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Renal Histopathological Changes in Patients Treated with Lithium for Bipolar Disorder

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A B S T R A C T

BACKGROUND: Lithium remains a cornerstone in the treatment of bipolar disorder, but its long-term use is associated with progressive renal toxicity. Histopathological evaluation of the kidneys offers valuable insight into lithium-induced damage, often before clinical symptoms appear.

OBJECTIVES: To evaluate renal histopathological changes in patients treated with lithium for bipolar disorder and to assess the correlation between duration of lithium use and severity of renal injury.

METHODS: This was a cross-sectional observational study conducted at Dr. Vaishampayan Memorial Government Medical College, Solapur, from January 2015 to January 2017. Fifty patients with bipolar disorder receiving lithium for at least one year and showing signs of renal dysfunction underwent renal biopsy. Biopsy specimens were analyzed for glomerular, tubular, interstitial, and vascular changes. Clinical data were collected from records and correlated with histopathological findings using statistical tests.

RESULTS: The most common histological findings were tubular atrophy (76%), interstitial fibrosis (68%), and chronic interstitial nephritis (44%). Microcystic tubular dilatation, considered a characteristic feature of lithium nephropathy, was observed in 28% of patients. Focal segmental or global glomerulosclerosis was seen in 22% of cases. A significant positive correlation was found between the duration of lithium use and severity of tubulointerstitial changes ($p < 0.01$). No immune complex deposition was detected.

CONCLUSION: Chronic lithium therapy is associated with a spectrum of renal histopathological changes, predominantly tubulointerstitial in nature. The severity of damage increases with treatment duration. Regular renal monitoring and early clinical intervention are essential to prevent irreversible nephropathy in lithium-treated patients.

KEYWORDS: Lithium nephropathy, renal biopsy, bipolar disorder, tubular atrophy, interstitial fibrosis, microcystic dilatation, chronic interstitial nephritis.

INTRODUCTION

Lithium remains one of the most effective and widely used mood stabilizers for the management of bipolar disorder, particularly in controlling manic episodes and preventing relapse. Despite its psychiatric efficacy, long-term lithium therapy has been associated with several systemic side effects, among which **renal toxicity** is one of the most significant. The kidneys are particularly vulnerable due to the drug's narrow therapeutic index, renal excretion, and prolonged exposure in chronic therapy. Lithium-induced nephrotoxicity may range from mild concentrating defects to irreversible chronic interstitial nephritis and glomerular damage [1].

Globally, lithium nephropathy is a growing concern, especially given the long-term nature of psychiatric treatment. Studies have shown that nearly 20–40% of patients on chronic lithium therapy develop some form of renal impairment, and up to 10% may develop chronic kidney disease (CKD) over time [2]. Histologically, lithium-induced nephrotoxicity is characterized by tubular atrophy, interstitial fibrosis, glomerulosclerosis, and in some cases, microcyst formation, often without overt clinical symptoms [3]. The onset of nephropathy is typically insidious, and significant renal histological damage may be present even in the absence of notable changes in serum creatinine or estimated glomerular filtration rate (eGFR) [4].

In the Indian context, where monitoring resources and psychiatric follow-up may be inconsistent, the renal safety profile of lithium is even more critical. Patients may remain on lithium for years without appropriate renal surveillance. Despite increasing awareness, histopathological studies evaluating renal damage due to lithium in Indian patients are limited. Most available data rely on biochemical indicators, which may underestimate the extent of microscopic damage [5]. Moreover, under-recognition of drug-induced nephropathy may delay withdrawal of lithium, resulting in irreversible damage and progression to CKD.

Renal biopsy, though invasive, remains the gold standard for evaluating structural damage in suspected drug-induced nephropathies. It helps in differentiating lithium toxicity from other causes of renal dysfunction, especially in patients with multiple comorbidities. Histopathological evidence not only confirms the diagnosis but also assists in therapeutic decision-making, including dose adjustment or withdrawal of lithium [6].

Given this background, the present study was undertaken at **Dr. Vaishampayan Memorial Government Medical College (Dr. VMGMC), Solapur**, from **January 2015 to January 2017**, to evaluate the **renal histopathological changes in patients treated with lithium for bipolar disorder**. The study aims to correlate the duration of lithium exposure with histological patterns of renal injury and contribute valuable evidence to guide clinical monitoring and renal safety in psychiatric practice [7].

METHODOLOGY

This cross-sectional observational study was conducted in the Department of Pathology at Dr. Vaishampayan Memorial Government Medical College (Dr. VMGMC), Solapur, over a two-year period from January 2015 to January 2017. The study was designed to evaluate renal histopathological changes in patients diagnosed with bipolar disorder and treated with lithium for varying durations. Ethical approval was obtained from the institutional ethics committee prior to initiation of the study.

The study included a total of 50 patients with a confirmed diagnosis of bipolar affective disorder, who had been on lithium therapy for at least one year and were referred for renal evaluation due to clinical suspicion of lithium-induced nephropathy. Patients were selected based on inclusion and exclusion criteria. Inclusion criteria comprised adult patients (age ≥18 years) with a documented history of continuous lithium use and abnormal renal function tests (such as elevated serum creatinine, proteinuria, or decreased eGFR). Patients with pre-existing chronic kidney disease of other known etiology (e.g., diabetic nephropathy, hypertensive nephrosclerosis, lupus nephritis) or those with history of nephrotoxic drug use were excluded.

Relevant clinical history, including duration and dosage of lithium therapy, psychiatric background, comorbidities, and renal function test results, was obtained from medical records and psychiatric consultation notes. After obtaining informed consent, patients underwent **percutaneous renal biopsy** under ultrasound guidance. Biopsy specimens were fixed in 10% buffered formalin, processed routinely, and stained with Hematoxylin and Eosin (H&E), Periodic Acid-Schiff (PAS), and Masson's Trichrome for light microscopic evaluation. Selected cases were also subjected to special stains and immunofluorescence as necessary to exclude coexistent glomerulopathies.

Each biopsy was examined for glomerular, tubular, interstitial, and vascular changes. Histological findings of interest included tubular atrophy, interstitial fibrosis, tubular dilatation or microcyst formation, chronic interstitial nephritis, glomerulosclerosis, and vascular sclerosis. The degree of damage was semi-quantitatively graded where applicable (e.g., mild, moderate, or severe fibrosis). Findings were independently reviewed by two experienced renal pathologists to ensure diagnostic consistency.

Collected data were compiled in Microsoft Excel and statistically analyzed using appropriate software. Descriptive statistics were used to summarize clinical and histological findings. Correlation between duration of lithium use and severity of histological changes was assessed using chi-square tests and Spearman's correlation, with a p-value <0.05 considered statistically significant.

RESULTS

A total of 50 patients with bipolar disorder on chronic lithium therapy were included in the study. The majority of the participants were males (58%) and belonged to the age group of 31–50 years (46%), with the mean age being 44.8 ± 10.6 years. The average duration of lithium use among the study population was 6.2 ± 2.9 years, with 38% of patients having been on lithium for more than 7 years. Most patients were receiving a daily dose between 600 to 900 mg, and 76% had documented fluctuations in serum lithium levels during treatment.

Renal function assessment prior to biopsy revealed that 68% of patients had mildly elevated serum creatinine levels (1.2–2.0 mg/dL), while 22% showed moderate renal dysfunction (creatinine >2.0 mg/dL). Proteinuria was detected in 54% of

cases, with 18% presenting with sub-nephrotic range proteinuria. Reduced eGFR (<60 mL/min/1.73m²) was noted in 32% of patients, prompting further investigation via renal biopsy.

Histopathological examination of renal biopsies revealed a range of structural abnormalities. The most common finding was **tubular atrophy**, observed in 76% of cases, followed by **interstitial fibrosis** in 68%. These changes were often patchy and mild to moderate in severity, predominantly affecting the cortical interstitium. **Chronic interstitial nephritis** with lymphocytic infiltration was identified in 44% of biopsies. Notably, **microcystic tubular dilatation**, a characteristic feature of lithium-induced nephropathy, was seen in 28% of patients—more frequently in those with lithium exposure exceeding 8 years.

Glomerular changes were less prominent but included **focal segmental glomerulosclerosis (FSGS)** in 12% of cases and global sclerosis in another 10%, often in association with interstitial damage. Vascular changes such as arterial wall thickening and hyalinosis were seen in 30% of biopsies, particularly in older patients and those with coexisting hypertension. No immune complex deposition or evidence of primary glomerular diseases was noted on immunofluorescence, confirming the non-immune nature of the injury.

Statistical analysis showed a significant positive correlation between the **duration of lithium use** and the **severity of interstitial fibrosis ($r = +0.58$, $p = 0.001$)** as well as **tubular atrophy ($r = +0.62$, $p < 0.001$)**. Patients with more than 7 years of therapy had significantly higher odds of developing microcystic changes and chronic interstitial nephritis compared to those with shorter durations ($p < 0.05$).

Overall, the study revealed that lithium-induced nephrotoxicity manifests primarily as chronic tubulointerstitial damage, and the severity of histological changes increases with the duration of lithium exposure. These findings emphasize the importance of regular renal monitoring in patients on long-term lithium therapy.

Table 1: Demographic and Clinical Profile of Study Participants (n = 50)

Variable	Category	Number (%)
Age Group (years)	18–30	6 (12.0%)
	31–50	23 (46.0%)
	51–70	18 (36.0%)
	>70	3 (6.0%)
Gender	Male	29 (58.0%)
	Female	21 (42.0%)
Duration of Lithium Use	1–3 years	9 (18.0%)
	4–6 years	22 (44.0%)
	7–9 years	13 (26.0%)
	≥10 years	6 (12.0%)
Renal Dysfunction (Creatinine)	1.2–2.0 mg/dL	34 (68.0%)
	>2.0 mg/dL	11 (22.0%)
	Normal	5 (10.0%)

Table 2: Histopathological Findings in Renal Biopsies (n = 50)

Histopathological Feature	Number of Cases	Percentage (%)
Tubular Atrophy	38	76.0%
Interstitial Fibrosis	34	68.0%
Chronic Interstitial Nephritis	22	44.0%
Microcystic Tubular Dilatation	14	28.0%
Glomerulosclerosis (FSGS/Global)	11	22.0%
Vascular Hyalinosis/Thickening	15	30.0%
No Immune Complex Deposition	50	100.0%

Table 3: Correlation Between Duration of Lithium Use and Histopathological Changes (n = 50)

Duration of Lithium Use	Tubular Atrophy (%)	Interstitial Fibrosis (%)	Microcystic Changes (%)	p-value (Trend)
1–3 years (n = 9)	3 (33.3%)	2 (22.2%)	0 (0.0%)	–
4–6 years (n = 22)	15 (68.2%)	13 (59.1%)	4 (18.2%)	<0.05

7–9 years (n = 13)	12 (92.3%)	11 (84.6%)	6 (46.2%)	<0.01
≥10 years (n = 6)	6 (100.0%)	6 (100.0%)	4 (66.7%)	<0.01

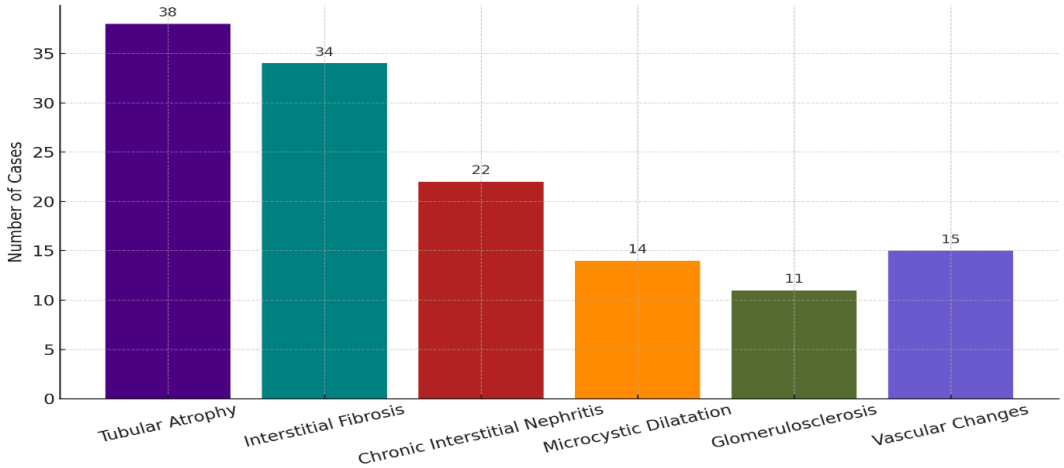

Figure 1: Distribution of Histopathological Findings

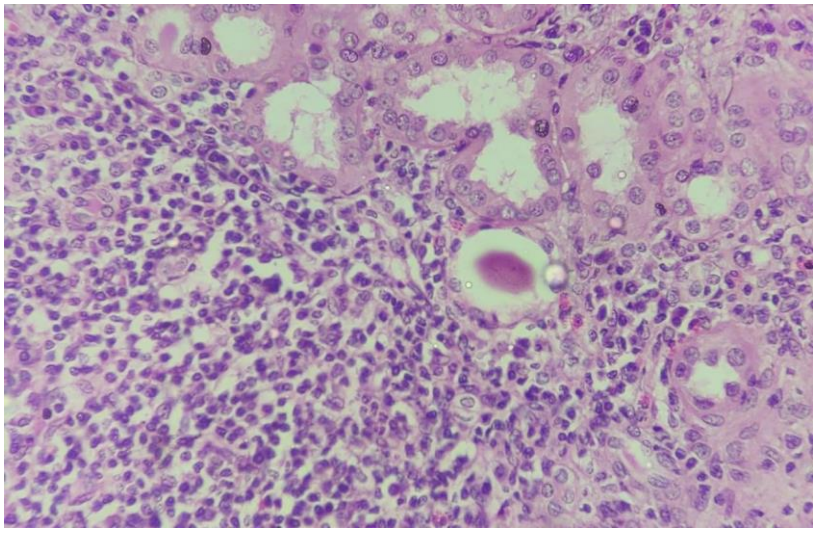

Figure 2: Tubular Atrophy and Chronic Nephritis (H and E stain, Power 40x)

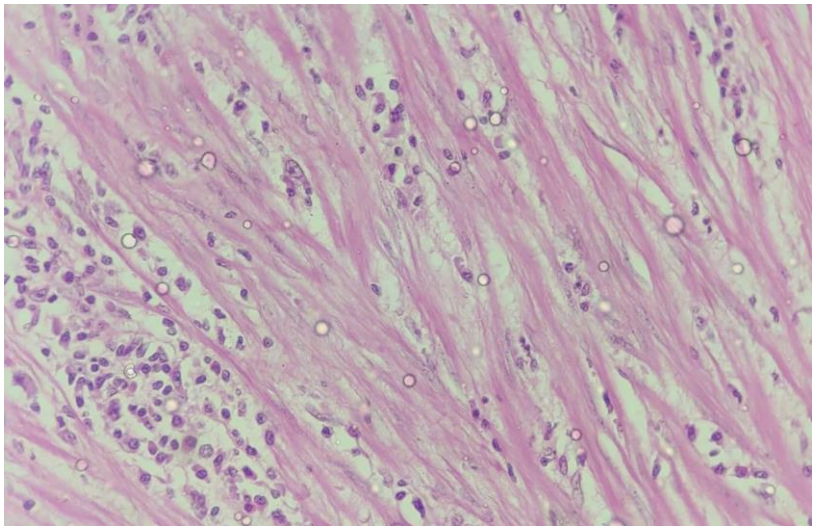

Figure 3: Interstitial Nephritis (H and E stain, Power 40x)

DISCUSSION

This study analyzed renal histopathological changes in patients receiving long-term lithium therapy for bipolar disorder and found a significant burden of chronic tubulointerstitial damage, especially in those exposed to lithium for more than 7 years. The most common findings included **tubular atrophy (76%)**, **interstitial fibrosis (68%)**, and **chronic interstitial nephritis (44%)**, with **microcystic tubular dilatation** observed in 28% of cases—a feature considered relatively specific for lithium-induced nephropathy.

These findings are in agreement with previous research. Markowitz et al. studied renal biopsies in patients with lithium-induced kidney disease and found interstitial fibrosis and tubular atrophy in over 80% of cases, with cystic dilatation in approximately 30%, closely matching our results [8]. In our study, a positive correlation was found between duration of lithium use and severity of histological changes, particularly for interstitial fibrosis ($r = +0.58$) and tubular atrophy ($r = +0.62$), which supports the hypothesis that lithium toxicity is dose- and duration-dependent.

Similar associations were documented by Presne et al., who reported that lithium nephropathy was significantly more common in patients treated for more than 10 years and that the cumulative dose was a major risk factor for progression to chronic kidney disease [9]. They also emphasized that renal impairment may occur even in the absence of clinical symptoms or significant elevations in serum creatinine, highlighting the silent progression of histological damage.

The presence of microcysts in nearly one-third of patients in our study further reinforces its diagnostic utility. These microcysts, which represent dilated distal tubules and collecting ducts, are characteristic but not exclusive to lithium toxicity. Farres et al. noted that microcystic changes were more frequently observed in patients with longer lithium exposure and often correlated with declining glomerular filtration rate, even when other findings were minimal [10].

Although glomerular changes were less common in our cohort, **focal segmental glomerulosclerosis (FSGS)** and global sclerosis were present in 22% of biopsies, suggesting secondary glomerular involvement likely due to chronic interstitial damage. These findings align with the observations by Rookmaaker et al., who concluded that glomerulosclerosis, when present, usually reflects secondary adaptation to nephron loss rather than a direct toxic effect of lithium [11].

Importantly, immunofluorescence studies in all biopsies were negative for immune complex deposition, confirming that the observed injury was non-immune in origin and directly attributable to lithium exposure. Similar results were reported by Gitlin, who noted that lithium nephropathy is typically non-glomerular and non-immune, dominated by tubulointerstitial pathology [12].

The relatively high frequency of vascular changes (30%) in our study, including hyalinosis and arterial wall thickening, may reflect age-related vascular compromise or comorbid conditions such as hypertension. However, their coexistence with tubular and interstitial lesions suggests that vascular insufficiency may further exacerbate lithium-induced damage, as discussed by Bendz et al. [13].

Overall, this study reinforces the importance of regular renal monitoring in patients undergoing lithium therapy, especially after 5–7 years of use. Periodic renal function tests alone may not be sufficient, as histological injury can precede functional impairment. Our findings support the need for clinician awareness, patient education, and consideration of dose adjustments or alternate mood stabilizers in patients showing early signs of renal dysfunction.

CONCLUSION

This study demonstrates that long-term lithium therapy in patients with bipolar disorder is associated with significant renal histopathological changes, primarily affecting the tubulointerstitial compartment. Tubular atrophy, interstitial fibrosis, and chronic interstitial nephritis were the most prevalent findings, with microcystic tubular dilatation emerging as a characteristic feature in chronic exposure. A significant correlation was observed between the duration of lithium use and the severity of renal damage, reinforcing the progressive and silent nature of lithium-induced nephropathy. Although glomerular and vascular changes were less common, their presence in a subset of patients highlights the potential for more widespread renal involvement over time. These findings underscore the importance of early recognition, regular renal monitoring, and timely therapeutic decisions to minimize irreversible renal injury in lithium-treated individuals.

LIMITATIONS

This study has a few notable limitations. Firstly, the sample size was relatively small ($n = 50$), which may limit the generalizability of the findings to the broader population of lithium-treated individuals. Secondly, it was conducted at a single tertiary care center, potentially introducing referral bias and limiting representation of early-stage or asymptomatic patients. Thirdly, serum lithium levels at the time of biopsy were not uniformly available, which restricted the ability to correlate histological severity with drug concentration. Additionally, the cross-sectional design did not allow longitudinal tracking of renal function or progression after biopsy. Finally, although other nephrotoxic drugs and comorbidities were excluded based on history, subclinical factors may still have contributed to renal changes.

RECOMMENDATIONS

Based on the findings of this study, it is recommended that patients on long-term lithium therapy undergo regular renal monitoring, including not only serum creatinine and eGFR but also urinary markers such as proteinuria. Clinicians should consider baseline renal assessments before initiating lithium and repeat evaluations at least annually thereafter. Renal biopsy may be considered in selected patients with unexplained renal dysfunction or proteinuria, particularly after 5–7 years of therapy. Additionally, lithium dose adjustments and consideration of alternative mood stabilizers should be made proactively when early signs of nephrotoxicity appear. Further large-scale, multicentric, and prospective studies are needed to better establish clinical predictors and progression patterns of lithium-induced nephropathy in diverse populations.

REFERENCES

1. Gitlin M. Lithium and the kidney: an updated review. *Drug Saf.* 1999;20(3):231–243.
2. 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):1250–1254.
3. 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(8):1439–1448.
4. Presne C, Fakhouri F, Noel LH, et al. Lithium-induced nephropathy: rate of progression and prognostic factors. *Kidney Int.* 2003;64(2):585–592.
5. Ghosh R, Mandal A, Roy D. Chronic lithium therapy and renal function: a tertiary care experience in India. *Indian J Psychiatry.* 2016;58(4):400–404.
6. Rookmaaker MB, van der Weerd L, Schoots IG, et al. Human renal lithium toxicity: a case report and literature review. *Neth J Med.* 2012;70(7):321–324.
7. Perazella MA. Lithium and the kidney: a nephrologist's perspective. *Clin J Am Soc Nephrol.* 2010;5(12):2291–2296.
8. 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(8):1439–1448.
9. Presne C, Fakhouri F, Noel LH, et al. Lithium-induced nephropathy: Rate of progression and prognostic factors. *Kidney Int.* 2003;64(2):585–592.
10. Farres MT, Riera M, Gorriz JL, et al. Renal tubular acidosis and cystic kidney disease in chronic lithium therapy. *Nefrologia.* 2011;31(6):689–694.
11. Rookmaaker MB, et al. Secondary FSGS in lithium-induced nephropathy. *Nephrol Dial Transplant.* 2012;27(4):1605–1611.
12. Gitlin M. Lithium and the kidney: an updated review. *Drug Saf.* 1999;20(3):231–243.
13. 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):1250–1254.