Renal failure occurs in chronic lithium treatment but is uncommon

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We sought to establish the prevalence of lithium-induced end-stage renal disease in two regions of Sweden with 2.7 million inhabitants corresponding to about 30% of the Swedish population. Eighteen patients with lithium-induced end-stage renal disease were identified among the 3369 patients in the general lithium-treated population, representing a sixfold increase in prevalence compared with the general population for renal replacement therapy. All lithium-treated patients were older than 46 years at end-stage renal disease with a mean lithium treatment time of 23 years with ten patients having discontinued lithium treatment an average of 10 years before the start of renal replacement therapy. The prevalence of chronic kidney disease (defined as plasma creatinine over 150 μmol/l) in the general lithium-treated population was about 1.2% (excluding patients on renal replacement therapy). Compared with lithium-treated patients without renal failure, those with chronic kidney disease were older and most were men but, as groups, their mean serum lithium levels and psychiatric diagnoses did not differ. We found that end-stage renal disease is an uncommon but not rare consequence of long-term lithium treatment and is more prevalent than previously thought. Time on lithium was the only identified risk factor in this study, suggesting that regular monitoring of renal function in these patients is mandatory.

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The toxicity of lithium and its diuretic action were well known to the early investigators of its beneficial effects in affective disorders.[1,2] Early lithium studies concluded that lithium-induced polyuria was reversible.[2] In 1977, the risk of irreversible lithium-induced kidney damage became an international concern, thanks to a landmark Danish kidney biopsy study[3] whose findings were confirmed by Aurell *et al.* 1981.[4] The concept of lithium nephropathy was defined in the same year[5] and includes structural tubular damage with interstitial fibrosis in the presence of no or minor glomerular damage. With this definition severe glomerular insufficiency or even end-stage renal disease (ESRD) was considered an unlikely event. Until 2000, only three cases of lithium-induced ESRD were known in the world literature.[6–8]

However, the main result of studies by Bendz *et al.*[9–11] during the 1980s was a high prevalence of apparently irreversible tubular and glomerular damage in patients who had been treated with lithium for 15 years or more ('long-term treatment'). In addition, they showed that the damage was progressive. Therefore, it is to be expected that some lithium-treated patients will reach ESRD after long-time treatment. Accordingly, two recent reports from the United States and France added further cases of lithium-induced ESRD and reported a 2–7‰ prevalence of this serious adverse effect of lithium treatment in ESRD populations.[12,13] Moreover, in addition to the tubular and interstitial changes, glomerular changes compatible with focal glomerular sclerosis were not infrequently seen in renal biopsies from patients with clinical lithium nephropathy. These patients also had increased protein excretion in the urine, sometimes even in the nephrotic range raising the suspicion of a 'direct glomerular' (that is, podocyte) toxicity of lithium.[12]

Nevertheless, the prevailing belief among psychiatrists today seems to be that lithium-induced uremia is practically nonexistent. In a recent publication—primarily intended for patients and their relatives—by one of the world's most prominent and influential lithium researchers, the problem is not even mentioned.[14]

Thus, the prevalence of lithium-induced uremia remained to be assessed in an epidemiological study of patients on renal replacement therapy (RRT). The Swedish Registry for Active Treatment of Uremia (SRAU)[15] offered a possibility to do this. In addition, information on the prevalence of

chronic kidney disease (CKD) among lithium-treated patients can provide an indication of the number of potential future candidates for RRT.

The aims of this study were to investigate the following:

1. The prevalence of patients with lithium-induced ESRD among all RRT patients in two defined regions in Sweden.
2. The prevalence of lithium-induced ESRD among all lithium-treated patients in these regions.
3. The prevalence of CKD (defined as plasma creatinine $>150\,\mu mol/l$) among all lithium-treated patients in the two regions.

RESULTS

Patients with lithium-induced ESRD treated with RRT in the two regions

Twenty-seven RRT patients declared previous or present lithium treatment, four of them erroneously. Another three lithium-treated patients had ESRD not caused by lithium, and two lithium-treated patients had started RRT after the prevalence date. Thus, 18 patients were identified to have ESRD caused by lithium alone or as a main etiological factor. Individual data are presented in Table 1.

In eight patients, lithium treatment began during the second half of the 1960s, in nine patients during the first half of the 1970s, and in one it began in 1980. Although regular monitoring of plasma creatinine levels did not become part of lithium safety routines until the end of the 1970s, we were in most cases able to trace the slow increase of plasma creatinine from normal to ESRD.

The male/female proportion among the lithium-RRT patients (39/61%) did not differ from that in the general lithium-treated population (41/59%). The women were older than the men at start of lithium-treatment and at start of RRT.

All lithium-RRT patients had been treated with lithium for at least 12 years, 16 of them (89%) $\geqslant$15 years. In 10 patients, lithium treatment was discontinued 3–16 years before the start of RRT. The residual renal function at the time of discontinuation of lithium varied considerably. Two female patients developed ESRD, despite discontinuation at plasma creatinine levels below 100 μmol/l. Both patients had lower serum creatinine levels ($<65\,\mu mol/l$) at start of lithium treatment and there was a gradual increase of the serum creatinine levels during treatment.

There was only one patient with a history of clinically evident lithium intoxication. He suffered from confusion, disorientation, tremor, and muscular rigidity for several weeks during the third year of treatment. The lithium dose at the time of intoxication was 48 mmol/24 h, and two consecutive serum lithium concentrations within 1 month were 2.2 and 1.7 mmol/l.

The prevalence of long-term lithium treatment

We received information on treatment duration from 12 lithium clinics comprising 27% of the lithium-treated

Table 1 | Individual data and mean (s.d.) on 18 patients with ESRD with lithium as the only or main contributing etiological factor[a]

No.	Male/ female	Age at prevalence point	Age at start of RRT[b]	Years on lithium before RRT[b]	Years between lithium discontinuation and start of RRT[b]	P-creatinine at lithium discontinuation μmol/l	Lithium intoxication, 0=no; 1=yes	Biopsy confirmed[c] lithium nephropathy (+)	Psychiatric diagnosis
1	M	52	46	26	Lithium continued	Not applicable	0	—	SCH
2	M	54	54	33	Lithium continued	Not applicable	0	—	SCH
3	M	63	54	>26	Lithium continued	Not applicable	1	+	BP
4	M	64	59	16	16.2	155	0	—	CP
5	M	67	65	25	9.3	190	0	+	BP
6	M	65	65	31	Lithium continued	Not applicable	0	+	BP
7	M	64	62	28	Lithium continued	Not applicable	0	—	CP
8	F	64	57	21	6.6	219	0	+	BP
9	F	56	51	12	7.0	142	0	+	BP
10	F	68	62	16	2.8	98	0	—	UP
11	F	67	64	17	9.6	144	0	+	SCH
12	F	76	74	35	Lithium continued	Not applicable	0	—	CP
13	F	78	73	20	10	274	0	—	BP
14	F	76	73	20	8.5	140	0	—	BP
15	F	60	58	13	16.1	94	0	—	BP
16	F	61	58	20	Lithium continued	Not applicable	0	+	BP
17	F	67	67	35	Lithium continued	Not applicable	0	—	BP
18	F	67	65	18	14.5	125	0	—	SCH
All	7/11	65 (7)	62 (8)	23 (7)	10.1 (4)	158 (55)	1	7+/11	10/1/3/4
M	7	61 (6)	58 (7)	26 (6)	12.7 (5)	173 (25)	1	3+/4	3/0/2/2
F	11	67 (7)	64 (8)	21 (8)	9.4 (4)	155 (62)	0	4+/7	7/1/1/2

Abbreviations: BP, bipolar disorder; CP, cycloid psychosis; SCH, schizophrenia; UP, unipolar disorder.
[a]The assessment of the causal association between the lithium treatment and ESRD was based on the following operational definitions: (1) lithium is the only possible etiological factor (patients nos. 1–14); (2) lithium is the main etiological factor (patients nos. 15–18).
[b]RRT, renal replacement therapy (dialysis or transplantation).
[c]Renal biopsy findings with structural tubular and interstitial changes and fibrosis compatible with lithium nephropathy.

patients in the two regions. Thirty-eight percent of the patients had been on lithium for 15 years or more, 60% for less than 15 years, while the information was either uncertain or missing in only 2% of the patients. We therefore estimate that the prevalence of long-term lithium treatment in the general lithium population was 39%.

The prevalence of RRT patients with lithium-induced ESRD

There was no difference in RRT prevalence between the two study regions neither in the general population nor in the lithium-treated population. The prevalence of patients with lithium-induced ESRD in the RRT population was 8.1‰ (95% confidence interval 4.4–11.8‰), and the prevalence of RRT patients in the lithium-treated population was 5.3‰ (95% CI 2.8–7.8‰), which means sixfold increases compared with the general population. The RRT prevalence in the estimated group of long-term lithium patients was 2.5 times higher than that of the entire lithium-treated population. We could not calculate standard morbidity rate as information on age and sex was unavailable in the long-term group (Table 2).

Chronic kidney disease in the lithium-treated population

The prevalence of lithium treatment in the general population was 1.3‰ (Table 2), and 12‰ of these patients had plasma creatinine levels $>150\,\mu mol/l$ (41 patients, excluding patients on RRT). Compared with all lithium-treated patients, those with nephropathy were older, and the sex ratio was reversed, although there was no difference in mean serum lithium levels or psychiatric diagnoses (Table 3).

Observed and expected lithium-induced ESRD in different age groups

Compared with the general population ESRD was three times more common among lithium-treated males and almost six times more common among lithium-treated females (Table 4). All lithium-RRT patients were older than 40 years when RRT was started or when they discontinued lithium. Standard morbidity rate for the two genders jointly was 433 (95% CI 265–672; $P<0.001$).

DISCUSSION

This is the first prevalence study of terminal lithium nephropathy in a large cohort of RRT patients from a general population of close to 3 million inhabitants in a country with good access to psychiatric and nephrology service and RRT facilities. The main finding of our study was the identification of 18 cases of lithium-induced ESRD resulting in a clearly increased morbidity rate.

The observed 8.1‰ prevalence of lithium-induced ESRD in RRT patients corresponds to close to 1 in 100 patients in the Swedish RRT population. This contrasts with the results of the only comparable study by Presne *et al.*[13] who found a 2‰ prevalence of lithium-treated patients among dialysis patients in France. The prevalence they reported is clearly an underestimation, as it included only questionnaire-responding centers with a 56% response rate and, in contrast to the present study, did not include transplanted patients.

Table 3 | Demographic and clinical data for all lithium patients and for those with plasma creatinine $>150\,\mu mol/l$ (CKD)

	All patients *n*=3369	CKD patients *n*=41
Mean plasma lithium concentration, mmol/l (s.d.; median; range)	0.59 (0.17; 0.60; <0.3–1.68)	0.58 (0.20; 0,59; 0.1–0.94)
Mean plasma creatinine concentration, μmol/l (s.d.; median; range)	81 (28; 78; 32–521)	207 (83; 174; 153–521)
Mean age, years (s.d.; median; range)	56 (15; 56; 18–99)	68 (11; 66; 48–94)
Sex M/F (%)	41/59	56/44
ICD 10 clinical diagnoses (%) BP/UP/CP/SCH/MISC	60/20/16/2/2	61/12/22/5/0

Abbreviations: BP, bipolar psychosis; CKD, chronic kidney disease; CP, cycloid and schizoaffective psychosis; MISC, miscellaneous; SCH, schizophrenia, schizotypal, delusional; UP, unipolar psychosis.

Table 2 | The various populations and the prevalences within them

	The populations	Skåne region	Västra Götaland region	Both regions
1	General population 31/03/2005	1,162,134	1,522,023	2,684,157
2	RRT population	994	1208	2202
3	Lithium-induced RRT patients (see also Table 1)	7	11	18
4	Lithium-treated population	1289	2080	3369
5	Patients treated with lithium ⩾15 years (estimate)	502	811	1313
6	Lithium patients with P-creatinine $>150\,\mu mol/l$	16	25	41
	The prevalences	‰	‰	‰
1	RRT patients in the general population	0.9	0.8	0.8
2	RRT patients in the lithium-treated population	5.4	5.3	5.3
3	Lithium-induced ESRD patients in the RRT population	6.9	9.0	8.1
4	RRT in patients on lithium ⩾15 years (estimate)	13.9	11.1	12.2
5	Lithium-treated patients in the general population	1.1	1.4	1.3
6	P-creatinine $>150\,\mu mol/l$ in the lithium-treated population	12.4	12.0	12.2

Abbreviations: ESRD, end-stage renal disease; RRT, renal replacement therapy.

Table 4 | Absolute numbers of individuals; observed and expected cases of ESRD in the lithium population; by sex and age

	Males					Females				
	General population		Lithium population			General population		Lithium population		
Age strata	All males	ESRD cases	All males	ESRD observed cases	ESRD expected cases	All females	ESRD cases	All females	ESRD observed cases	ESRD expected cases
0–19	320,233	20	5	0	0.0003	303,828	13	3	0	0.0001
20–24	80,509	18	26	0	0.0058	78,816	8	21	0	0.0021
25–34	179,605	74	119	0	0.0490	173,898	51	134	0	0.0393
35–44	191,956	176	216	0	0.1980	184,662	121	281	0	0.1841
45–54	173,672	251	293	2	0.4235	170,780	152	437	0	0.3889
55–64	172,598	356	380	3	0.7838	170,326	175	535	4	0.5497
65–74	107,585	266	216	2	0.5341	118,311	179	340	4	0.5144
75–84	74,729	202	94	0	0.2541	102,546	103	197	3	0.1979
85–99	22,650	23	18	0	0.0183	48,649	14	46	0	0.0132
Missing			3	0	Unknown			5	0	Unknown
Total	1,323,537	1386	1370	**7**	2.2669	1,351,816	816	1999	11	1.8897

Abbreviation: ESRD, end-stage renal disease.

We took great care to ascertain the completeness of data on the prevalence of RRT patients with lithium-induced ESRD. We believe that the prevalence is representative of the prevalence of lithium-induced ESRD, as the proportion of ESRD patients not treated by RRT in Sweden is estimated to be less than 5% based on previous regional surveys (SRAU, unpublished data). In addition, the sixfold increase of RRT prevalence was identical between the RRT population and the lithium population, indicating that both our population data are sufficiently complete.

The medical records were reviewed by three of the authors, and only patients who fulfilled the established criteria were included as lithium-induced ESRD. Nevertheless, some RRT patients with previous lithium treatment may have escaped identification. In contrast, it is highly unlikely that patients with non-lithium-induced ESRD were included among the patients judged to have lithium-induced ESRD.

It may be argued that RRT patients who had discontinued lithium before RRT should not be considered members of the current lithium-induced ESRD population. We concluded from the case histories that these patients would have continued with lithium, had it not been for their renal insufficiency. Their exclusion from the lithium-induced ESRD population would misleadingly reduce the size of the problem.

In Sweden, renal biopsies are not routinely performed to establish the diagnosis of lithium nephropathy but may be performed to confirm the diagnosis or to evaluate the extent of irreversible structural changes. In five reexamined cases with renal biopsies performed before ESRD, the findings were compatible with the findings as previously described by Aurell *et al.*[4] and more recently by Markowitz *et al.*[12] with distinct chronic tubulointerstitial inflammation, dilated tubules, and including microcysts in three cases in addition to glomerulosclerosis. The other two patients had distinct lithium nephropathy findings in their renal biopsies. In three cases, the biopsies were performed more than 6 years after discontinuation of lithium treatment. In two additional but not reexamined cases, the originally reported findings were compatible with the same criteria. The biopsy findings clearly support the diagnosis of lithium nephropathy.

In this study, 10 out of 18 patients progressed to ESRD in the course of several years, despite having discontinued lithium treatment. Progress to ESRD after discontinuation of lithium treatment has been observed by others as early as 1979.[6] More recently, Markowitz *et al.*[12] found among 6514 kidney biopsies 24 (3.7‰) lithium-treated patients, all of them with CKD and with a renal histopathology compatible with lithium nephropathy. There were follow-up data from 3 months to 11 years on 19 patients, 18 of whom had discontinued lithium at the time of biopsy. Eight of them progressed to ESRD. The plasma creatinine level at the time of biopsy was a predictor for ESRD. Only one out of 10 patients with plasma creatinine levels <2.5 mg/dl (≈ 220 μmol/l) progressed to ESRD after 11 years, in three of them plasma creatinine declined, whereas seven out of nine patients with plasma creatinine levels >2.5 mg/dl progressed to ESRD. Lepkifker *et al.*[16] reported similar findings in a retrospective study of 114 lithium-treated patients. In 15 of 24 patients (21%) whose renal function gradually deteriorated, dose reduction or discontinuation of lithium resulted in stabilization of plasma creatinine levels. In the remaining nine patients renal function worsened in spite of lithium discontinuation. Similarly, Presne *et al.*[13] reported progress to ESRD in three patients within 2–13 years after discontinuation of lithium.

In the lithium-treated population, we ascertained the number of patients (3369) through personal contact with all psychiatric clinics in the regions. All had designated registers that covered their lithium-treated patients. In addition, we contacted all private psychiatrists who were registered at the public health-care authorities. The reported prevalence of lithium-treated patients should therefore be close to the true prevalence.

As regular measurements of plasma creatinine levels are part of the current follow-up routines, we were able to assess

the prevalence of patients with CKD. We defined CKD in this patient population by a routine serum creatinine level of >150 μmol/l obtained at a scheduled outpatient follow-up visit. Our conservative definition of CKD, P-creatinine >150 μmol/l, indicates a significant impairment of renal function and practically eliminates the bias of temporary renal function alterations.

Our data do not permit conclusions about risk factors for ESRD, except lithium treatment time. Sixteen (89%) out of 18 lithium patients on RRT had been treated long-term and none for less than 12 years. Among CKD patients, an estimated 90% had been on lithium for 15 years or more. Still, the majority of patients on lithium treatment have normal plasma creatinine levels even after many years on lithium and do not progress to ESRD.[11] Similarly, we cannot say which is the safe level of renal function for continuation or discontinuation of lithium treatment. Lithium intoxication was not a risk factor because only one patient had a history of lithium intoxication. The distribution of gender and of psychiatric diagnoses corresponds with other contemporary studies on lithium patients.[17–19] The individual factors that determine the initiation of irreversible nephropathy remain to be explored.

Several of the patients in our study had been exposed to high lithium doses and high serum lithium levels during the 1960s and 1970s. Standard (as opposed to standardized) serum lithium levels at the time was 0.8–1.2 mmol/l.[20] According to notes in the charts, serum lithium levels as high as 1.3 mmol/l were considered 'acceptable'. The nephrotoxic effect of lithium was obvious in some of these future ESRD patients with a pronounced polyuria already after a few years on lithium. It was not until the pharmacokinetics of lithium became the foundation of standardized serum lithium for the monitoring of treatment,[21] and the irreversibility of lithium nephropathy became common knowledge[3] that scientifically based safety routines gradually developed. They included lower and individualized serum lithium levels[22,23] resulting eventually in the average 0.59 mmol/l serum lithium level of our current lithium-treated population.

There are limitations to the study. The identification of lithium-induced ESRD patients was to some extent based on the recollection by RRT patients of previous lithium-treatment and on data from medical records. The diagnosis was established from clinical data, and renal biopsy was available in only seven patients. To mitigate these limitations, we applied stringent criteria for the identification of patients with lithium-induced ESRD on RRT. This is a cross-sectional point-prevalence study reflecting the therapeutic practice during the foregoing decades. Most patients started their treatment during an era when neither the serum levels of lithium nor renal function were monitored according to the modern standards that may limit the predictive power of the results. It remains, however, to be seen whether today's use of lithium, including lower and individualized dosages will diminish the risk for ESRD. Our finding of CKD prevalence 12.2‰ in the general lithium population indicates that this may not be the case.

In conclusion, lithium-induced ESRD exists and is a serious long-term side effect of lithium treatment and more prevalent than previously thought. The time on lithium treatment is a major risk factor and development of ESRD is not uncommon (>1%) among long-term lithium patients. The risk of renal failure as a consequence of long-term treatment may persist even after lithium discontinuation. Lithium is a very important and widely used therapeutic agent for bipolar disorders, and as the number of patients on long-term treatment is increasing more patients may be at risk of nephropathy. Also, the risk factors for progression of CKD despite discontinuation of lithium treatment are yet to be defined. Regular monitoring of renal function remains mandatory.

PATIENTS AND METHODS

The study began on 1 January 2005 and the inclusion of RRT patients was on 31 March 2005. This is the prevalence date.

The Swedish Registry for Active Treatment of Uremia

Data since the 1960s on patients on RRT performed as dialysis or renal transplantation have been collected in a national registry in Sweden, SRAU.[15] All patients on RRT should be reported to the registry and the coverage of the ESRD population in Sweden is almost 100%. Patients in the registry are followed throughout the life. At the prevalence date 31 March 2005, there were 7266 RRT patients in Sweden, giving a prevalence of 802 patients p.m.p.

Study populations

Two regions in Sweden were selected for this study, Skåne and Västra Götaland. At the prevalence day, these two regions comprised 29.8% of the total population in Sweden (9,014,921 inhabitants), each including two fairly large urban areas, several smaller cities, and rural areas. Two study populations were identified. The first population consisted of prevalent RRT patients with lithium-induced ESRD. This was a cross-sectional study and only patients alive on treatment were included. Among the 2202 RRT patients in these regions, 49% were on dialysis and 51% had a renal transplant. A second population was made up of patients treated with lithium and with CKD, defined as serum creatinine levels >150 μmol/l.

Lithium-induced ESRD among RRT patients—the first population

The SRAU data were used to identify patients on RRT at the different units in the two regions. They were interviewed about previous or present lithium treatment. Patients with an alleged history of lithium treatment had their medical records scrutinized by the study group, evaluating the cause of ESRD, the psychotropic treatment, and the ICD 10 chart diagnosis on which the lithium treatment was based. The diagnosis of lithium nephropathy as cause of ESRD was based on the following criteria:

- confirmed history of lithium treatment;
- absence of other renal diagnosis and post-renal obstruction;
- positive history of symptoms of diabetes insipidus;
- renal biopsy findings—when available—of tubular and interstitial changes compatible with lithium nephropathy;

- no evidence of potentially toxic drug treatment before lithium treatment;
- no evidence of hypertension, renal disease, or dysfunction before lithium treatment;
- progressive increase of serum creatinine levels or decrease of glomerular filtration rate over years;

On the basis of these criteria, patients with a confirmed history of lithium exposure were diagnosed as

- lithium nephropathy is the only cause for ESRD—all criteria;
- fulfilled lithium nephropathy is the main cause for ESRD—all criteria fulfilled but occurrence of concomitant disease after start of lithium treatment;
- lithium nephropathy is only a contributing cause for ESRD—criteria not fulfilled

Only data from patients in the two first categories were included in the analysis of data.

Renal biopsy. Renal biopsy was performed in seven patients as indicated in Table 1. Five cases were reexamined, whereas in two cases the biopsies could not be retrieved. The biopsies were performed when glomerular filtration rate was in the range 30–50 ml/min, and in three patients more than 6 years after discontinuation of lithium treatment.

CKD among lithium-treated patients—the second population

To establish the prevalence of lithium treatment in the two regions, all psychiatric clinics and private psychiatrists were inquired in writing about data on their lithium-treated patients, including sex, age, psychiatric diagnosis, serum lithium, and plasma creatinine levels. A cutoff limit of plasma creatinine level $>150\,\mu mol/l$ was used to identify patients with CKD. The collection of data was complete by May 2007.

Statistics

Conventional statistical methods were used to describe the salient features of the study populations. We calculated age-standardized prevalence by indirect standardization with the general population in the study as standard population. We calculated standard morbidity rate as the ratio multiplied by 100 of observed to expected number of ESRD in the lithium population under the assumption of identical prevalence of ESRD between the lithium population and the general population. For the calculation of the 95% confidence interval, we used a web-based calculator,[24] choosing the Mid-P exact test.

Ethics

The study was approved by the Regional Ethical Review Board in Lund (Regionala Etikprövningsnämnden i Lund) and performed in accordance with the Declaration of Helsinki.

DISCLOSURE

All the authors declared no competing interests.

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