

Influence of hypothyroidism on renal function of lithium-treated patients

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Dear editor

Several studies have shown that lithium maintenance treatment for bipolar disorder (BD) is associated with chronic kidney disease (CKD).^{1–3} Three recent and large controlled studies concluded that lithium treatment, within recommended serum levels, may increase the risk of induced end-stage renal disease by twofold^{1,2} or, alternatively, CKD is associated with BD independent of drug treatment.³ Moreover, review of the safety data on lithium shows a 0–5 mL/min reduction in glomerular filtration rate and a clear reduction in urinary concentrating capacity, during an observation period of 1 year.⁴

However in any case, it should not be excluded the possibility that these associations were a result of bias. In this sense, because the risk of developing thyroid disorders, which is probably the main safety concern of lithium treatment, we would like to highlight the prevalence of hypothyroidism among BD patients as an important possible confounding variable for the associations between lithium treatment and CKD.

Indeed, we know that lithium produces thyroid dysfunction (eg, raised thyroid-stimulating hormone and decreased free thyroxine, among other alterations)^{4,5} in a high proportion of patients. We also know that there is a close relationship between thyroid and renal function, with hypothyroid patients displaying elevated serum creatinine levels, characterized by slower and incomplete recovery after prolonged periods of severe hypothyroidism, and reductions in glomerular filtration rate.⁶ These are the main thyroid-related alterations in renal function.

In summary, lithium produces renal dysfunction, which manifests diabetes insipidus and reduction of urine-concentrating ability as the most common renal complications of lithium-derived therapy. Diabetes insipidus, initially reversible upon lithium withdrawal, may become irreversible as a result of structural damage over time.⁴

Moreover, findings from some authors support a link between mood disorders and thyroid dysfunction, such as higher thyrotropin-releasing hormone stimulated thyroid-stimulating hormone levels observed in naïve BD-II patients, as a differential biological feature,⁷ among others.^{8–10}

Finally, to continue the above described relationships between thyroid function, renal function and lithium, it is necessary to point out that overt and/or subclinical hypothyroidism and/or diabetes insipidus, two of the most important lithium-induced secondary effects, can be managed entirely by dose reduction, although combination therapy or lithium-substitution could be necessary in some cases.²

In the context of there being a close relationship between BD and thyroid-alterations, between renal and thyroid function, and between lithium treatment and hypothyroidism,

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Table 1 Demographic, therapeutic, and clinical characteristics of the Actur Sur cohort of patients affected by mood disorders

Anthropometrics (n=53)	
Male, n (%), patients	28 (52)
Age, year (mean ± SD)	54±15
Height, cm (mean ± SD)	166±9
Weight, kg (mean ± SD)	79±14
Diagnoses (DSM-IV), n (%)	
Bipolar disorder	28 (53)
Schizoaffective disorder	14 (27)
Unspecified mood disorder	11 (20)
Other psychiatric drug (in combination with lithium), n (%)	
Antidepressants	7 (14)
Antipsychotics	38 (71)
Benzodiazepines	23 (43)
Mood stabilizers	10 (18)
Lithium treatment	
Dose, mg Li (mean ± SD)	182±60
Creatinine clearance, mL/min (mean ± SD)	86±26
Lithium clearance, mL/min (mean ± SD)	1.3±0.4
Serum level, mEq/L (mean ± SD)	0.7±0.2
Follow-up period, years (mean ± SD)	23±7
Results, n (%) [two-proportion Z-test] patients	
Lithium cessation due to subclinical hypothyroidism	10 (19) [Z=5.1] [#] ; P<0.001] [*]
Lithium cessation due to eGFR <40 mL/min/1.73 m ²	5 (9)
Thyroxin-treated patients (on lithium + lithium cessation)	18 (34)

Notes: * vs data of subclinical hypothyroidism from Hollowell et al.¹³ #95% CI (asymptotic) 0.0888–0.2012 of difference.

Abbreviations: CI, confidence interval; SD, standard deviation; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition; eGFR, estimated glomerular filtration rate.

we would like to raise the need to further consider the status of thyroid function in order to avoid bias when describing the effects of lithium treatment on renal function.

In fact, alterations in renal function and mood dysfunction could be related to the status of the thyroid function, particularly subclinical and/or overt hypothyroidism, and result in variability of lithium-therapy regimens (eg, cessation of treatment, changes in dosage, or combination therapy). Therapeutic variability, which we observed using data obtained from a post hoc analysis of Actur–Sur cohort, including all psychiatric outpatients referred to our Actur Sur mental health unit in Zaragoza, Spain (Table 1). The results showed that the changes in the treatment of lithium, aforementioned, are present in a high percentage of patients affected by mood disorders, including BD and schizoaffective disorder.

Thus, taking into account the changes that lithium produces on the thyroid gland, and its relation to mood disorders (eg, BD, schizoaffective disorder), it is evident that to give

maximum validity to any current clinical study concerning renal toxicity of lithium, the following should be considered: initial and final thyroid status of patients, use of equi-effective doses of lithium to reach a target range of 1.0–1.1 mEq/L for free thyroxin levels, and stratification of patients according to thyroid activity.^{11,12} In this manner, we would avoid any bias, due to the thyroid gland status present in BD patients (with or without lithium treatment).

In conclusion, there are methodological hurdles still to be overcome in the standardization of clinical study design in renal toxicity of lithium therapy, with thyroid abnormalities being one of the principal areas of variability, documented among patients with BD.

Disclosure

The author reports no conflicts of interest in this communication.

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