

# LITHIUM NEPHROTOXICITY

JOBSON LOPES DE OLIVEIRA<sup>1</sup>, GERALDO BEZERRA DA SILVA JÚNIOR<sup>2</sup>, KRASNALHIA LÍVIA SOARES DE ABREU<sup>1</sup>, NATÁLIA DE ALBUQUERQUE ROCHA<sup>1</sup>, LUIZ FERNANDO LEONAVICIUS G. FRANCO<sup>1</sup>, SÔNIA MARIA HOLANDA ALMEIDA ARAÚJO<sup>3</sup>, ELIZABETH DE FRANCESCO DAHER<sup>4\*</sup>

Study conducted at the Department of Clinical Medicine, School of Medicine, Universidade Federal do Ceará, Fortaleza, Ceará, Brazil

## \*Correspondence:

Rua Vicente Linhares,  
1198  
Fortaleza - CE, Brazil  
CEP: 60135-270  
Phone: (85) 3224-9725  
ef.daher@uol.com.br

Lithium has been widely used in the treatment of bipolar disorder. Its renal toxicity includes impaired urinary concentrating ability and natriuresis, renal tubular acidosis, tubulointerstitial nephritis progressing to chronic kidney disease and hypercalcemia. The most common adverse effect is nephrogenic diabetes insipidus, which affects 20-40% of patients within weeks of lithium initiation. Chronic nephropathy correlates with duration of lithium therapy. Early detection of renal dysfunction should be achieved by rigorous monitoring of patients and close collaboration between psychiatrists and nephrologists. Recent experimental and clinical studies begin to clarify the mechanisms by which lithium induces changes in renal function. The aim of this study was to review the pathogenesis, clinical presentation, histopathological aspects and treatment of lithium-induced nephrotoxicity.

KEY WORDS: Lithium. Toxicity. Kidney failure. Nephritis, Interstitial.

## INTRODUCTION

Lithium has been used therapeutically for almost 150 years. In the nineteenth century, Garrod and Hammond advocated the use of lithium salts for the treatment of gout and uric acid nephrolithiasis. Almost a century later, Cade, after observing the calming effect of lithium on guinea pigs, reported highly successful results in 10 manic patients who received the drug in 1949<sup>1</sup>. However, in that same year, the Food and Drug Administration (FDA) withdrew the drug from the U.S. market following the death of several patients due to lithium intoxication. Those patients, with heart failure or hypertension, received lithium chloride salts as a substitute for table salt. Therefore, studies on the effects of lithium as a mood stabilizer progressed slowly and only in 1970 the FDA approved its use in the treatment of mania<sup>1</sup>.

Lithium is now the drug of choice for the treatment of bipolar disorder, preventing recurrence and suicide attempts. Its use has successfully caused a dramatic decrease in manic and depressive symptoms in 70 to 80% of patients<sup>2</sup>. However, despite such great success, lithium has a narrow therapeutic index, with therapeutic serum levels between 0.6 and 1.5 mEq/L<sup>3,4</sup>. In the initial phase of treatment, excessive thirst, nausea, diarrhea, epigastric pain, muscle weakness and fatigue are symptoms that cause great discomfort to patients, often leading to low adherence to medication<sup>3</sup>. The most common neurologic symptom is tremor, affecting

25-50% of users. Lithium can also often cause flattening or inversion of T waves on electrocardiogram (ECG), but clinically important cardiovascular effects are rare, except in cases of intoxication<sup>1</sup>. Symptoms of toxicity generally correlate with serum lithium concentration in acute intoxication, but may vary in patients on chronic lithium therapy<sup>5</sup>, leading to the need for hemodialysis at severe levels<sup>1</sup>. Risk factors for the development of lithium intoxication include advanced age, overdose, renal failure, drugs that affect renal function (nonsteroidal anti-inflammatory drugs [NSAIDs], angiotensin-converting enzyme [ACE] inhibitors, thiazide diuretics), decreased circulating blood volume (cirrhosis, congestive heart failure, nephrotic syndrome), decreased dietary sodium intake, diabetes mellitus, and diabetes insipidus induced by chronic lithium therapy<sup>4</sup>.

Lithium-induced nephrotoxicity is a complication known since lithium was introduced in the treatment of mood disorders<sup>6-8</sup>. Renal complications include impairment of tubular function (particularly the development of nephrogenic diabetes insipidus and renal tubular acidosis) and progressive chronic kidney disease (secondary to lithium-induced chronic tubulointerstitial nephritis)<sup>7</sup>. Hyperparathyroidism and hypercalcemia are also adverse effects of chronic lithium therapy. This review aimed to discuss clinical and laboratory alterations, pathophysiology and treatment of lithium-induced nephrotoxicity.

1. Graduação em Medicina - Alunos da Universidade Federal do Ceará, Fortaleza, CE

2. Graduação em Medicina - Especialista em nefrologia. Mestrando em Ciências Médicas pela Universidade Federal do Ceará, Fortaleza, CE

3. Mestrado em Clínica Médica - Doutoranda em Ciências Médicas pela Universidade Federal do Ceará, Fortaleza, CE

4. Doutorado em Nefrologia - Professora da Universidade Federal do Ceará, Fortaleza, CE

### Pharmacological aspects of lithium

Lithium is a monovalent cation, with molecular weight of 7 daltons, of the family of alkali metals, the same of sodium and potassium. Typically, its concentration in body fluids is not significant ( $< 0.2$  mEq/L). When administered orally, either as lithium citrate (liquid) or carbonate (capsule), lithium is completely absorbed in the upper gastrointestinal tract in about eight hours. Peak plasma levels occur one to two hours after oral administration of standard preparations and about four hours after administration of sustained-release preparations, in which these levels can continue to rise for three to four days in case of acute poisoning<sup>4,5</sup>.

Binding of lithium to serum proteins is less than 10%, being distributed in total body water with a volume of distribution of 0.7 to 0.9 L/kg. Tissue distribution of lithium occurs with preferential uptake in certain tissues. For example, significant delays are observed in reaching steady state concentrations in the brain compared to plasma concentrations.

Half-life of lithium within plasma varies considerably from patient to patient. In individuals with a normal glomerular filtration rate (GFR), lithium has an elimination half-life of 12 to 27 hours after a single dose. In elderly individuals and patients on chronic lithium therapy, its elimination half-life can increase considerably to approximately 60 hours<sup>9</sup>.

Lithium is excreted almost entirely by the kidneys and is freely filtered by the glomeruli. Fractional excretion of lithium is 20%, and 60% of the filtered lithium is reabsorbed in the proximal tubule and 20% in the loop of Henle and the collecting duct<sup>9</sup>. In the proximal tubule, lithium is reabsorbed similarly to sodium. Thus, states in which the need for sodium is increased (such as polyuria, diarrhea, congestive heart failure, cirrhosis, and use of NSAIDs) lead to an increase in the fraction of lithium reabsorbed, resulting in elevated serum levels of this cation<sup>4</sup>. Even at therapeutic levels, lithium itself may facilitate retention of the drug by inducing polyuria and volume depletion<sup>5</sup>.

Conversely, any insult that reduces proximal tubule sodium reabsorption, such as carbonic anhydrase inhibitors, aminophylline, and osmotic diuretics, will stimulate lithium renal excretion, leading to decreased plasma lithium concentration<sup>4</sup>.

Several proteins that normally transport sodium in the nephron can also transport lithium, such as the sodium-hydrogen cotransporter in the proximal tubule (NHE3), the Na-K-2Cl cotransporter in the thick ascending limb of the loop of Henle, and the epithelial sodium channel (ENaC) in the cortical collecting tubule. ENaC's permeability to lithium is 1.5-2-fold higher than its permeability to sodium<sup>7</sup>. In contrast, lithium affinity in the basolateral Na/K-ATPase pump is at least an order of magnitude less than that for sodium or potassium<sup>4</sup>. Table 1 summarizes the main pharmacological aspects of lithium.

### Lithium-induced tubular dysfunction

The most prevalent form of lithium-induced renal injury is impaired urinary concentrating ability<sup>10</sup>, which can be detected about eight weeks after lithium initiation<sup>11</sup>. In a study involving 1,172 patients on chronic lithium therapy, Boton et al.<sup>11</sup> found that impairment of urinary concentrating ability was present in at least 54% of 1,105 unselected individuals. Initially reversible after cessation of lithium, tubular dysfunction translates into overt and irreversible polyuria and polydipsia with continued treatment, affecting 20 to 40% of patients<sup>12</sup>. This is the typical clinical picture of nephrogenic diabetes insipidus, which is resistant to the action of arginine vasopressin (AVP)<sup>10</sup>.

### Physiology of urinary concentrating mechanism

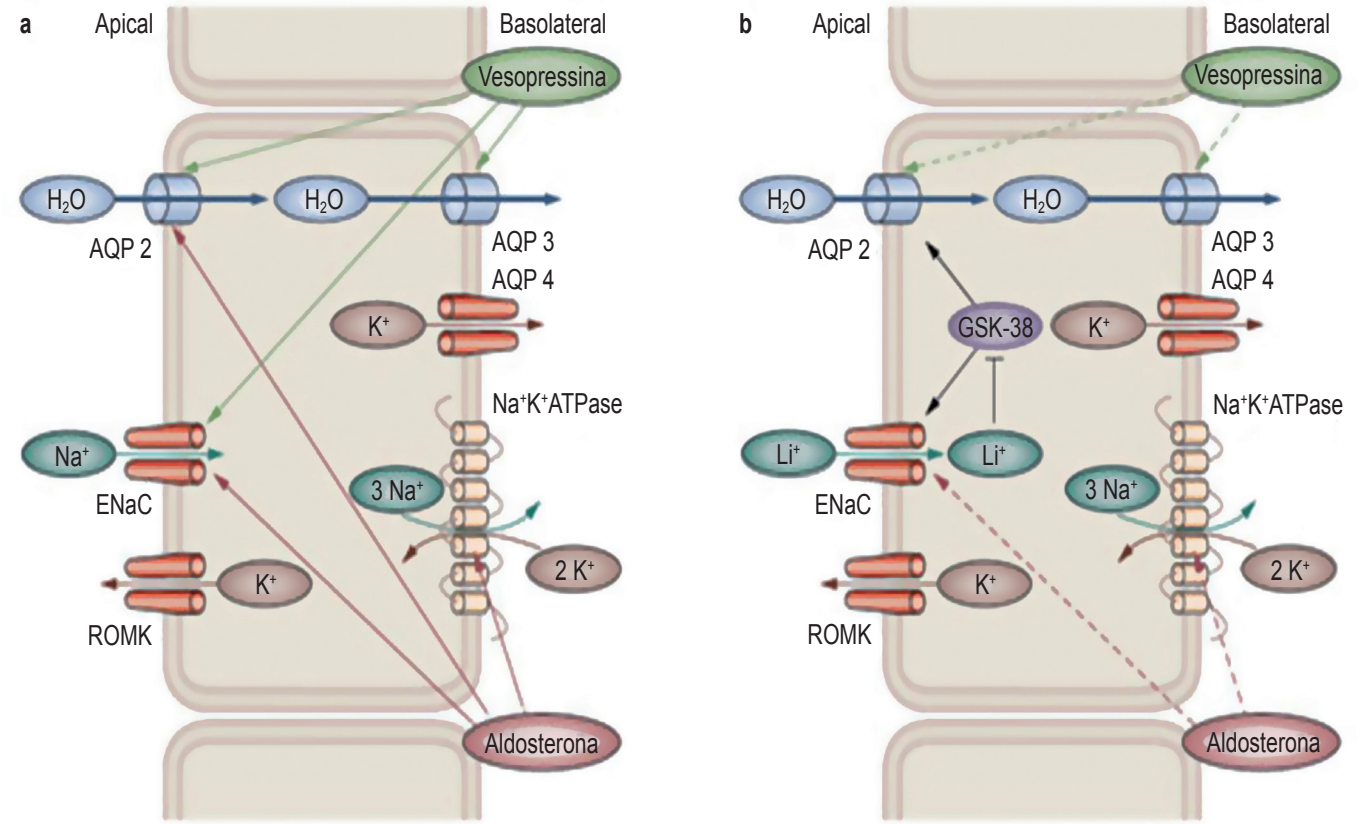
Two key processes are the basis of urinary concentrating ability in mammals. The first factor is the generation of a hypertonic medullary interstitium and the second is the insertion of water channels, the aquaporins, into the apical (AQP2) and basolateral (AQP3 and AQP4) membranes of the collecting duct, allowing tubular water reabsorption through a concentration gradient between the collecting duct lumen and the hyperosmotic medullary interstitium<sup>10,13,14</sup>. In response to increased serum osmolality, AVP is released from the posterior pituitary, binds to V2 receptors in the basolateral membrane of collecting duct cells and, through the activation of adenylyl cyclase, triggers a series of intracellular events that culminate in the insertion of AQP2 molecules in the apical membrane, which is facing the tubular lumen.

**Table 1 - Pharmacological aspects of lithium**

Molecular weight	7 daltons
Therapeutic plasma levels	0.6 - 1.5 mEq/L
Peak plasma level time	0.5 - 2 hours; up to 72 hours after overdose
Volume of distribution	0.7 - 0.9 L/kg
Bioavailability	95%
Plasma protein binding	10%
Elimination half-life	24 hours; up to 60 hours during chronic lithium therapy

Source: Timmer RT, Sands JM. Lithium Intoxication. *J Am Soc Nephrol* 1999; 10: 666-674.

**Figure 1 – Transport of water, sodium and potassium in the principal cell of the collecting duct under physiological conditions (a) and in the presence of lithium (b). For further explanation, see text. Source: Grünfeld JP, Rossier BC. Lithium nephrotoxicity revisited. *Nat Rev Nephrol* 2009; 5: 270-276**



This process results in increased water permeability in this segment of the nephron, providing an antidiuretic effect<sup>13</sup>.

In addition to regulating the final concentration of urine, the collecting duct is also important in regulating fluid and electrolyte balance. About 5% of filtered sodium is reabsorbed in this nephron segment. In collecting duct principal cells, sodium passively crosses the apical membrane through the amiloride-sensitive epithelial sodium channel (ENaC) along an electrochemical gradient maintained by the Na/K-ATPase pump of the basolateral membrane. Moreover, these cells also secrete potassium through a K channel of the apical membrane. The whole process is controlled by aldosterone, a mineralocorticoid hormone that mediates gene transcription of ENaC, basolateral Na/K-ATPase pump and apical K channel<sup>14</sup> (Figure 1).

**Pathogenesis of lithium-induced nephrogenic diabetes insipidus**

The molecular mechanisms underlying lithium-induced water diuresis and natriuresis are far from well established<sup>7</sup>. The postulated mechanisms include inhibition of adenylyl cyclase, decreased density of AVP receptors, and reduced

expression of AQP2<sup>6</sup>. However, Li et al.<sup>15</sup> showed that the development of lithium-induced nephrogenic diabetes insipidus is dissociated from adenylyl cyclase activity. A study of healthy volunteers who received lithium carbonate for four weeks showed a significant reduction in urinary AQP2 excretion and in desmopressin (dDAVP)-stimulated urinary concentrating ability<sup>16</sup>. In the rat kidney medulla, administration of lithium for 25 days induced a decrease in AQP2 expression<sup>17</sup>.

Filtered lithium enters collecting duct cells via ENaC, which has permeability to lithium 1.5-2-fold higher than to sodium. However, unlike sodium, lithium is not exported from the cell by the Na/K-ATPase, thus accumulating intracellularly. Lithium promotes the inhibition of glycogen synthase kinase 3 (GSK-3), an enzyme that controls the transport of water and sodium via AQP2 and ENaC, respectively. As a result of the effects of lithium, the cell becomes less responsive to the effects of aldosterone and AVP7 (Figure 1).

Another hypothesis to explain the development of nephrogenic diabetes insipidus arose from the observation that lithium can induce cyclooxygenase 2 (COX-2) expression in the kidney medulla via GSK-3 inhibition. Both COX-1 and COX-2 are expressed by the kidneys, and prostaglandins

synthesized by them have been suggested to play an important role in lithium-induced polyuria<sup>18</sup>.

#### Treatment of lithium-induced nephrogenic diabetes insipidus

Amiloride is the treatment of choice for lithium-induced nephrogenic diabetes insipidus. This drug not only blocks sodium entry via ENaC, but also inhibits lithium entry into collecting duct principal cells. Amiloride partially restores the urinary concentrating ability, and this is associated with increased urinary AQP2 excretion<sup>10</sup>.

#### Tubular acidosis resulting from the use of lithium

Another tubular dysfunction resulting from long-term lithium treatment is hyperchloremic metabolic acidosis. This condition is believed to result from decreased proton secretion in the collecting duct and/or excessive backdiffusion of acid equivalents<sup>7</sup>.

#### Lithium-induced nephropathy

Lithium-induced tubulointerstitial nephritis is characterized by the presence of cortical and medullary interstitial fibrosis and tubular atrophy<sup>19</sup>. In 1977, Hestbech et al.<sup>20</sup> demonstrated for the first time these changes on renal biopsy specimens from a small group of patients treated with lithium for 2-15 years. In the same study, cortical and medullary tubular cysts occurred in 62.5% of specimens, and tubular dilatation in 33%<sup>19</sup> (Figure 2). Studies using magnetic resonance (MRI) imaging, although not required for diagnosis, can also reveal the presence of renal microcysts in many patients<sup>21</sup>(Figure 3).

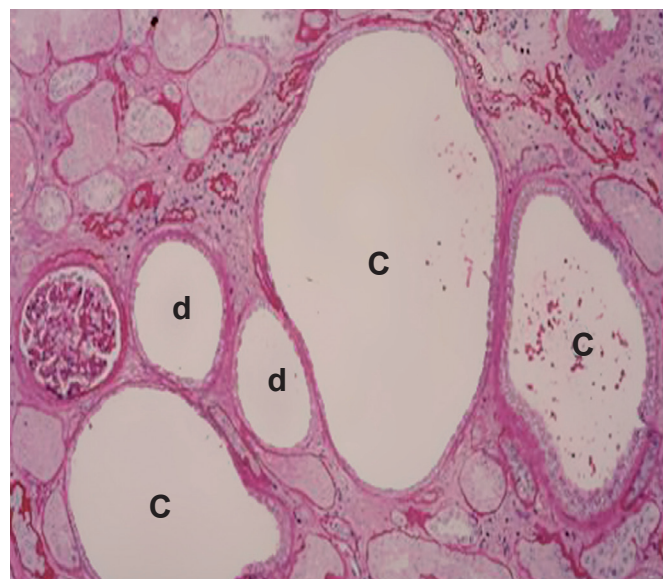
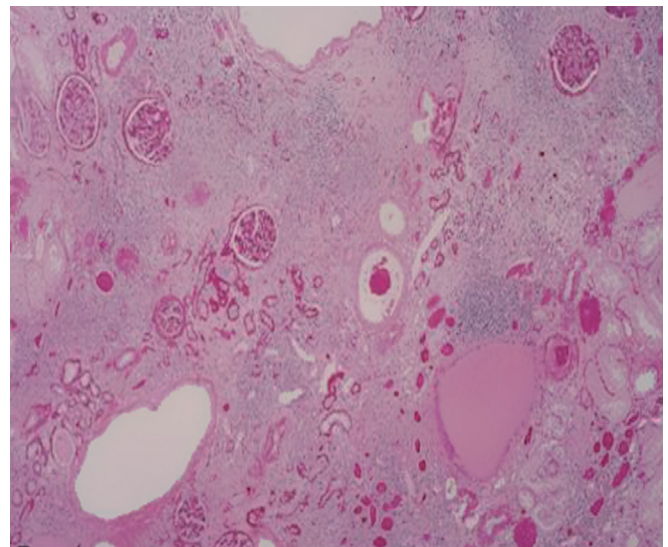
Data in the literature concerning glomerular involvement in lithium-induced nephrotoxicity are still scarce<sup>19</sup>. Proteinuria is not a common finding, being generally of low severity (< 1 g/day)<sup>22</sup>. The occurrence of nephrotic syndrome is rare, and only 26 cases have been reported to date<sup>19,22</sup>. Markowitz et al.<sup>19</sup>, in a study examining renal biopsies from 24 patients on long-term lithium treatment, found a surprisingly high prevalence of focal segmental glomerulosclerosis (50%) and global glomerulosclerosis (100%), sometimes of equivalent severity to the chronic tubulointerstitial damage. The mechanism of glomerular injury may be secondary to direct cellular toxicity of lithium, resulting in minimal change disease or secondary focal segmental glomerulosclerosis<sup>6</sup>. In minimal change disease, some patients recover after lithium withdrawal, suggesting a strong etiologic relationship<sup>23</sup>.

#### Risk factors for lithium-induced nephropathy

The main risk factor for the progression of lithium-induced nephropathy is the duration of drug administration<sup>24</sup>. Once-daily regimens seem to be less deleterious than multiple daily dosing regimens, perhaps because of the possibility of renal tubular regeneration in those receiving a single daily dose. On the other hand, patients who switched from one regimen to another did not show significant changes in tubular function, except when the switch occurred before five

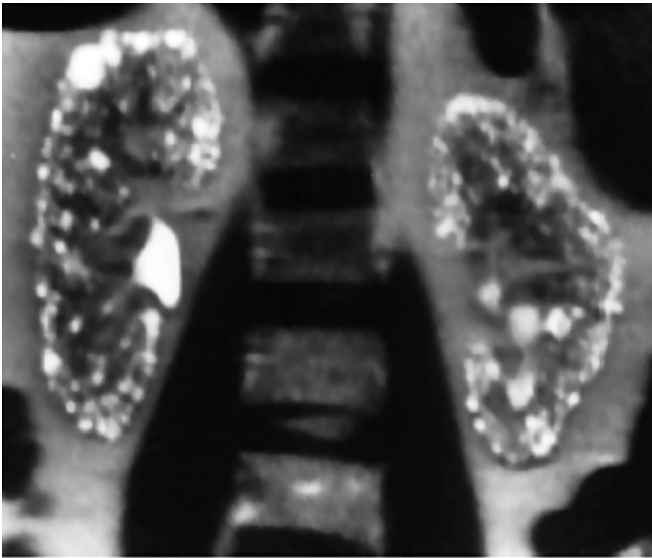
years of treatment<sup>25</sup>. Other risk factors for the progression of renal injury include current lithium therapy, concomitant use of nephrotoxic drugs, advanced age, episodes of lithium intoxication, and presence of comorbidities such as hypertension, diabetes mellitus, hyperparathyroidism, and hyperuricemia<sup>8,26-28</sup>.

**Figure 2 – Left: Severe tubulointerstitial nephropathy with the additional finding of focal tubular cysts arising in a background of severe interstitial fibrosis and tubular atrophy. PAS stain, x40. Right: High-power view (x100) of tubular cysts (c) lined by simple cuboidal epithelium, along with adjacent tubules with dilatation (d). Source: Markowitz GS, et al. Lithium nephrotoxicity: a progressive combined glomerular and tubulointerstitial nephropathy. J Am Soc Nephrol 2000; 11: 1439-1448**





**Figure 3 – Magnetic resonance image in a 68-year-old patient shows abundant microcysts in the cortical and medullary regions of both kidneys. Source: Farres MT, et al. Chronic lithium nephropathy: MR imaging for diagnosis. Radiology 2003; 229: 570-574**



#### **Pathogenesis of lithium-induced nephropathy**

The pathogenic mechanisms by which lithium causes tubulointerstitial nephritis and glomerular injury are not well understood<sup>7</sup>. Lithium plays a role as a modulator of the pathway for inositol monophosphate, which results in decreased inositol levels and inhibition of cell cycle<sup>29</sup>. Thus, accumulation of lithium in cells of the distal nephron via ENaC could account for chronic tubulointerstitial damage<sup>7</sup>. Tam et al.<sup>23</sup> proposed that the modulation of the phosphoinositol pathway may also play a role in the pathogenesis of minimal change disease after lithium treatment.

#### **Lithium-induced nephropathy and chronic kidney disease (CKD)**

The relationship between lithium and the onset of progressive chronic kidney disease (CKD) was a controversial topic in the past. Johnson<sup>26</sup> suggests that lithium-induced chronic renal failure is very unusual. A study comparing 107 patients on lithium therapy with psychiatric control patients showed no relationship between creatinine clearance and duration of lithium treatment and lithium dosages<sup>30</sup>.

The risk of developing CKD in patients on long-term lithium treatment has now been well established by several clinical, histopathological and epidemiological studies<sup>7,19,24</sup>. A French study of 54 patients with lithium-induced nephropathy demonstrated a mean annual loss of creatinine clearance of 2.29 mL/min<sup>24</sup>. In that country, the prevalence of lithium-related chronic end-stage renal disease (ESRD)

is estimated as 2 per 1000 dialysis patients, accounting for 0.22% of all ESRD cases<sup>24</sup>. The progression of lithium-induced CKD is slow, requiring a period of 10 to 20 years to progress to end-stage renal failure<sup>7,24</sup>. This may explain why the association between CKD and lithium use was not well accepted in the past.

#### **Treatment of lithium-induced nephropathy**

Close monitoring of renal function of patients on lithium treatment is crucial for early detection of lithium-induced nephropathy<sup>6</sup>. Serum creatinine levels should be measured every two months during the first six months of lithium therapy and every year thereafter<sup>27</sup>.

Cases in which impaired renal function is detected raise a dilemma<sup>7</sup>. Continuous lithium treatment is known to reduce the risk of suicide among patients with bipolar disorder<sup>31</sup>. Moreover, the risk of early recurrence of bipolar disorder appears to increase following discontinuation of lithium<sup>32</sup>. Some patients, whose illness has been well controlled with lithium, refuse to switch or discontinue therapy. Thus, the decision to substitute lithium with another mood stabilizer should involve the patient, the psychiatrist and the nephrologist<sup>7,24</sup>.

The probability of recovery of renal function after lithium withdrawal increases when estimated creatinine clearance is greater than 40 mL/min<sup>24</sup> and when serum creatinine levels are less than 220  $\mu$ mol/L<sup>19</sup>. A point at which the discontinuation of lithium no longer alters the course of renal disease probably exists, that is, the process of renal fibrosis continues to progress despite removal of the triggering agent<sup>24</sup>.

In addition to renal function, other predictors of poor prognosis are the extent of interstitial fibrosis on renal biopsy and the presence of proteinuria<sup>7,24</sup>. This condition should be adequately managed to reduce the progression of CKD.

Whether amiloride can prevent the long-term effects of lithium nephropathy is not yet known. If such preventive action is identified, this finding might strongly suggest that lithium exerts a primary cytotoxic effect that is limited to the principal cells of the collecting duct and mediated by the entry of this cation through ENaCs<sup>7</sup>.

#### **Lithium-induced hypercalcemia and hyperparathyroidism**

An underrecognized side effect of lithium therapy is hyperparathyroidism with associated hypercalcemia and hypocalciuria<sup>33</sup>. The prevalence of hyperparathyroidism among chronic lithium users (> 10 years) is approximately 10-15%<sup>34</sup>. The prevalence of lithium-induced hypercalcemia is higher in patients with renal failure, in whom urinary excretion of calcium is reduced<sup>7</sup>. Nephrolithiasis and nephrocalcinosis may result from hypercalcemia in these patients<sup>7</sup>.

#### **Pathogenesis of lithium-induced hyperparathyroidism and hypercalcemia**

One mechanism proposed to explain lithium-induced hyperparathyroidism is based on changes in calcium-sensing

receptor sensitivity in the parathyroid gland, causing a decrease in the set point for secretion of parathyroid hormone (PTH)<sup>33,35</sup>. If not corrected, persistent hyperparathyroidism and resultant hypercalcemia may exacerbate psychiatric manifestations and lead to deleterious effects on bone mineral metabolism, urinary excretion and blood vessels<sup>33</sup>.

### Treatment of lithium-induced hyperparathyroidism and hypercalcemia

The treatment of hypercalcemia in chronic lithium users may be clinical or surgical. Ablation of a single parathyroid adenoma usually leads to normocalcemia, even in patients who continue to receive lithium<sup>34</sup>. Some authors do not recommend parathyroidectomy for the treatment of hypercalcemia in these cases<sup>35</sup>, due to risks and technical difficulties in cases of multiglandular disease (50% of cases)<sup>7,33</sup>. Recently, cinacalcet, a calcimimetic drug, has been used for clinical treatment of hyperparathyroidism secondary to lithium. This drug enhances calcium-sensitive receptor sensitivity in the principal cells of the parathyroid gland, reducing the threshold for activation of these receptors to extracellular calcium. As a result, PTH secretion decreases, with consequent reduction in serum calcium levels<sup>33,35</sup>. Serum calcium concentration should be measured every one to two years to detect hypercalcemia<sup>7</sup>.

### CONCLUSION

For over half a century, lithium has been the most widely used drug in the treatment of bipolar disorder. Lithium nephrotoxicity may present in different ways, from early alterations, such as nephrogenic diabetes insipidus and metabolic acidosis, to lesions secondary to chronic lithium therapy, such as hypercalcemia, tubulointerstitial nephropathy, and CKD. Blockade of the ENaC, such as by using amiloride, in the treatment of nephrogenic diabetes insipidus, is based on the observation of the key role played by these channels in the pathogenesis of this disease. Monitoring of serum creatinine and calcium levels in patients on lithium treatment is mandatory for early detection of CKD and hypercalcemia. The decision to discontinue lithium therapy raises a dilemma, and should therefore be made jointly by the psychiatrist, the nephrologist and the patient. Paradoxically, lithium therapy is so effective in treating bipolar disorder that some patients are lost to follow-up, regular biochemical monitoring is not performed and, therefore, the discovery of renal failure is delayed.

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