
بسم الله الرحمن الرحيم

Lithium & kidney

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Introduction

Over the past few decades, lithium carbonate has been used as an effective therapeutic agent for the treatment of bipolar affective disorders. Lithium is an extremely potent mood stabilizer and provides protection against both manic and depressive episodes.

Lithium also plays a substantial role in reducing suicidal deaths among bipolar patients. However, the use of lithium is accompanied by significant concern for its narrow therapeutic index and potential for multiorgan injury.

Chronic lithium ingestion in patients with bipolar (manic depressive) illness has been associated with several different forms of kidney injury. Nephrogenic diabetes insipidus (NDI) is the most common renal side effect of lithium therapy .

- **The predominant form of chronic kidney disease associated with lithium therapy is a chronic tubulointerstitial nephropathy. Although the majority of studies show infrequent and relatively mild renal insufficiency attributable to lithium therapy, end-stage kidney disease (ESKD) secondary to lithium-associated chronic tubulointerstitial nephropathy does occur in a small percentage of patients. The prevalence of ESKD is reported as 1.5% in patients on lithium .**

  Relatively less is known about potential glomerular toxicity of lithium, particularly the nephrotic syndrome.

  Minimal change disease and focal segmental glomerulosclerosis (FSGS) are a few glomerular manifestations of lithium nephrotoxicity.

  Additional kidney manifestations of lithium exposure include renal tubular acidosis and hypercalcemia.

- **Pathophysiology**

Lithium is a **univalent cation** of the white metal series, closely related to both sodium and potassium, but having no known role in human physiology.
Lithium is **completely absorbed by the GI tract**. The drug is not protein bound and is **completely filtered at the glomerulus**. The majority of the filtered load is reabsorbed by the proximal tubule, but significant amounts are also absorbed in the loop of Henle and the early distal nephron. Up to **90% of the filtered load is reabsorbed by the nephron**, **60% in the proximal tubule**, and the remainder in the **thick ascending limb of the loop of Henle, the connecting tubule, and the cortical collecting duct**.
Lithium can substitute for sodium in several sodium channels, particularly the sodium-hydrogen exchanger in the proximal tubule (NHE3), the sodium/potassium/2chloride exchanger in the thick ascending limb of the loop of Henle (NKCC2), and the epithelial channel of the cortical collecting tubule (ENaC).

Lithium can affect kidney function in several ways**. Acutely and chronically, lithium salts produce a natriuresis** that is associated with an **impaired regulation of the expression of the epithelial sodium channel in the cortical collecting tubule**.

Specifically, lithium use **partially inhibits the ability of aldosterone to increase apical membrane ENaC expression**, resulting in inappropriate sodium losses.

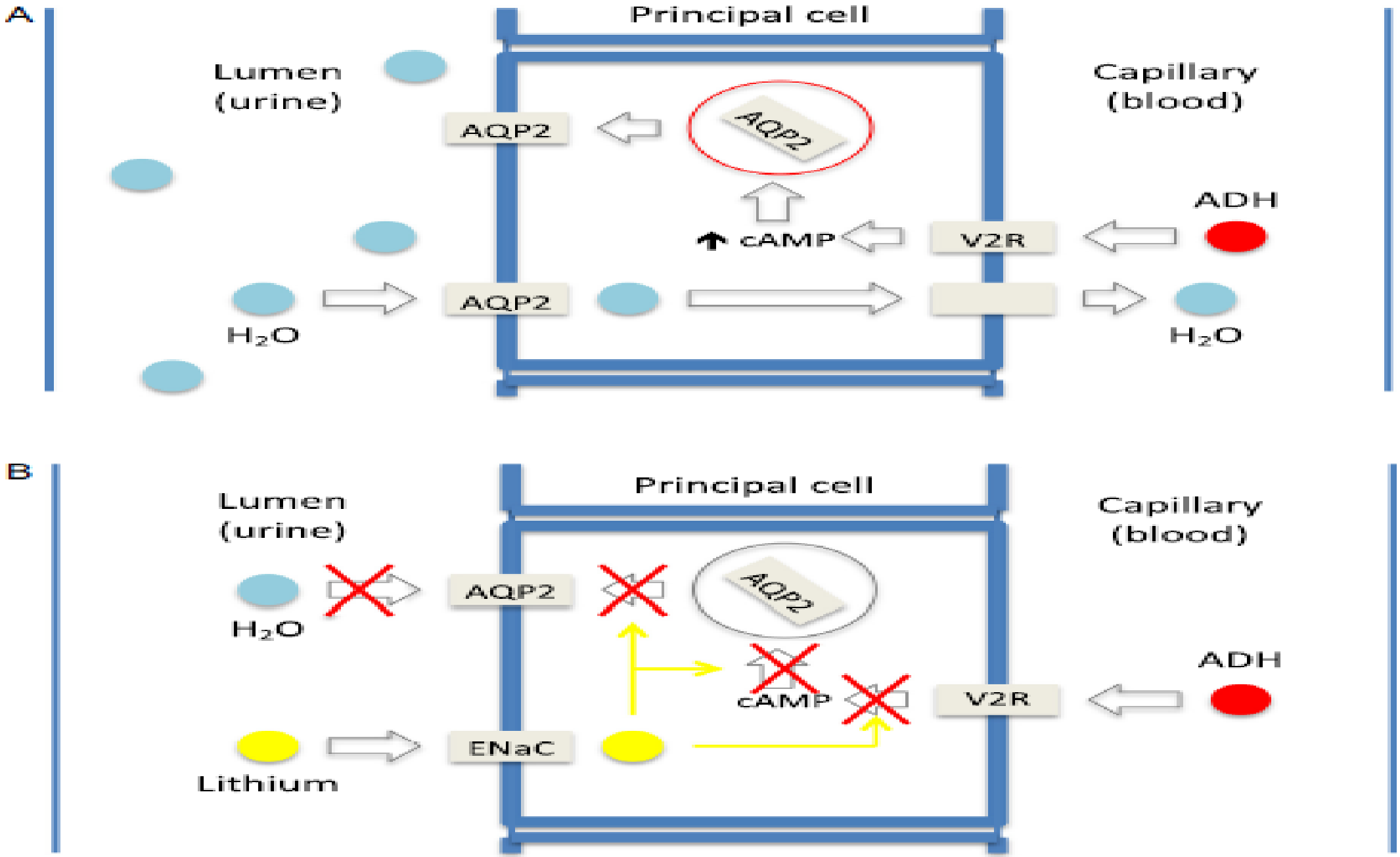
The most common complication of long-term lithium therapy is nephrogenic diabetes insipidus.

- At the cellular level, antidiuretic hormone (ADH) is released from the posterior pituitary in response to increases in serum **osmolarity or decreases in effective circulating volume,** and this hormone acts on **V2 receptors** in **the basolateral membrane of the principal cells in the cortical and medullary collecting tubules**. The net result of the cascade involving a G protein (guanyl-nucleotide regulatory protein) and adenylate cyclase is an increase in the intracellular cyclic adenosine monophosphate (**cAMP**) level, which can play a dual role in antidiuresis regulation. cAMP acutely **stimulates protein kinase A,** which **facilitates the insertion of aquaporin-2 (AQP2) water channels**. These water channels are preformed and stored in cytoplasmic vesicles in the apical plasma membrane of the principal cells. This process leads to increased water permeability and, thus,antidiuresis.

Over extended periods of time, increased cAMP levels also increase the production of AQP2 water channels at the genetic level by promoting a untranslated region of the AQP2 gene. Lithium **impairs the ADH stimulatory effect on adenylate cyclase, thereby decreasing cAMP levels**.

Li and colleagues have also performed studies suggesting that the ability of lithium to produce nephrogenic diabetes **insipidus may be independent of its effect on cAMP generation and related to decreased AQP2 mRNA levels.** Thus, lithium most likely **impairs water permeability in the principal cells by inhibiting water channel delivery and, over a prolonged period of time, by suppressing channel production**.

A minority of reports, however, propose that lithium-induced **partial central diabetes insipidus** may play a role in the polyuria that may develop in patients who **show a modest response to exogenous ADH**. Other studies show that **ADH levels in patients treated with lithium are normal or elevated.**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Lithium

Patients with urineconcentrating defects resulting from lithium treatment usually **take weeks to months to recover following discontinuation** of the drug; in rare situations, the problem can persist for years. Early reports in psychiatric patients suggested that this **persistent concentrating impairment may be linked to underlying renal histological damage and may be worse with neuroleptic use and prolonged lithium therapy.**

In a 1987 review, Boton and colleagues showed a **54% correlation** between impaired **urine-concentrating ability and the duration and total dosage of lithium treatment**. Lithium may also be responsible for a **distal tubular acidification defect**.The defect is believed to be **a variant of incomplete distal renal tubular acidosis**, whereby the effect is exerted **from the luminal side**, requiring lithium cell entry. Patients taking lithium have **normal phosphate and ammonia excretion**. Lithium is **not known to cause significant hyperkalemia**.

The role of lithium in the production of **acute renal failure** is well accepted. The cause is generally **due to severe dehydration and volume depletion due to the combination of natriuresis and water diuresis accompanied by elevated lithium levels, altered mental status, and subsequent poor oral intake.** Acute renal failure has also been described as a **result of lithium-induced neuroleptic malignant syndrome**.

However, controversy still exists over its role in chronic renal failure. Boton and colleagues estimated (from an analysis of more than 1000 patients) that 85% of patients on long-term lithium therapy had normal glomerular filtration rates (GFRs); the remaining 15% had GFRs of more than 2 standard deviations below the age-corrected normal values, but very few patients had values less than 60 mL/min.

Extensive reviews in 1988 and 1989 suggested that **monitored long-term lithium treatment does not adversely affect the GFR**, despite other reports of concurrent histological damage. Prospective studies of patients taking stable **lithium also failed to show a decline in GFR in the absence of acute lithium intoxication**.

Although **a minimal increase in the protein excretion rate** has been reported in some patients who were taking lithium for at least 2 years, **overt proteinuria is not a common complication**. A rare association between minimal-change nephrotic syndrome and lithium administration has also been described.

Lithium does **not appear to adversely affect proximal tubular function.**

- **Epidemiology**

Lithium is currently a drug of choice for treating persons with bipolar depression and is widely used in this population. Approximately**0.1 % of the US population** is **undergoing lithium treatment** for psychiatric problems.
Approximately **20-54%** of these patients have **symptoms Of urine-concentrating defects** during and after lithium use, and up to **12%** develop **frank diabetes insipidus**. Some patients continue to have this problem for years after discontinuing lithium.
Of note, approximately **30%** of patients taking lithium **experience at least one episode of lithium toxicity**, correlating with a decrease in glomerular filtration rate.
A study from the **Netherlands**, the incidence of chronic kidney disease **(CKD)** in patients treated with lithium **was 0.012 cases per exposed patient-year**.
Longer duration of lithium exposure increased the odds of reaching stage 3 CKD.
In patients who developed stage 3 CKD, the average decline in estimated glomerular filtration rate (eGFR) was **1.8 mL/min/year**. **The incidence of stage 4 CKD was only,0.0004 per patient-year.**

It has been suggested that 15% to 20% of patients receiving lithium therapy develop a slowly progressive decline in glomerular filtration rate, which usually does not fall below 40 to 60 mL/minute.

Progressive renal failure with a serum Cr greater than 176 µmol/L,solely attributed to lithium therapy, is thought to be uncommon.

This means that clinicians should not immediately discontinue lithium therapy at the earliest signs of renal dysfunction. Rapid withdrawal of lithium has also been associated with bipolar relapse.

Table 1 Risk factors for lithium induced nephropathy and their proposed mechanisms

Risk Factor	Proposed Mechanism
Duration of lithium therapy	Prolonged lithium exposure leading to irreversible structural changes within the kidney parenchyma
Age	Age related decline in eGFR, polypharmacy, medical comorbidity
Lower initial eGFR	Reduced nephron mass, background tubulointerstitial damage
Female gender	Unclear mechanism
Cumulative lithium dose	Prolonged lithium exposure leading to irreversible structural changes within the kidney parenchyma
Other concomitant CKD risks (hypertension, diabetes mellitus)	Concomitant tubulointerstitial damage, nephrosclerosis
Concomitant use of nephrotoxic medications	Disruption of tubulo-glomerular feedback, volume contraction, drug-interactions
Prior episodes of lithium toxicity	Higher lithium concentrations, induction of acute kidney injury with subsequent chronic damage
NDI	Volume contraction leading to elevated lithium concentrations, may be surrogate marker for morphological changes occurring within the kidney tubules

- **Presentation**

Generally, lithium nephrotoxicity will occur **within a month of onset of use** of the drug, manifested **predominantly by polyuria and polydipsia**. The onset of these symptoms may also occur in the presence of **accelerating dose regimens**. Initially, these symptoms are reversible but may **become permanent with long-term use and/or chronically high serum lithium levels**.

NDI could manifest as early as **two to four months after initiating** therapy.

The **decreased density of AQP2** results in **subclinical polyuria in the short term**.

Polyuria becomes more evident after a prolonged duration of therapy due to the eventual loss of principal cells. Polyuria, defined as a 24-hour urine output of greater than 3 L, is the **most common complication in an otherwise asymptomatic patient who has a plasma lithium level consistent with therapeutic dosing.**

Nocturia can be a useful marker of polyuria. Up to **68% of patients report at least 1 urination episode per night.**

When acute kidney injury occurs in the setting of lithium toxicity, the patients generally will exhibit other signs of lithium toxicity, such as **obtundation**. In particular, **elderly patients** with acute kidney injury may **develop delirium, with confusion, tremors, and ataxia**.

-Patients with **lithium nephrotoxicity** may exhibit signs of **modest volume depletion, including orthostatic hypotension, tachycardia, and dry mouth**. With **severe dehydration, patients will show evidence of hypernatremia, including altered mental status .**

CIN is a **predominant form of chronic kidney disease** typically encountered in patients with exposure to lithium for **more than fifteen years.No significant proteinuria or hematuria is noticeable on urine analysis.**

- **Laboratory Studies**

A **chemistry panel** may help identify **electrolyte abnormalities** that may be causing the **patient's concentrating defect and natriuresis** (**ie hypernatremia, hypokalemia, hypercalcemia, elevated BUN and creatinine**).
Uncontrolled diabetes mellitus may cause similar findings from osmotic diuresis; however, in that disorder, the serum glucose level will be elevated.

Urine and serum osmolality may help determine if the patient has **a concentrating defect. Urine osmolality will be less than 100 mOsm/kg** despite **normal or higher-than-normal serum osmolality.**

High urine output accompanied by elevated blood urea nitrogen (BUN) and serum creatinine levels can be **due to volume depletion** with any **polyuric syndrome, such as nephrogenic diabetes insipidus, central diabetes insipidus, or osmotic diuresis; the polyuric phase of acute renal failure; or chronic renal failure**.

Assess the patient's **lithium level**: Check the **plasma vasopressin** level **to rule out central diabetes insipidus**.

Perform **full toxicology screen to exclude the possibility of multiple toxin ingestion, particularly in the case of suicide attempts.**

- **Other Tests**
- **Water deprivation test**

This test **documents whether the patient has a concentrating defect**.

First, **baseline measurements of urine and serum osmolality and electrolytes** are obtained. Strict water deprivation is then imposed for **4-18 hours** (**usually 8 h**).

Urine output and weight are carefully monitored before and after fluid deprivation. **Serum and urine osmolality and electrolyte levels** are measured **hourly** after initiation of fluid deprivation. **A patient without a concentrating defect should have a 2- to 4-fold increase in urine osmolality**.

- **Vasopressin challenge**

This test **differentiates central and nephrogenic diabetes insipidus**. Following the water deprivation test, **5 U of vasopressin** is administered subcutaneously (ie, vasopressin **as 5 U of aqueous arginine vasopressin or 1 mcg of desmopressin SC or 10 mcg of desmopressin by nasal spray). Serum and urine osmolality are measured 1-2 hours later.**

Patients with **complete central diabetes insipidus** fail to increase their urine osmolality after water deprivation (ie, concentrating defect),but they have **more than a 50% increase in urine osmolality** from baseline after vasopressin administration. Patients with **nephrogenic diabetes insipidus** also fail to show an increase in urine osmolality after deprivation (ie, concentrating defect) but have less than **a 10% increase in urine osmolality from baseline after vasopressin** administration. Reports have described patients with **combined central and nephrogenic** defects who show a **10-50% increase** in urine osmolality.

- **Imaging Studies**

MRI examination of the kidneys, while **not necessary for diagnosis, has demonstrated the presence of renal cysts in many patients** .

clinicians can use T2-weighted MRI to **determine if renal dysfunction is related to lithium.**

These are described as **microcysts and can be quite numerous**.

MRI can detect renal microcysts in approximately **100% of patients receiving chronic lithium treatment and have renal insufficiency .**

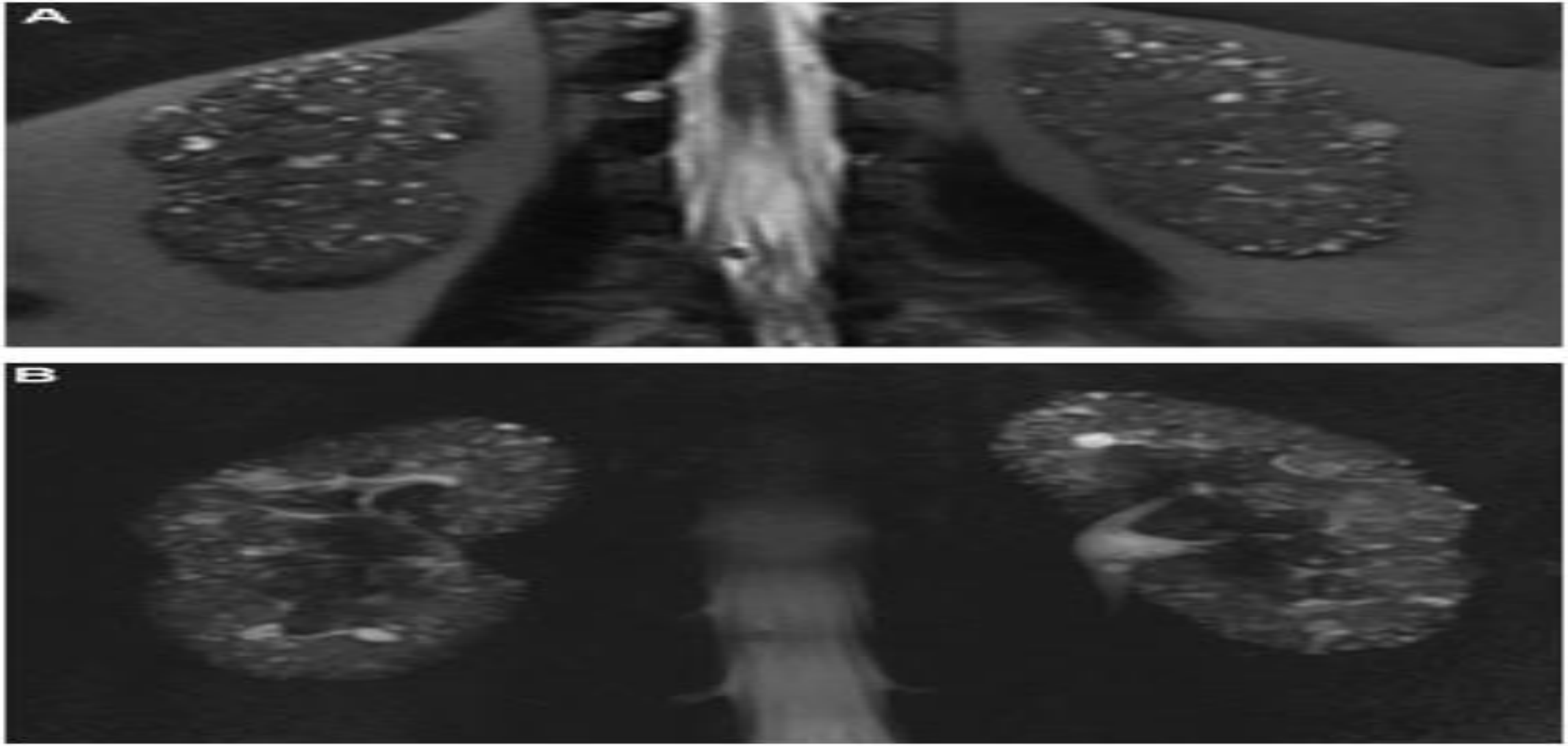

Figure 1. Magnetic resonance (MR) images of the kidneys in a 59-year-old woman who has been receiving lithium treatment for more than 20 years. A. Fat attenuated T2-weighted MR image in the coronal plane (TR/TE – 1250/90 msec). B. Fat attenuated heavily T2-weighted MR image in the coronal plane (TR/TE – 6000/600 msec) show multiple, hyperintense microcysts in the cortex and medulla of both kidneys.

frontiers in Pharmacology

ORIGINAL RESEARCH
published: 07 January 2022
doi: 10.3389/fphar.2021.784298

Determinants of Kidney Function and Accuracy of Kidney Microcysts Detection in Patients Treated With Lithium Salts for Bipolar Disorder

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- **Objectives**: Early kidney damage during lithium treatment in bipolar disorder is still hypothetical. We aimed at identifying the **determinants of a decreased measured glomerular filtration rate (mGFR) and the accuracy of kidney MRI imaging in its detection.**

Methods: In **this cross-sectional cohort study, 217 consecutive lithium-treated patients underwent mGFR and kidney MRI** with **half-Fourier turbo spin-echo and Single-shot with long echo time sequences**.

- **Results**: **Median age** was **51** [**27–62**] years, and **median lithium treatment duration was 5 [2–14] years. 52%of patients had a stage 2 CKD**.

In multivariable analysis, **the determinants of a lower mGFR** were a **longer lithium treatment duration** (β −0.8 [−1; −0.6] ml/min/1.73m2 GFR decrease for each year of treatment), **a higher age** (β −0.4 [−0.6; −0.3] ml/min/1.73m2 for each year of age, p < 0.001), **albuminuria** (β −3.97 [−6.6; −1.3], p 0.003), **hypertension** (β −6.85 [−12.6; −1.1], p 0.02) and **hypothyroidism** (β −7.1 [−11.7; −2.5], p 0.003).

Serum lithium concentration was not associated with mGFR.

Renal MRI displayed renal microcyst(s) in **51%** of patients, detected as early as **1 year after lithium treatment initiation.**

mGFR and lithium treatment duration were strongly correlated in patients with microcysts (r −0.64, p < 0.001), **but not in patients with no microcysts** (r −0.24, p 0.09).

The **presence of microcysts was associated with the detection of an mGFR <45** ml/min/1.73m2 (AUC 0.893, p < 0.001**, sensitivity 80%, specificity 81%**for a **cut-off value** of **five microcysts**).

- **Conclusion**: **Lithium treatment duration and hypothyroidism strongly impacted mGFR independently of age, especially in patients with microcysts**.

MRI might help detect early lithium-induced kidney damage and inform preventive strategies.

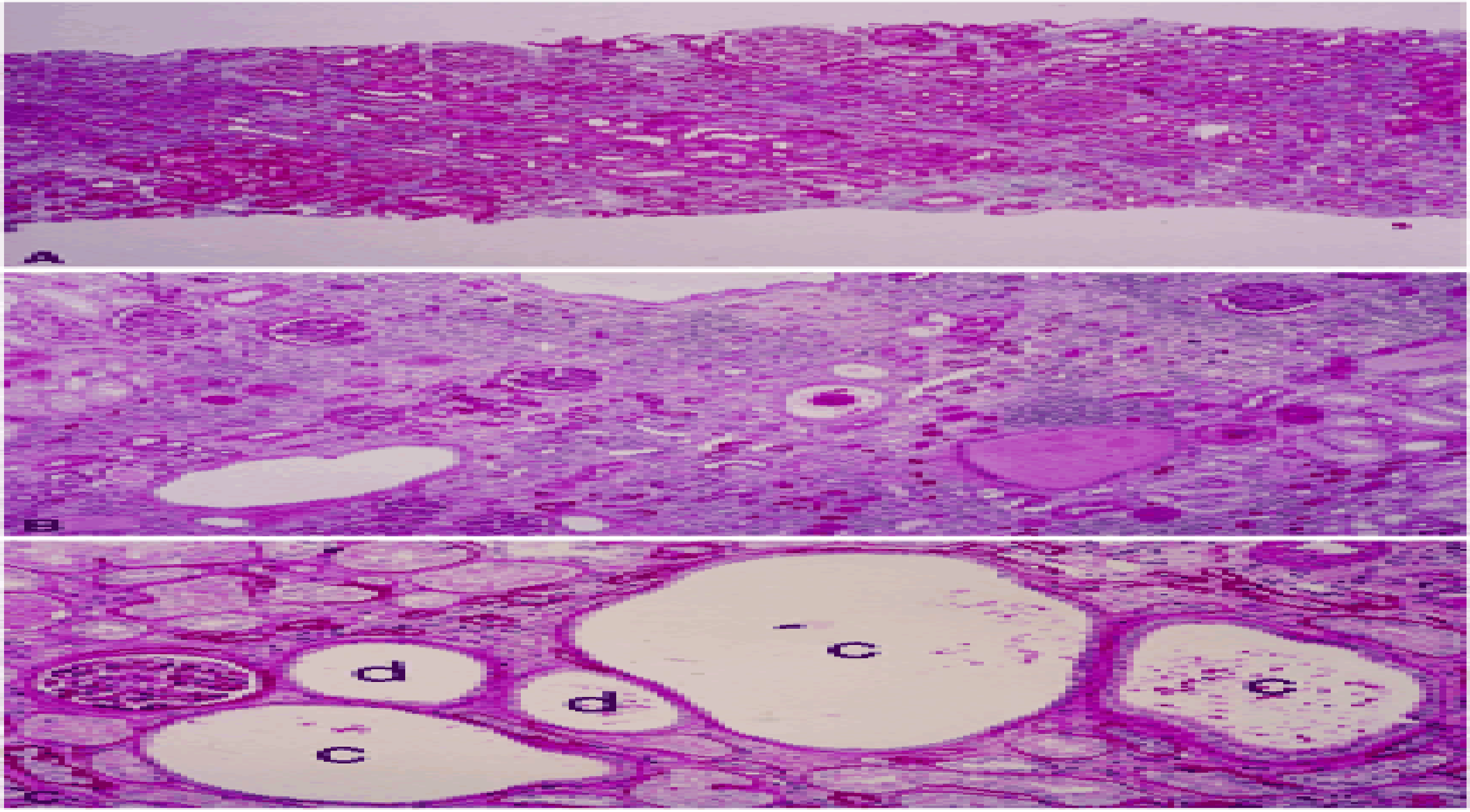
• Histologic Findings

The histology of acute renal lesions associated with lithium intoxication tends to involve the distal nephron and includes acute tubular necrosis with nonspecific changes such as distal tubular flattening, proximal tubular necrosis, and cytoplasmic vacuolation and cellular and nuclear polymorphism of the distal tubular epithelial cells. In 1978, Kincaid-Smith described a more specific acute lesion consisting of glycogen deposition in the swollen and vacuolated cytoplasm of the distal tubular epithelial cells. These lesions can reverse when lithium administration is stopped.

The development of chronic renal lesions with prolonged lithium use is controversial. Earlier studies have cited interstitial fibrosis, tubular atrophy, and glomerulosclerosis among the chronic changes attributed to lithium. Furthermore, studies suggested that these lesions correlated clinically with the duration of lithium use and concomitant neuroleptic treatments.

Other more specific chronic lesions include distal tubular dilation and microcyst formation.

No evidence indicates that chronic glomerular lesions persist after discontinuing lithium.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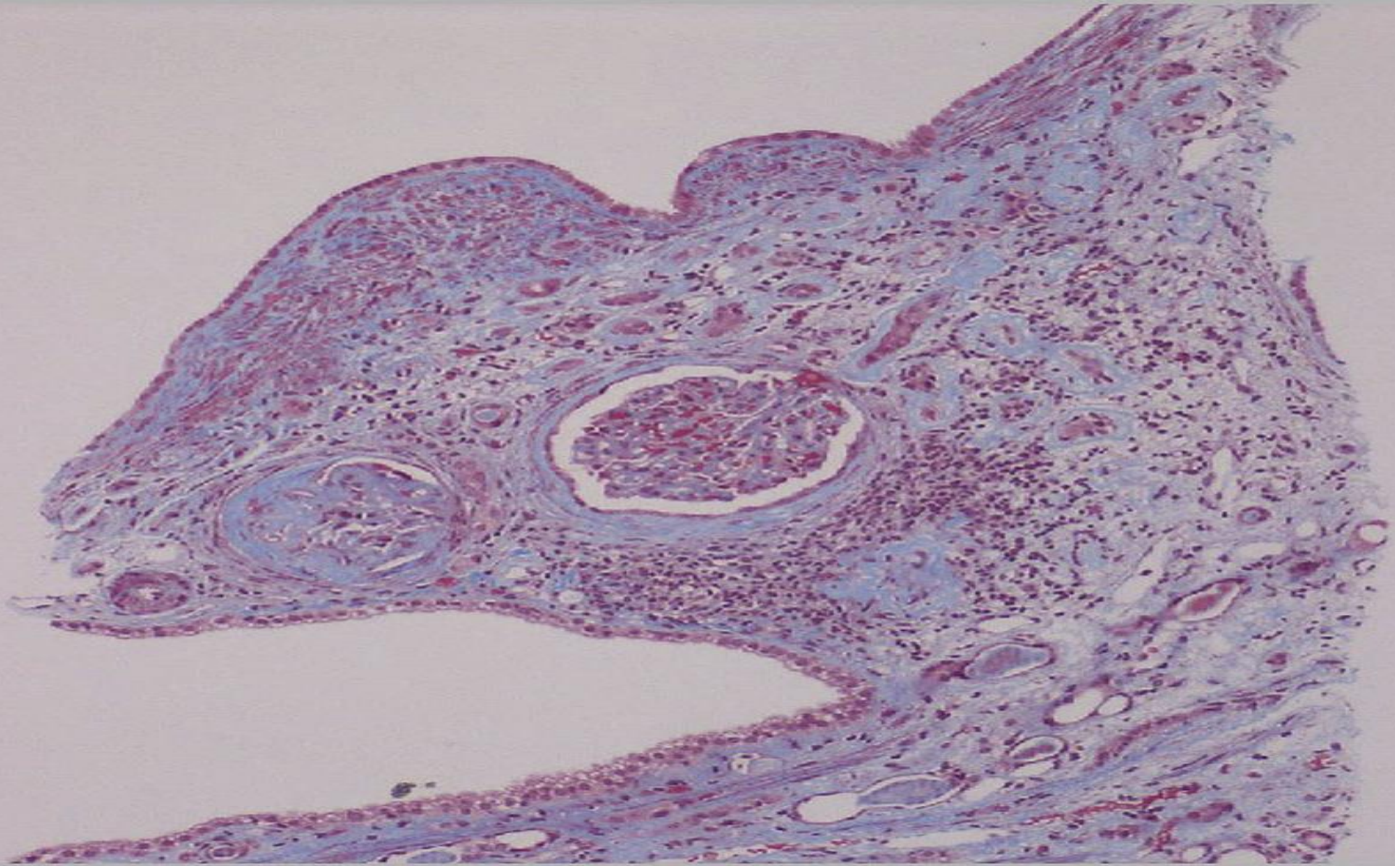

- **Lithium Intoxication**

  Lithium (usually as lithium carbonate) has a **very narrow therapeutic range** (serum lithium concentration [Li+] usually between **0.6 and 1.3** mmol/L) and is **sensitive to modest changes in kidney function**.

  Acute-on chronic lithium toxicity most often results from AKI from other causes (such as dehydration from diarrhea) Or from **rapid escalation of the dose**. Acute overdose can rapidly produce high lithium concentrations.

Hemodialysis effectively clears lithium, which has a molecular weight of **7 Da**. Its volume of distribution is near 1 L/kg. Due to **high intracellular concentrations**, [Li+] often **rebounds after hemodialysis** due to redistribution from the intracellular space.

Indications for hemodialysis depend upon the [Li+], kidney function, and neurological symptoms. The EXTRIP Workgroup recommends **hemodialysis** when **[Li+] > 4 mEq/L** or if the patient has a **decreased level of consciousness,seizures**, or **life-threatening dysrhythmias**,regardless of the [Li+]. CRRT is an acceptable alternative if hemodialysis is unavailable or inadvisable.

- **Treatment**

The treatment of lithium nephrotoxicity depends on the severity of the toxicity and chronicity as well as the presence of related abnormalities.
The acute lithium nephrotoxicity picture is dominated by evidence of volume depletion, obtundation, and the potential for cardiovascular collapse. These patients will frequently require close monitoring and aggressive fluid replacement even dialysis; therefore, the intensive care unit is the most appropriate site for these patients.

Correcting electrolyte abnormalities in patients with acute disease is critical. Treatment should be initiated with parenteral fluids to replete hypovolemia (normal saline at 200-250 mL/h), followed by administration of hypotonic fluid (0.5% normal saline). Once volume status is restored, then a forced diuresis should be initiated by the administration of parenteral furosemide or bumetanide accompanied by continued intravenous hypotonic fluid administration to maintain volume status.

For patients with lesser degrees of lithium toxicity, this therapy will be adequate to treat the condition. For patients with greater degrees of lithium toxicity, generally with lithium levels of greater than 4 mEq/L, dialysis is indicated.

The chronic lithium nephrotoxicity picture is dominated by polyuria and evidence of chronic kidney disease. Polyuria can be treated with medications, such as diuretics and nonsteroidal anti-inflammatory drugs (NSAIDs).

The potassium-sparing diuretic amiloride is the most established therapy for the polyuria associated with lithium use. Amiloride is thought to block lithium uptake into the principal cells of the cortical collecting tubule through epithelial channels (ENaC), allowing the principal cells to regain responsiveness to antidiuretic hormone.

In an animal model of lithium-induced nephrogenic diabetes insipidus, acetazolamide reduced polyuria as effectively as hydrochlorothiazide plus amiloride.

Case reports describe successful use of acetazolamide in patients with lithium-induced nephrogenic diabetes insipidus that had failed to respond to treatment with standard agents. In contrast, a study by de Groot et al in six patients with a lithium-induced urinary concentrating defect found evidence against the use of acetazolamide treatment. Two patients withdrew from the study because of adverse effects, and the remaining four showed no change in urine output or clinically relevant changes in maximal urine osmolality. Three of the four patients experienced an increase in serum creatinine levels, indicating a decreased glomerular filtration rate (GFR). The **authors postulate that the reduction in polyuria in animal studies is the result of the decrease in GFR.**

The **chronic kidney insufficiency can be treated using therapy that would routinely be used for any cause of chronic kidney disease.**

Evidence of chronic kidney disease is an indication for discontinuation of the drug being administered and for consideration of alternative medications for treatment of the patient's psychiatric disorder.

- **Diuretics**
- **Class Summary**

Decrease extracellular fluid and promote proximal tubular resorption that is not ADH dependent. Ultimately**, less free water is transmitted to distal collecting tubules, which is where the urine-concentrating defect is located; therefore, the polyuria decreases**. However,extracellular fluid depletion can also **increase the risk of lithium intoxication** by **enhancing lithium reabsorption at the proximal tubule**.

Diuretics have **a gradual onset of action** and **are less useful in an acute setting**.

- **Amiloride**
  Prevents uptake of lithium by epithelial cells. Has **less potential for lithium toxicity** because has a **weak natriuretic effect** and **is less likely to increase lithium level by causing volume contraction**. Has the **advantage** of being **potassium-sparing; hypokalemia itself may potentiate**

a defect in concentrating ability. Also induces **less extracellular fluid contraction** than thiazides**.**

- **Hydrochlorothiazide**
  Thiazides **may require potassium supplementation**; **more often associated with lithium toxicity.** **Inhibits reabsorption of sodium in distal tubules**, **causing increased excretion of sodium and water as well as potassium and hydrogen ions**. Equivalent dosages of other thiazide preparations may be used. **Use same dose range effective for treating hypertension.**

- **Nonsteroidal Anti-inflammatory Drugs**

- **Class Summary**

Have an **antiprostaglandin** effect in rats. Inhibiting prostaglandin **increases cAMP in the collecting tubules**, which **promotes water Resorption**. NSAIDs also inhibit the production of **prostaglandin that regulates glomerular blood flow** and therefore **decreases the GFR and urine flow to the distal tubules**. Physicians do **not recommend long-term NSAID therapy.**

- **Indomethacin (Indocin, Indochron ER)**

Rapidly absorbed; metabolism occurs in **liver** by demethylation, deacetylation, and glucuronide conjugation. Inhibits prostaglandin synthesis.
One case report exists of **IV ketorolac** used **in acutely ill patient failing to respond to indomethacin**.

- **Follow-up**
- **Further Outpatient Care**

Some reports recommend testing the patient's **renal-concentrating ability, 24-hour urinary volume, and creatinine clearance before** initiating lithium therapy and at **1-year** intervals.

Schou recommends regular measurements of **serum lithium and creatinine** every **2-6 months** .

Further Inpatient Care

Patients with **severe cases of volume depletion with associated electrolyte abnormalities (ie, hypernatremia**) may require **ICU** care.

Once aggressive diuresis is initiated or dialysis is performed for acute toxicity, lithium levels should be sequentially checked to ensure that rebound toxic levels and/or delayed gastrointestinal absorption leading to recurrent toxicity do not occur.

- **Prevention**

A systematic review by Schoot et al found very limited evidence on prevention of lithium-induced nephrogenic diabetes insipidus and lithium nephropathy, but recommended using a once-daily dosing schedule and targeting the lowest serum lithium level that is effective.

Lithium has a low therapeutic index; monitor levels closely to prevent acute lithium intoxication and identify diabetes insipidus nephropathy promptly, because early diagnosis and treatment can prevent further progression and permanent damage.

6 ways to protect the kidneys while prescribing lithium :

1. Avoid toxicity

The link between lithium and renal dysfunction may be explained by exposure to toxic lithium levels. Toxic levels **kill renal cells**, and that damage builds up every time the level rises above the toxic line.

This theory is confirmed by a handful of studies, which have found **that lithium does not seem to harm the kidneys when kept below 0.8 mmol/L but renal impairments rise with the number of toxic exposures.** This is welcome news if proven true, because **the recommended level for lithium maintenance** is **0.6-0.8** mmol/L. **Higher levels (up to 1.2 mmol/L) are usually only necessary for acute mania.**

2. Keep the level low

Keeping the **lithium level as low as possible** can prevent renal impairment.

The ideal level needs to be **personalized and tends to fall with age**.

For patients **over 60**, the recommended level is **0.4-0.6 mmol/L**, compared with **0.6-0.8 mmol/L for younger adults**. The **brain is more porous in later life**, allowing **more lithium to enter the CNS even when the serum level is relatively low**.

- **3.Dose lithium once a day**

Dosing lithium **once in the evening reduces the risk of renal problems**. It also makes pharmacologic sense: Lithium's **half-life is 18 to 24 hours**. There is **no specific cap on the number of milligrams that can be given in a single dose**, because **lithium's risks depend on the serum level rather than the milligrams**.

If high serum levels are needed to treat active mania, dosing twice a day may be necessary to avoid toxic peaks.

The line of toxicity is different for each patient because it's defined by symptoms. Older patients may experience toxicity at a 0.8 level, while younger adults may show no signs of toxicity-or even adverse effects-at 1.2 mmol/L.

- **4. Drinking and urinating too much**

- **Polyuria and polydipsia** are common adverse effects of lithium (**30% to 80%**), and they **are not always benign**. When severe, they may indicate nephrogenic diabetes insipidus (NDI), which means that changes in the renal tubules are impeding the kidneys ability to concentrate the urine. Those changes **raise the risk of future renal impairments.**
- **Besides stopping lithium, the main treatment for NDI is amiloride**, a potassium sparing diuretic (**5 mg po qd**). Amiloride may **prevent further renal problems** by **reducing fibrotic changes in the kidneys**. This medication is best managed through **consultation with the medical team** because it carries a risk of **hyperkalemia, particularly in patients with renal insufficiency or diabetes**.
- NDI is diagnosed by testing **urine osmolality, urine sodium, serum sodium, serum creatinine, and a 24-hour urine for volume.**

- **5-Consider N-Acetylcysteine**
- N-Acetylcysteine (**NAC)** is an antioxidant that can **protect and even reverse renal toxicity, including toxicity from lithium.**
  NAC is part of a healthy diet, and the capsule form is safe, well-tolerated (the main risk is constipation), and inexpensive. However, there is another reason to use NAC in bipolar disorder. This supplement is **effective for bipolar depression** in some, but not all, studies, and those benefits are more pronounced in the medically ill.
  The dose **in bipolar disorder** (**2000 mg/day**) is about **twice the amount that was used for renal protection (10 mg/kg).**
- **6- Measure**
- **Renal function** should be monitored every **3 to 6 months** on lithium.
  Older patients **benefit from more frequent monitoring**, as do those with **a history of toxicity, high serum levels, or drug interactions. Creatinine is usually sufficient**, but a more accurate measure of renal function is the estimated glomerular filtration rate (**eGFR**), which can be easily calculated from the creatinine (you will also need the height and weight to adjust for "body surface area").

- **Prognosis**

Patients with urine-concentrating defects from lithium treatment usually take weeks to months to recover following discontinuation of lithium.

In rare situations, the problem can persist for years.

Acute kidney injury associated with lithium toxicity has an excellent prognosis.

Chronic kidney disease associated with lithium use only uncommonly will completely resolve but generally will not progress if the medication is discontinued and other nephrotoxic agents, such as nonsteroidal anti-inflammatory drugs, or hypertension are minimized.

- **Nephrotic Syndrome**

lithiumhas **infrequently** been associated with the nephrotic syndrome. **Most cases are due to minimal change disease**, but focal segmental glomerulosclerosis **(FSGS) has also been described**.

The pathophysiology of glomerular lesions involves **direct epithelial and podocyte injury** leading to features suggestive of nephrotic syndrome. Proteinuria generally begins within **1.5 to 10 months after the onset of therapy** and, in **minimal change disease, completely or partially resolves in most patients one to four weeks after lithium is discontinued .**

In several patients**, reinstitution of lithium led to recurrent nephrosis**. **Corticosteroids have occasionally been required to induce remission**; it is possible that the minimal change disease in such cases was unrelated to lithium.

- **The relationship to FSGS is less clear**. In three patients, for example, cessation of lithium did not lead to resolution of the disease, suggesting either **no relation to lithium or possible secondary FSGS due to tubular injury induced by chronic lithium therapy**. However, it is **unclear how the discontinuation of lithium therapy impacts the clinical course of glomerular disease**.

- **RENAL TUBULAR ACIDOSIS**

The **tubular defect in the distal nephron can also impair the ability to maximally acidify the urine**. This is most often manifested as the **incomplete form of type 1 (distal) renal tubular acidosis**, in which the **urine pH is persistently above 5.3 but the extracellular pH and bicarbonate concentration are within the normal range .**

- **Hyperparathyroidism and Hyypercalcemia** Another complication of **long-term therapy** with lithium carbonate is hyperparathyroidism, with associated **hypercalcemia** and **hypocalciuria**.

There are several mechanisms by which lithium may increase serum calcium levels:

- **Increasing the threshold for the calcium-sensing mechanism** within the parathyroid gland .Thus, parathyroid hormone **(PTH) secretion continues despite the presence of hypercalcemia.**
- Inducing **PTH overproduction via inhibiting the action of glycogen synthase kinase 3b (GSK-3b).**
- **Inhibiting calcium transport (influx)** across cell membranes.

As hypercalcemia develops, **it is further confounded by kidney failure and its progression, which leads to decreased urinary calcium excretion (hypocalciuria**). Other findings associated with lithium induced hypercalcemia-hyperparathyroidism include a **normal serum phosphorus level and an elevated serum magnesium level.**

There is a higher proportion of patients (33 percent) who develop parathyroid hyperplasia in those with lithium-induced hyperparathyroidism compared with the proportion of hyperparathyroidism affecting the general population. This is probably **the reason why acute withdrawal of lithium does not necessarily translate into any significant change in serum calcium levels**. Because simple discontinuation of lithium carbonate therapy does not always lead to normalization of serum-intact PTH and calcium levels, **surgical parathyroidectomy has been a common option in those patients.**

Case reports have been published in which the use of **cinacalcet** ,a calcimimetic, **decreased or normalized the serum calcium, with some reduction of serum-intact PTH levels**, similar to its effect in patients with primary hyperparathyroidism, thereby **averting the need for surgical treatment**. It is believed that **cinacalcet can neutralize the effects of lithium on the calcium-sensing receptor of the parathyroid gland**. However, the mechanisms that underlie this effect remain undefined.