our study, 10 ml of venous blood and spot urine samples were taken from the patients and the control group after 10-12 hours of fasting to evaluate the kidney functions.

2.3. Evaluation of Kidney Functions

GFR is considered as the best indicator of kidney function and calculation of it is based on serum creatinine. In this study, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula was used to calculate the estimated GFR (eGFR) values of the patients. The CKD-EPI formula includes serum creatinine values, patient's age, gender, and race variables [18].

2.4. Measurement of Biochemical Parameters

The following parameters were examined by respective methods. Fasting blood sugar (FBS): by the hexokinase method; HBA1C: by high performance liquid chromatography (HPLC) method; creatinine and protein in urine: by the immunoturbidimetric method; blood urea nitrogen (BUN): by kinetic UV test; serum creatinine: by the colorimetric Jaffe method; serum Sodium (Na), Potassium (K), and Chlorine (Cl): by indirect ion selective electrode (ISE) method; serum Magnesium (Mg): by colorimetric method; serum Calcium (Ca) and Phosphorus (P): by photometric method; parathormone (PTH), thyroid stimulating hormone (TSH), anti-TPO, anti-TG: by the ECLIA (Electrochemiluminescence Immunassay) method; Vitamin D (25-OH D3): by ultrahigh performance liquid chromatography (UHLPC) method.

2.5. Statistical analysis

IBM SPSS 21 Package Program was used in the statistical evaluation of the data. Data are presented as mean, standard deviation, median, minimum, maximum, percentage and number. The normal distribution of continuous variables was analyzed using the Shapiro Wilk test. In the comparisons between two groups with numerical variables, the Independent Samples T test was used when the normal distribution condition was met, and the Mann Whitney U test was used if it was not. In the comparison of continuous variables with more than two groups, the ANOVA test was used when the normal distribution condition was met, and the Kruskal Wallis test was used when it was not. The comparison between categorical variables was made with Chi-square test and Fisher's Exact test. In the comparison of two continuous variables, Pearson correlation test was used if the normal distribution condition is met, and the Spearman correlation test was used if it was not, and the statistical significance level was accepted as $p<0.05$.

3. Results

51 BD patients and 38 healthy control groups were included in the study, and both groups were matched for age and gender. There were 35 women and 16 men in the patient group; 27 female and 11 male participants in the control group, and the mean ages were calculated as 51.47±11.41 and 48.92±11.77 in the patient and control groups, respectively. (p=0.307).

The mean duration of lithium treatment of the patients was 205.41±95.83 months, and the patient who received lithium treatment for the shortest period of time used it for 72 months and the patient who received lithium treatment for the longest period of time used it for 396 months. There are 17 participants with a good response to lithium, 31 with a moderate response, and 3 participants with a poor response.

Patients whose lithium blood levels were measured above 1.2 mEq/L at least once during their follow-up were included in the patient group with a history of lithium intoxication, and a history of lithium intoxication was found in 13 (25.49 %) patients. While the treatment of 17 patients (33.33 %) was continued with lithium alone, the treatment of 34 patients (66.66 %) was continued with at least 2 psychotropic drugs. The clinical features of the patient group are shown in Table 1.

Biochemical parameters were compared between the groups and eGFR levels were found to be significantly lower in the patient group. Serum creatinine, uric acid, Ca, Cl, Mg, PTH, Anti-TG and urinary creatinine parameters were significantly higher in the patient group; 25-OH D3, HGB, HCT, and urine density were found to be significantly lower in the patient group. The comparison of the groups in terms of biochemical parameters is shown in Table 2.

Table 1: Clinical characteristics of the patient group.

Clinical Variable	Yes (N ,%)	No (N, %)	Total (N, %)
Psychotic Feature	42 (82.35 %)	9 (17.65 %)	51 (100 %)
History of Lithium Intoxication	13 (25.49 %)	38 (74.5 %)	51 (100 %)
Lithium Monotherapy	17 (33.33 %)	34 (66.66 %)	51 (100 %)
Good Response Rate to Lithium	17 (33.33 %)	34 (66.66 %)	51 (100 %)
Psychiatric Co-Diagnosis	6 (11.76 %)	45 (88.24 %)	51 (100 %)
History of Suicide Attempt	10 (19.6 %)	41 (80.4 %)	51 (100 %)
Alcohol Use	9 (17.64 %)	42 (82.36 %)	51 (100 %)
Smoking	24 (47.05 %)	27 (52.95 %)	51 (100 %)
History of ECT	22 (43.13 %)	29 (56.87 %)	51 (100 %)
Thyroid Hormone Replacement	22 (43.13 %)	29 (56.87 %)	51 (100 %)

ECT: Electroconvulsive Therapy.

While hypercalcemia (Serum Ca>10.4 mg/dl) was detected in 6 individuals in the patient group, hypercalcemia was not detected in any individual in the control group (p=0.036). BUN and Anti-TPO variables did not show a statistically significant difference between the two groups. While proteinuria was detected in 4 people, there was no participant in the control group with proteinuria, but this difference did not have statistical significance.

Correlations between age, duration of lithium use, mean lithium levels and serum PTH levels and parameters reflecting renal functions were examined. As a result of the analysis, there was a weak correlation between age and BUN and serum creatinine; a moderate and inverse correlation was found between age and eGFR. A weak correlation between the lithium-use duration and BUN, Ca, and urine density; a moderate correlation between uric acid, serum creatinine and eGFR were found. There was a weak correlation between mean lithium blood level and serum creatinine and eGFR.

A weak correlation was found between PTH levels and uric acid, serum creatinine, urine density and eGFR variables. Correlations between clinical variables and biochemical parameters and kidney functions are shown in Table 3.

The mean lithium blood levels of the patients for the last 1 year were determined, and the parameters reflecting the kidney functions of the patients whose mean lithium blood level was above and below 0.8 mEq/L were compared. The serum creatinine and PTH values of the patients whose lithium blood levels were above 0.8 mEq/L were found to be statistically significantly higher. Comparison of serum PTH and creatinine levels of patients divided into two groups according to mean lithium level is shown in Table 4.

The biochemical values of patients who responded well and moderately/poorly to lithium treatment were compared, but no significant difference was found between the groups in any parameter.

The results in Table 5 were obtained when the kidney functions were re-evaluated by excluding the participants who used oral antidiabetic and/or antihypertensive drugs and whose HBA1C values were >5.6 mg/dl.

According to the results obtained, serum creatinine, uric acid, PTH, and Ca parameters were significantly higher in patients; eGFR, 25-OH D3, urine density, and urinary creatinine parameters were found to be significantly lower.

The eGFR level of 8 out of 51 patients was found to be below 60 ml/min/1.73 m2, which is prognostically important, and these patients were referred to the nephrology outpatient clinic for examination and treatment.

4. Discussion

4.1. Findings Related to Glomerular Functions

Although the view that lithium is one of the causes of chronic renal failure is not widely accepted [10], epidemiological and clinical data indicate that lithium increases the risk of chronic renal failure [19]. However, the details about the incidence, process and severity of this clinical presentation are unclear. Serum creatinine elevations are detected in some patients, which are seen in advanced ages and can be stabilized by reducing the lithium dose; whereas other patients may experience elevations in serum creatinine levels and progressive renal failure despite discontinuation of lithium therapy [3]. In the light of the analyzes performed, the only significant indicator in the progression to ESRD was that a serum creatinine level of 2.5 mg/dl and above at the time of biopsy was considered as a factor predicting ESRD [5]. In a study, it was stated that the probability of recovery of impaired renal function is higher in patients with a creatinine clearance above 40 ml/min when lithium is discontinued, and the deterioration in renal function continues progressively in most patients with a creatinine clearance below 40 ml/min [17].

Table 2: Comparison of biochemical parameters of patient and control groups.

	Patient Group				Control Group					
	N	Mean	SD	Median	N	Mean	SD	Median	t , Z*	p
Creatinine	51	.91	.40	.80	38	.70	.16	.67	3.493	<.001
Uric Acid	46	5.8	1.5	5.9	38	4.7	1.3	4.5	3.662	<.001
eGFR	51	87.47	25.57	95.00	38	103.68	16.38	108.16	3.393	.001
Cl	50	104.06	2.82	104.00	38	102.00	2.27	102.00	3.683	<.001
Ca	51	9.88	.40	9.90	38	9.46	.33	9.50	5.246	<.001
Mg	49	.94	.36	.89	36	.83	0.05	0.84	2.277	0.023
PTH	50	79.92	72.00	69.00	38	48.46	19.75	44.08	3.782	<.001
Urine Density	50	1010	5	1008	36	1016	8	1015	3.827	<.001
Creatinine Urine	48	76.75	52.36	53.29	34	131.60	97.31	104.73	2.805	0.005

Table 3: Relationship between clinical variables and biochemical parameters and kidney functions.

		BUN	CRE	EGFR
Lithium Use Duration	Correlation Coefficient	.481	.698	-.571
	p	<0.001	<0.001	<0.001
	N	51	51	51
Age	Correlation Coefficient	.482	.375	-.617
	p	<0.001	0.007	<0.001
	N	51	51	51
Mean Lithium Level	Correlation Coefficient	.184	.344	-0.306
	p	0.184	0.013	0.029
	N	51	51	51
PTH	Correlation Coefficient	.062	0.48	-0.444
	p	0.668	< 0.001	0.001
	N	50	50	50

Table 4: Comparison of serum PTH and creatinine levels of patients divided into two groups according to mean lithium level.

		Mean Lithium Level		Z	p
		< 0.8	>= 0.8		
CRE	N	26	25	2.167	0.03
	Median	.76	.90		
PTH	N	25	25	2.775	0.006
	Median	55.92	79.78		

Table 5: Comparison of the biochemical parameters of the patient and control groups after exclusion of individuals with HBA1C values >5.6 mg/dl using antihypertensive and/or oral antidiabetic drugs.

	Group				
	Patient		Control			
	N	Median	N	Median	Z	p
EGFR	36	96.00	30	108.84	-3.227	0.001
Creatinine	36	.79	30	.65	-3.318	0.001
PTH	36	69.00	30	45.07	-3.310	0.001
25-OH D3	30	9,3	29	18.6	-2.259	0.024
Urine Density	35	1007	28	1005	-3.542	<0.001
Creatinine Urine	34	65.71	28	110.92	-2.716	0.007
Uric Acid	34	5.6	30	4.2	-2.909	0.004
Group		N	Mean	SD	t	p
Serum Calcium (CA)	Patient	36	9.8731	.43532	4.591	< 0.001
	Control	30	9.4367	.31237		

The results we obtained in our study show that there is a significant decrease in the glomerular functions of the patients being treated with lithium. The longer the lithium used, the higher the risk of glomerular pathology. These results are in line with studies reporting that long-term lithium use causes deterioration in glomerular functions [20]. Although the shorter average duration of lithium use in studies reporting contrary results suggests that lithium-related glomerular damage becomes more pronounced in long-term use.

In our study, serum uric acid levels were also found to be significantly higher in patients. This result, which is thought to be caused by the decrease in renal metabolism of uric acid, supports the presence of glomerular damage in patients. As far as we know, there is no study showing a direct relationship between lithium use and hyperuricemia. It can be thought that the high serum uric acid levels obtained in our study may be related to the decreased glomerular filtration rate.

While proteinuria was observed in 4 people in the patient group, proteinuria was not detected in the control group, but there was no statistical difference between the two groups. eGFR and serum creatinine levels were within normal limits in 3 of 4 patients with proteinuria. Tubular proteinuria may be seen in the course of chronic tubulointerstitial changes due to lithium. However, since the subtype of this proteinuria could not be determined in our study, it was not possible to make a further comment. Significant proteinuria (>2 g/day) is an indicator of glomerular damage [21]. It is not possible to detect a glomerular pathology with a single measurement, since false positive results may be seen. For this reason, repeating the examination to increase reliability is recommended. Another important point is the relationship between proteinuria and urine density. For example, proteinuria when urine density is 1,030 (++) may not be significant, whereas proteinuria when urine density is 1,005 (+) may reflect a severe proteinuria [22]. A daily protein loss

of <150 mg/day in the urine is considered physiological. Calculation of the total protein/creatinine ratio (mg/mg) in spot urine has been shown to reflect daily protein excretion. It is also unaffected by urine concentration and volume [23]. In terms of a glomerular pathology, we think that it would be more informative to examine the total protein/creatinine ratio and microalbuminuria in addition to proteinuria in the spot urine.

Since additional diseases such as hypertension and diabetes mellitus may impair glomerular functions, statistical analysis was performed again, excluding people with diseases that may affect glomerular functions other than lithium use. In the analysis performed with 36 patients and 30 control groups, excluding individuals using oral antidiabetic and/or antihypertensive drugs and have HBA1C levels>5.6 mg/dl from both groups, eGFR levels were found to be significantly lower and serum creatinine and uric acid levels were found to be significantly higher in patients. Despite the exclusion of factors other than lithium in the patient group, significant loss of glomerular function indicates that lithium use alone is an important risk factor. However, in clinical practice, it is important to prevent and treat diabetes and hypertension, which cause renal dysfunction in patients using lithium.

In our study, eGFR was found below the critical limit in 8 (15.68 %) of 51 patients and required further nephrological evaluation. Some studies also suggest that lithium intoxication episodes may pose a risk for long-term renal failure [24]. It is known that a history of lithium intoxication is more common in patients with renal failure, it is also stated that a slow but increasing rise in creatinine levels may also be a messenger of lithium intoxication [13]. In a recent study, it was determined that a single lithium blood level value measured above 1 mmol/L causes a significant acute decrease in the GFR levels of patients. It was emphasized that it is not known whether these acute decreases in renal functions observed in this patient group are compensated in the long term, and that lithium blood level measurements should be performed at least every 3 months [25]. Similarly, in our study patients with serum lithium levels above 0.8 mEq/L in the last year had higher serum creatinine levels compared to patients with low lithium levels, which is an important finding showing the disruptive effect of lithium. In a study, the kidney functions of 77 patients with a history of lithium intoxication were examined. It was found that the serum creatinine values before intoxication did not differ significantly from the serum creatinine values measured at least one month after the intoxication, and the increased creatinine levels returned to normal levels after a short time [26]. There is not enough information in the literature about the extent to which lithium intoxication attacks affect kidney functions in the long term. In our study, 13 patients (25.49 %) had a history of lithium intoxication, and serum creatinine, GFR and uric acid parameters reflecting glomerular functions of these patients did not show a significant difference compared to the patient group without a history of intoxication. Although this suggests that acute changes in kidney functions in patients with lithium intoxication may improve to a certain extent in the long term, studies investigating the long-term effects of lithium intoxication are needed.

4.2. Findings Related to Tubular Functions

Impaired urinary concentration ability is the most common renal side effect observed due to lithium treatment. The incidence of nephrogenic diabetes insipidus (NDI) among patients treated with lithium ranges from 20 % to 87 % [15]. In our study, urine density showing tubular functions was found to be significantly lower in the patient group and this is consistent with the literature.

4.3. Findings Related to Calcium Metabolism

One of the studies investigating whether there is a correlation between long-term lithium use and calcium metabolism has reported that the risk of developing hypercalcemia in patients using lithium for 15 years is 3 to 6 times higher than the normal population [27]. Similarly, calcium and PTH levels were found to be significantly higher in the patient group in our study. While hypercalcemia was detected in 6 people in the patient group, it was not detected in the control group. In another study, PTH and calcium values of 31 patients who were started on lithium treatment were compared with measurements after an average of 18 months of follow-up. It was found that PTH levels increased significantly during lithium treatment, but there was no significant change in ionized and total calcium levels. It was found that 5 of 31 patients whose PTH levels were within the reference range before follow-up developed hyperparathyroidism after follow-up [28]. In another study, 18 % of 423 patients in whom the prevalence of lithium-related hyperparathyroidism was attempted to be determined had lithium-related hyperparathyroidism, and 43 % had vitamin D insufficiency [29]. It is known that vitamin D deficiency can cause elevations in PTH levels [30]. In our study, 25-OH D3 levels were found to be significantly lower in the patient group. However, no significant relationship was found between PTH levels and 25-OH D3 levels. This result suggested that lithium use affects the functions of the parathyroid gland independently of vitamin D levels. Higher PTH and calcium levels in the patient group indicate a higher risk in terms of cardiac diseases, osteoporosis and renal diseases in the patient group using lithium. This situation requires clinicians to be more careful about these side effects.

5. Conclusion

Our study was conducted in a specialized mood outpatient clinic in the patient group with regular prospective follow-up and long-term lithium use, and it was found that the parameters indicating kidney functions such as creatinine, uric acid, calcium, PTH levels were higher, eGFR, Vitamin D, urine density

were lower than the controls, and in fact, about one of the 7 patients (n=8/51, 15.68 %) deteriorated critically, one quarter of the patients had a toxic level of lithium, and this situation was associated with impaired renal function and high PTH levels, duration of lithium use was moderately correlated with uric acid, and creatinine levels, and eGFR. Considering that even though the treatment was terminated, the glomerular pathology progressed irreversibly after a point, so the need for careful monitoring of the kidney functions of the patients receiving lithium conservation therapy was re-emerged in this study. The results reveal the usefulness of investigating proteinuria, total protein/creatinine ratio, and microalbuminuria in the urine, apart from serum markers, for a glomerular pathology. Before starting lithium conservation therapy, renal functions, especially eGFR, should be evaluated and repeated every 6 months, and lithium blood levels should be checked at least every 3 months. According to the results of the research, it can be recommended to continue the treatment of the patients with the lowest possible therapeutic blood levels, to determine the response level to lithium in the clinical follow-up, and to discontinue lithium in patients who do not benefit from the treatment. Since there are still gaps in the mechanism and process of lithium nephrotoxicity, studies with large sample sizes and long follow-up periods are needed.

Limitations of the Study

This study has some limitations, such as the relatively small number of cases, the inability to completely exclude other factors that may affect kidney functions other than lithium use, and due to sample having patients using lithium a moderate or longer period, the lack of data on patients who used lithium for a much longer period of time, the lack of data on patients who have used lithium for a long time and discontinued. In addition, the cross-sectional design of our study creates some limitations in establishing a causal relationship. Nevertheless, the strength of the study is that the patients were a carefully selected and regularly monitored cohort in a specialized mood outpatient clinic.

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Conflict of Interests

The authors declare no conflict of interest.

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Author Contributions

Conceived and designed the analysis: SÇ, BA, HY. Collected the data: BA, RT. Contributed data or analysis tools: BA, RT. Performed the analysis: BA, RT. Wrote the paper: BA, RT. Language editing: SÇ, HY. Final approval: SÇ, HY.

Ethical Approval

The protocol of the study was approved by Istanbul University Non-Interventional Clinical Research Ethics Committee (File no: 2015/1999).

Data sharing statement

All data relevant to the study are included in the article.

Consent to participate

All participants read the consent form and understand the study being described.

Informed Consent

Written informed consent was obtained from all patients at the of the study.

References

1. Nielsen RE, Kessing LV, Nolen WA, Licht RW. Lithium and Renal Impairment: A Review on a Still Hot Topic. *Pharmacopsychiatry*. 2018; 51(5):200-205.
2. Yatham LN, Kennedy SH, Parikh SV et al. The evolution of CANMAT Bipolar Disorder Guidelines: Past, present, and future. *BD*. 2013; 15:58-60.
3. Azab AN, Shnaider A, Osher Y, Wang D, Bersudsky Y, Belmaker RH. Lithium nephrotoxicity. *Int J Bipolar Disord*. 2015; 3:1-9.
4. Hestbech J, Hansen HE, Amdisen A, Olsen S. Chronic renal lesions following long term treatment with lithium. Kidney Int. 1977; 12(3):205-13.
5. Markowitz GS, Radhakrishnan J, Kambham N, Valery AM, Hines WH, D'Agati VD. Lithium nephrotoxicity: A progressive combined glomerular and tubulointerstitial nephropathy. J *Am Soc Nephrol*. 2000; 11(8):1439-48.
6. Golshayan D, Nseir G, Venetz JP, Pascual M, Barbey F. MR imaging as a specific diagnostic tool for bilateral microcysts in chronic lithium nephropathy. *Kidney Int.* 2012; 81(6):601.
7. Wells JE, Cross NB, Savage RL, Parkin L, Horsburgh S, Richardson AN. Renal replacement therapy associated with lithium nephrotoxicity in New Zealand. *N Z Med J*. 2015; 128(1425):77-83.
8. Davis J, Desmond M, Berk M. Lithium and nephrotoxicity: A literature review of approaches to clinical management and risk stratification. *BMC Nephrol*. 2018; 19(1):305.
9. Johnson GFS, Hunt GE, Duggin GG, Horvath JS, Tiller DJ. Renal function and lithium treatment: Initial and follow-up tests in manic-depressive patients. *J Affect Disord.* 1984; 6(3-4):249-63.
10. Boton R, Gaviria M, Batlle DC. Prevalence, Pathogenesis, and Treatment of Renal Dysfunction Associated With Chronic Lithium Therapy. *Am J Kidney Dis.* 1987; 10(5):329-45.
11. McCann SM, Daly J, Kelly CB. The impact of long-term lithium treatment on renal function in an outpatient population. *Ulster Med J*. 2008; 77(2):102-5.
12. Bendz H, Aurell M, Balldin J, Mathé AA, Sjödin I. Kidney damage in long-term lithium patients: A cross-sectional study of patients with 15 years or more on lithium. *Nephrol Dial Transplant.* 1994; 9(9):1250-54.

13. Lepkifker E, Sverdlik A, Iancu I, Ziv R, Segev S, Kotler M. Renal insufficiency in long-term lithium treatment. *J Clin Psychiatry.* 2004; 65(6):850-56.

14. 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(12):1075-83.

15. McKnight RF, Adida M, Budge K, Goodwin GY, Geddes JR. Lithium toxicity profile: A systematic review and meta-analysis. *Lancet*. 2012; 379(9817):721-28.

16. Fogo AB, Lusco MA, Andeen NK, Najafian B, Alpers CE. AJKD Atlas of Renal Pathology: Lithium Nephrotoxicity. *Am J Kidney Dis*. 2017; 69(1):e1-e2.

17. Presne C, Fakhouri F, Noel LH et al. Lithium-induced nephropathy: Rate of progression and prognostic factors. *Kidney Int*. 2003; 64(2):585-92.

18. Matsushita K, Mahmoodi BK, Woodward M et al. Comparison of risk prediction using the CKD-EPI equation and the MDRD study equation for estimated glomerular filtration rate. *JAMA-J Am Med Assoc*. 2012;307(18):1941-51.

19. Aiff H, Attman PO, Aurell M, Bendz H, Schön S, Swedlund J. End-stage renal disease associated with prophylactic lithium treatment. *Eur Neuropsychopharmacol*. 2014; 24(4):540-44.

20. Tredget J, Kirov A, Kirov G. Effects of chronic lithium treatment on renal function. *J Affect Disord.* 2010; 126(3):436-40.

21. González-Buitrago JM, Ferreira L, Lorenzo I. Urinary proteomics. *Clinica Chimica Acta*. 2007; 375(1-2):49-56.

22. McPherson RA, Ben-Ezra J. Basic Examination of Urine. In: Henry's Clinical Diagnosis and Management by Laboratory Methods. 24th Ed. **2011**.

23. D'Amico G, Bazzi C. Pathophysiology of proteinuria. *Kidney Int*. 2003; 63(3):809-25.

24. Kehoe RF. A cross-sectional study of glomerular function in 740 unselected lithium patients. *Acta Psychiatr Scand*. 1994; 89(1):68-71.

25. Kirkham E, Skinner J, Anderson T et al. 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(11):e006020.

26. 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(10):1008-19.

27. Bendz H, Sjödin I, Toss G, Berglund K. Hyperparathyroidism and long-term lithium therapy - A cross-sectional study and the effect of lithium withdrawal. *J Intern Med*. 1996; 240(6):357-65.

28. Albert U, De Cori D, Aguglia A et al. Effects of maintenance lithium treatment on serum parathyroid hormone and calcium levels: A retrospective longitudinal naturalistic study. *Neuropsychiatr Dis Treat.* 2015; 11:1785-91.

29. Meehan AD, Humble MB, Yazarloo P, Järhult J, Wallin G. The prevalence of lithium-associated hyperparathyroidism in a large Swedish population attending psychiatric outpatient units. *J Clin Psychopharmacol.* 2015; 35(3):279-85.

30. Boudou P, Ibrahim F, Cormier C, Sarfati E, Souberbielle JC. A very high incidence of low 25 hydroxy-vitamin D serum concentration in a French population of patients with primary hyperparathyroidism. *J Endocrinol Invest*. 2006; 29(6):511-15.

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