Clinical studies on long-term lithium treatment and kidney failure

Harald Aiff

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Department of Psychiatry and Neurochemistry

Institute of Neuroscience and Physiology

Sahlgrenska Academy at University of Gothenburg

UNIVERSITY OF GOTHENBURG

Cover photo: Salar de Atacama, Chile. The world's largest and purest active source of lithium.

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harald.aiff@neuro.gu.se

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"I occasionally laugh and tell him that his imperturbability is worth three hundred milligrams of lithium a day to me, and it is probably true."

Kay Redfield Jamison, An Unquiet Mind: A Memoir of Moods and Madness

ABSTRACT

Background: Lithium enjoys the strongest evidence among today's mood stabilisers for long-term relapse prevention of bipolar disorders, and has been shown to reduce the risks of completed and attempted suicides. However, the benefits of lithium are restricted by its adverse side effects, the most serious being the progression of renal insufficiency to end-stage renal disease (ESRD). The risk of lithium-induced ESRD (Li-ESRD) was generally acknowledged in the 1970s. As a result of these findings, much stricter lithium treatment routines, intended to reduce the lithium burden on the kidneys, were introduced in Sweden in the early 1980s. However, the impact of these modern treatment principles remains unclear.

Aims of the thesis: To estimate the prevalence of lithium-associated ESRD (ESRD from all causes in lithium users), and to evaluate the role of lithium in the pathogenesis of ESRD; to test the hypothesis that modern lithium treatment routines have eliminated the risk of Li-ESRD (lithium classified as the sole or main cause of ESRD), and to study the prevalence and extent of kidney damage during the course of long-term lithium treatment in patients who started lithium treatment after 1980.

Patients and Methods: We used the Swedish Renal Registry to search for lithium-treated patients with ESRD among 2644 patients with chronic renal replacement therapy (RRT), either dialysis or transplantation, within two geographical areas in Sweden with 2.8 million inhabitants. The Swedish Prescribed Drug Register was used to estimate the number of lithium patients in the two regions. The prevalence date was December 31, 2010. We reviewed the medical records of patients with suspected Li-ESRD to verify the exposure to lithium treatment, the diagnoses of Li-ESRD according to specified criteria, and the date of starting the lithium treatment. Serum lithium and creatinine levels were retrieved for 4879 patients examined between January 1, 1981, and December 31, 2010. The estimated glomerular filtration rate (eGFR) was calculated according to the Revised Lund-Malmö equation and chronic kidney disease (CKD) stages were defined using the KDOQI guidelines. Only patients who started their lithium treatment during the study period and had at least ten years of cumulative treatment were included.

Results: The prevalence of ESRD patients with RRT in the lithium user population was 15.0‰ (95% CI 9.7-20.3) and the relative risk of ESRD with RRT in the lithium user population compared with the general population was 7.8 (95% CI 5.4-11.1). No patient with Li-ESRD started lithium treatment later than 1980. There was an annual increase in median serum creatinine levels already from the first year of treatment among 630 patients treated for more than ten years. About one third of those patients had CKD stage 3-5 (eGFR <60 mL/min/1.73m^2) and almost 5% reached CKD stage 4 or 5 (eGFR <30 mL/min/1.73m^2).

Conclusions: The thesis corroborates earlier findings that Li-ESRD is an uncommon but not rare condition and gives a reasonably well-founded estimate of its prevalence. Modern lithium treatment may have eliminated the risk of Li-ESRD, as no patient with Li-ESRD started lithium treatment later than 1980. The reduced risk of Li-ESRD is probably due to less lithium exposure with lower plasma levels and lithium discontinuance when indicated on the basis of monitoring of renal function. However, a substantial proportion of patients who are treated with lithium for more than a decade develop signs of renal dysfunction and it remains to be shown whether there is still a risk of progression to Li-ESRD, but at a slower pace than earlier. The results support continuous monitoring of kidney function during long-term lithium treatment.

Keywords: Affective disorders, Lithium, Adverse effects, Chronic Kidney failure

SAMMANFATTNING

Litium är det mest väldokumenterade återfallsförebyggande läkemedlet, och rekommenderas i första hand vid långtidsbehandling av bipolära sjukdomar, som utgör en kärngrupp inom det psykiatriska sjukdomspanoramat. Dess användbarhet begränsas dock av biverkningar varav den mest allvarliga är bestående njurskador. Denna biverkan av litiumbehandling påvisades redan under 1970-talet vilket medförde en kraftfull omprövning av dåtida behandlingsrutiner. I syfte att minska risken för njurskador förändrades behandlingsprinciperna som, från början av 1980-talet, kom att kännetecknas av individuellt anpassad, lägsta möjliga dosering av litium och regelbunden kontroll av njurfunktionen. Det är emellertid oklart om dessa behandlingsprinciper haft avsedd effekt.

Det övergripande syftet var att undersöka om nutida behandlingsprinciper undanröjt risken för terminal njursvikt och vidare att studera prevalensen av njurskador vid långtidsbehandling med litium.

Samtliga dialys och transplantationsenheter i Västra Götaland och Skåne har medverkat i studien. Alla patienter vid dessa behandlingsenheter har tillfrågats om de någon gång tagit litium. För de patienter som bejakat litiumbehandling och lämnat skriftligt godkännande (endast 2 avböjde att medverka) har journalgranskning genomförts liksom för under studieperioden avlidna patienter som registrerats i Svenskt Njur Register (SNR). Prevalensen av litiumbehandlade patienter har beräknats utifrån uppgifter om förskrivning i Läkemedelsregistret. Serumkreatinin analyserades över tid avseende patienter som behandlats med litium mer än 10 år utifrån data i Laboratoriets för klinisk kemi register vid Sahlgrenska Universitetssjukhuset.

Prevalensen av terminal njursvikt, som identifierats via SNR, var 15 promille i den litiumbehandlade populationen och den relativa risken för terminal njursvikt var 7.8 gånger större för litiumbehandlade än för normalbefolkningen. Ingen patient med litiumorsakad terminal njursvikt hade påbörjat sin litiumbehandling efter 1980. Den genomsnittliga kreatininnivån ökade kontinuerligt redan från första behandlingsåret för 630 patienter med mer än 10 års litiumbehandling. Omkring en tredjedel av dessa patienter fick med tiden en försämrad njurfunktion förenlig med kronisk njursjukdom.

Avhandlingen bekräftar att litium kan ge upphov till bestående njurskador och ger en välgrundad skattning av prevalensen. Fyndet att ingen patient som påbörjat litiumbehandling efter 1980 hade utvecklat terminal njursvikt tyder på att nutida behandlingsprinciper och säkerhetsrutiner kan ha undanröjt eller markant minskat risken för litiumorsakad terminal njursvikt, sannolikt genom minskad exposition för litium genom lägre serumnivåer och/eller att behandlingen avslutas vid försämrad njurfunktion. Emellertid utvecklar allt fort en betydande andel långtidsbehandlade patienter tecken på kronisk njursjukdom varför risken för terminal njursvikt inte kan uteslutas och kontroll av njurfunktionen är av vital betydelse vid litiumbehandling. Framtida studier bör analysera betydelsen av den ackumulerade dosexponeringen, inverkan av somatisk komorbiditet och vilka faktorer som i praktiken styr behandlingens duration.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Aiff, H; Attman, PO; Aurell, M; Bendz, H; Schön, S; Svedlund, J.
End-stage renal disease associated with prophylactic lithium treatment.
European Neuropsychopharmacology 2014; 24(4):540-4

II. Aiff, H; Attman, PO; Aurell, M; Bendz, H; Schön, S; Svedlund, J.
The impact of modern treatment principles may have eliminated lithium-induced renal failure.
Journal of Psychopharmacology 2014; 28(2):151-4

III. Aiff, H; Attman, PO; Aurell, M; Bendz, H; Ramsauer, B; Schön, S; Svedlund, J.
Effects of ten to thirty years of lithium treatment on kidney function.
Manuscript

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ABBREVIATIONS

ACE	Angiotensin-Converting Enzyme
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration Equation
Cr-EDTA	Chromium-51-labelled ethylenediamine
ECG	Electrocardiography
eGFR	Estimated Glomerular Filtration Rate
ESRD	End-Stage Renal Disease
GFR	Glomerular Filtration Rate
GSK-3β	Glycogen-Synthase kinase 3β
IMP	Inositol Monophosphatase
KDOQI	Kidney Disease Outcomes Quality Initiative Equation
Li-ESRD	Lithium-Associated End-Stage Renal Disease
LM-REV	Lund-Malmö Revised Equation
MDRD	Modification of Diet in Renal Diesase Study Group Equation
NDI	Nephrogenic Diabetes Insipidus
NICE	National Institute for Health and Care Excellence
NKF	National Kidney Foundation
NORIP	Nordic Reference Interval Project
NSAID	Non-Steroidal Anti-Inflammatory Drug
PTH	Parathyroid Hormone
RRT	Renal Replacement Therapy
SBU	Swedish Council on Health Technology Assessment
SNR	Svenska Njurregistret (SRR)
SRR	Swedish Renal Registry
VGR	Västra Götaland Region

INTRODUCTION

Historical background of lithium therapy

The Lange brothers

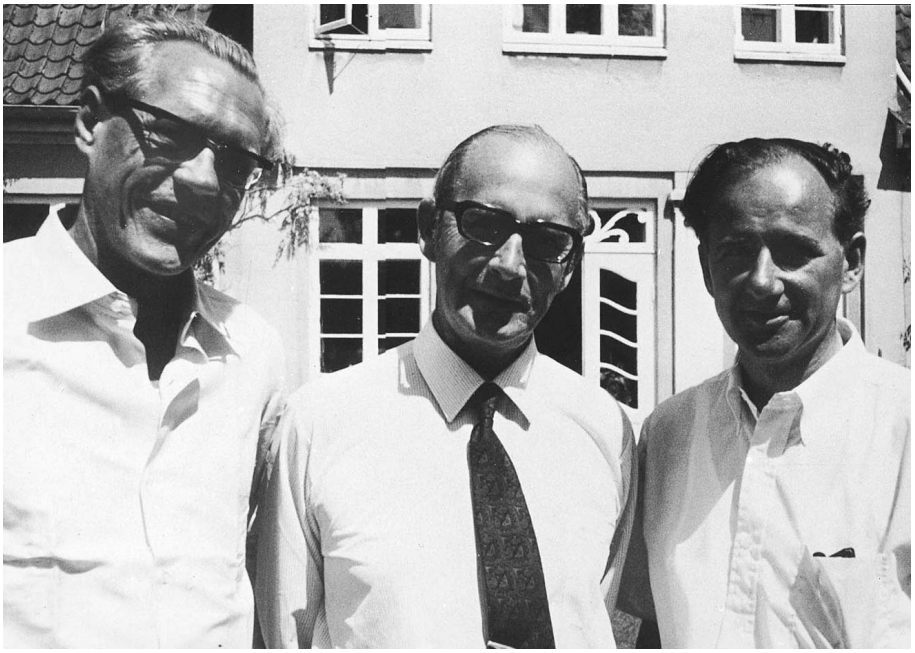
In 1886, the Danish neurologist and physiologist Carl Lange published an article called "On Periodical Depressions and their Pathogenesis." He used a lithium mixture to prevent periodic depression. His brother Fritz Lange published a book in 1894 called "The Most Important Groups of Insanity," where he described the treatment of depression with lithium carbonate. The findings of the brothers were acknowledged at the time but were later forgotten.

John Cade

John Cade (1912-1980) was an Australian psychiatrist working in Bundoora Repatriation Mental Hospital, outside Melbourne. He conducted experiments with urine from mentally ill patients from the hospital and injected it intraperitoneally into the abdomen of guinea pigs. His hypothesis was that the urine from manic-depressive and schizophrenic patients might contain toxic substances that could explain their psychiatric illness, and elicit symptoms in the test animals; however, he found no difference in urine toxicity between ill patients and controls. To determine if urate could be the toxic component in urine, he wanted to inject the animals with only urate, but as this is insoluble in water, he combined urate with lithium; i.e., lithium urate. When he injected the animals with this substance, they became lethargic. He soon discovered that it was the lithium, and not the urate, which caused this effect. After testing lithium on himself for a couple of weeks, he then tried lithium therapy on patients at the asylum. The effect on manic patients was extraordinary, and he published his findings in the *Medical Journal of Australia* (Cade, 1949). Some patients in this study, who had been admitted due to mania for many years, could be discharged after a couple of months and return to normal life. He found little effect, however, on schizophrenic patients. (Johnson, 1984)

Schou, Baastrup and Hartigan

The studies by Cade were replicated by some researchers, but due to a lithium toxicity scandal in the United States at the end of the 1940s, many psychiatrists were afraid to use lithium due to the risk of intoxication. (Schou and Grof, 2006).



Poul Christian Baastrup, John Cade and Mogens Schou.
The three founding fathers of lithium therapy.

A Danish researcher, Mogens Schou, made a double-blind trial that proved the effects of lithium against mania (Schou et al., 1954). Lithium was closely monitored to avoid intoxication. Other researchers replicated this trial during the following years.

Even though lithium worked well against mania, it was not expected that it could have a prophylactic effect against both depression and mania. This effect was independently discovered by Hartigan (Hartigan, 1963) and Baastrup (Baastrup, 1964). These findings encouraged Schou and Baastrup to conduct a longitudinal follow-up study in patients with many recurrences, to determine whether lithium would have a preventive effect. Their data were published in 1967 (Baastrup and Schou, 1967). The study showed that lithium had strong prophylactic properties in the prevention of new occurrences of mania and depression.

Some psychiatrists were not convinced by the new evidence, and therefore Baastrup and Schou carried out a double-blind study with lithium and placebo in patients with recurrent depression (Baastrup et al., 1970). The study produced irrefutable proof of lithium's prophylactic properties.

Lithium Therapy

Pharmacodynamics

The mechanism of action of lithium, a seemingly simple substance, is still a mystery. Lithium has several mechanisms of action in the brain, but it is unclear which mechanism is responsible for the mood-stabilising properties. Lithium also inhibits inositol monophosphatase (IMP), an enzyme responsible for the breakdown of inositol phosphates to free inositol. It is unclear to what extent this contributes to the mood-stabilising properties. Lithium inhibits the glycogen synthetase kinase 3β (GSK3β) enzyme through different pathways, both in the brain and in the kidneys. As GSK3β phosphorylates different transcription factors that turns on genes for cell growth, inflammation, neuroprotection and differentiation, this pathway might be important for the effects of lithium (Young, 2009) (Jope, 2003). It also enhances brain-derived neurotropic factor signalling (Chiu and Chuang, 2010).

Prophylactic lithium treatment

Lithium is still used in the acute treatment of mania, but an atypical antipsychotic together with a benzodiazepine is used more often. (Geddes and Miklowitz, 2013)

For this reason, the most common use for lithium today is as prophylactic treatment for bipolar disorder, both depression and mania. Lithium is used either alone or in combination with another mood stabiliser, such as valproate or lamotrigine, and/or with an atypical antipsychotic. Good lithium response is associated with a high initial severity of symptoms, an episodic pattern of both mania and depression, absence of mixed episodes, and high age at onset (Kleindienst et al., 2005, Backlund et al., 2009).

Lithium has a polarity index (Popovic et al., 2012) of 1.39, which means that it is somewhat more effective preventing mania than depression. One meta-analysis of five placebo-controlled lithium maintenance trials showed that lithium reduces the risk of manic relapses by 38% and depressive relapse by 28% (Geddes et al., 2004). According to the NICE guidelines (NICE, 2006), lithium, together with olanzapine and valproate, are recommended as first-line prophylaxis for bipolar disorder. Lithium has also been shown to reduce the risks of completed suicides and attempts. The anti-suicidal effect may be exerted by the reduction in the number of mood disorder relapses, but also by decreasing aggression and possibly impulsiveness (Goodwin et al., 2003, Baldessarini et al., 2006, Cipriani et al., 2013).

In some cases, lithium can be used as an augmenting agent together with an antidepressant in unipolar depression (Chang et al., 2013) and as a prophylactic for unipolar depression (Davis, 2006).

Side effects of lithium

In addition to the renal side effects, which are discussed separately, lithium treatment also has other negative effects.

Intoxication

The difference between recommended lithium concentrations (0.6-0.8 mmol/L) and toxic levels (>1.5 mmol/L) is small. Lithium treatment must therefore be closely monitored. A change in clearance, reduced salt intake, gastroenteritis, use of other medication affecting the kidneys (thiazides, NSAID, ACE inhibitors) or dehydration may lead to slow onset intoxication that may be lethal. The risk of intoxication due to suicide attempts in a disease with suicidal ideation as a part of the depressive phase must also be considered. In mild intoxication (1.5-2.0 mmol/L), the patients experience lethargy, drowsiness, coarse hand tremor, muscle weakness, nausea, vomiting and diarrhoea. Moderate toxicity (2.0-2.5 mmol/L) is associated with confusion, dysarthria, nystagmus, ataxia, myoclonic twitches and ECG changes. Severe toxicity (>2.5mmol/L) can be

life-threatening, include seizures, acute renal insufficiency and coma (Timmer and Sands, 1999).

Thyroid

Lithium interferes with the release of thyroid hormone and leads to clinically significant hypothyroidism. In a long-term study of lithium-treated patients, 30% had substitution treatment (Bendz et al., 1994). The odds ratio in a meta-analysis was 5.78 (McKnight et al., 2012). It is therefore important to follow thyroid hormones during lithium therapy, and substitute with levothyroxine if necessary.

Parathyroid

Lithium treatment is associated with increased levels of blood calcium and parathyroid hormone in 25% of patients (Bendz and Aurell, 2004). The point prevalence of persistent hypercalcaemia and surgically verified hyperparathyroidism was 3.6% and 2.7%, respectively, in a study by Bendz et al., 1996. The observed incidence of hyperparathyroidism over 19 years was 6.3%. Calcium and PTH levels should therefore be monitored during lithium treatment. Hyperparathyroidism is associated with osteoporosis and other bone deficiencies, but also weakness and fatigue, depression, and bone pain. Surgical removal of the parathyroid glands is sometimes necessary (Szalat et al., 2009).

Weight gain

Clinically significant weight gain is a common side effect of lithium therapy. Excessive weight gain is cited as one of the primary reasons why patients stop taking the drug. Excessive weight gain related to lithium therapy, amounting to more than 4.5 kg, is experienced by 25% of patients (Nemeroff, 2003). In a study on long-term treatment, 20% had weight gain above 10 kg (Vestergaard et al., 1980).

Gastrointestinal side effects

A common complaint is diarrhoea. This can be caused by the use of lithium sulphate, a slow-release substance that reaches the colon and causes diarrhoea (Persson, 1974). Switching to another lithium substance, for example, lithium carbonate, may help many patients.

Skin complications

An increased risk of skin disease has been reported, and women seem to be at greater risk than men (Sarantidis and Waters, 1983); however, the total incidence seems to be low (McKnight et al., 2012, Mitkov et al., 2014). The most frequent cutaneous reactions reported with lithium use are psoriasis, acneiform eruptions, folliculitis, alopecia, and exanthems (Gupta et al., 1995).

Neurological and cognitive side effects

Forty-five per cent of patients complain of hand tremor. This can sometimes be socially embarrassing or professionally troublesome (Vestergaard et al., 1980). The problem seems to be more common among men. Non-selective beta-blockers can be used to alleviate the symptoms.

Some patients experience lethargy, fatigue, memory impairment and emotional flattening. A meta-analysis shows impairment of psychomotor speed and impairment of verbal memory. (Pachet and Wisniewski, 2003).

Teratogenic effects

Lithium should be avoided during the first trimester, if possible, as some studies have shown an increased risk of heart malformation. Data from the Swedish Birth Register only shows a slight increase in all birth defects (3% vs. 2.1%), but this was not significant. Lithium use should be avoided during breastfeeding, due to the risk of accumulation (Janusinfo, 2014).

Nephropathy

Nephropathy means damage to or disease of the kidneys. Nephropathy can be divided into different subcategories, depending on whether it is an inflammatory or non-inflammatory condition. It can also be categorised by location; glomeruli (glomerulopathy), tubular (tubulopathy), or interstitial.

The manifestations of glomerular disease are characterised by haematuria and proteinuria caused by increased glomerular permeability.

The interstitial nephropathies are characterised by initially intact glomeruli; however, with an acute or chronic inflammatory response in the tubules and interstitially. The symptoms, if any, may be discrete and remain undetected for many years. The causes of interstitial nephropathy are diverse, including kidney damage after an infection, obstruction (cancer, kidney stone, prostate hyperplasia), and nephrotoxic substances (NSAID, penicillin, lithium).

Different methods may be employed to evaluate the diagnosis and severity of nephropathy. The gold standard is *kidney biopsy*, which gives a sample of the affected kidney that can be used for light microscopy, electron microscopy and different immunohistochemical analyses. The risk of complications of a kidney biopsy is small, but the method is only used when other diagnostic methods are insufficient.

Glomerular Filtration Rate

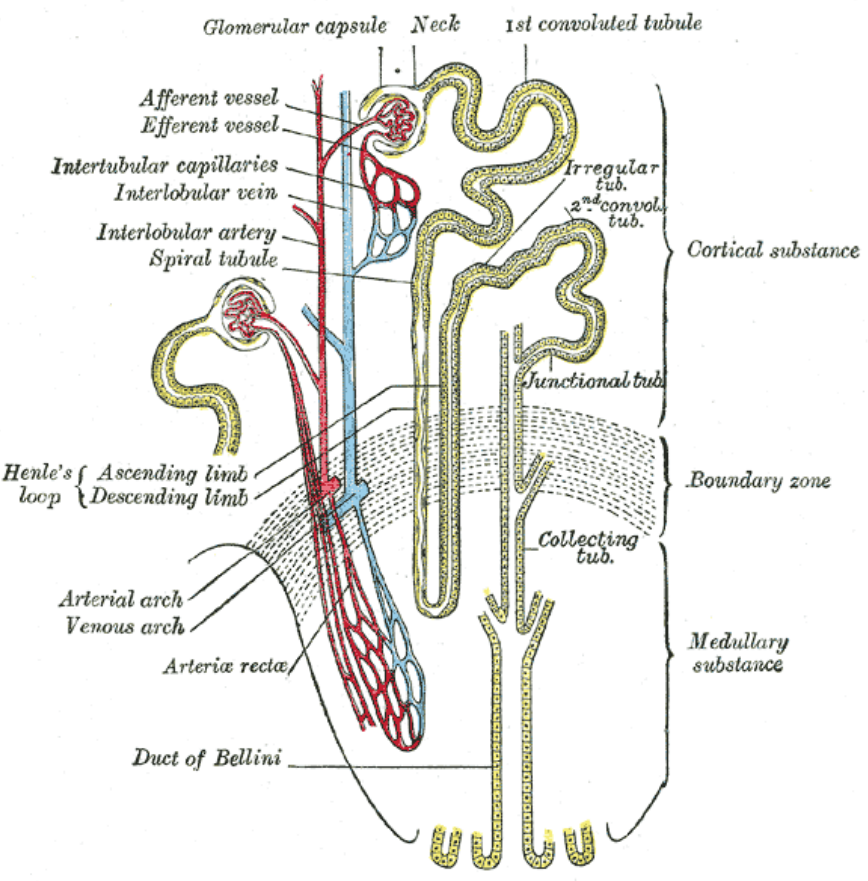
The filtration capacity of the glomeruli is the most important aspect of kidney function and measured as the glomerular filtration rate (GFR), which is the amount of plasma that is cleared of a specific substance over time by the kidneys. When the substance is not reabsorbed in the distal tubule and freely filtered through the glomeruli, and not protein-bound, the GFR of that substance is called the *renal clearance*. It is generally standardised to the unit mL/min/1.73m^2. If U is the concentration of the substance in urine, V is the urine volume, P is the concentration of the substance in plasma, and t is the time of collection, then:

$$Clearance = \frac{U \times V}{P \times t}$$

Measurement of renal clearance requires collection of the urine during a certain time period, and it is therefore often replaced by measurements of the *plasma clearance* of the substance. The plasma clearance, or GFR, can be measured by injecting a substance that is freely filtrated through the glomeruli and not reabsorbed (e.g., inulin, iohexol or Cr-EDTA). After injection, the level of the substance in plasma is measured at specific time intervals and the elimination rate (i.e., the GFR) is calculated.

eGFR and creatinine

The most commonly used marker for estimation of the GFR (eGFR) is the creatinine concentration in plasma. Creatinine is released from muscle tissue to plasma. It may also come from ingested meat or creatinine food supplements. Creatinine is freely filtrated through the glomeruli, and the creatinine plasma level is an indirect indication of the GFR, as the creatinine level is assumed to be at steady state in plasma. By using the creatinine level, together with age, gender and ethnic origin, different equations can be applied to estimate the GFR; for example, the MDRD (Modification of Diet in Renal Diesase), the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) and the


Glomerular capsule
Neck
1st convoluted tubule
Afferent vessel
Efferent vessel
Intertubular capillaries
Interlobular vein
Interlobular artery
Spiral tubule
Irregular tub.
2nd convol. tub.
Cortical substance
Functional tub.
Henle's loop
Ascending limb
Descending limb
Boundary zone
Collecting tub.
Arterial arch
Venous arch
Arteriæ rectæ
Medullary substance
Duct of Bellini

The Nephron

revised Lund-Malmö equation, with fairly good prognostic values. The equations have been validated in different studies with clearance measurements and can be used primarily as a screening tool.

The creatinine level in plasma differs between individuals, but an increasing creatinine level in the same patient indicates decreasing kidney function. The disadvantages of the eGFR from creatinine is that the creatinine level in plasma is not only dependent on the GFR, but also on the production of creatinine, which, in turn, is dependent on the amount of muscle tissue and ingestion of meat. Some creatinine is also excreted by the tubule, which may result in a spuriously high eGFR. The eGFR can thus overestimate the GFR, especially when the GFR is low, and underestimate normal or supranormal GFR (SBU, 2013).

The GFR normally decreases with age. Between 20 and 50 years of age, it decreases by 4 mL/min/1.73m^2, and after the age of 50, it decreases by approx. 10 mL/min/1.73m^2 per 10 years (Granerus and Aurell, 1981). Serum creatinine concentrations, however, do not normally increase with age, as the impairment of kidney function is counterbalanced by the decreasing muscle mass (NORIP, 2014).

Staging of Chronic Kidney Disease

Chronic Kidney Disease (CKD) is staged from 1 to 5, according to the GFR (NKF, 2002). Stage 1 is kidney damage without GFR reduction (above 90 mL/min/1.73m^2), and stage 5 is terminal renal insufficiency with a GFR < 15 mL/min/1.73m^2, often requiring dialysis. See Table 1.

Prevalence

In the general population the prevalence of moderately reduced kidney function (eGFR<60 mL/min/1.73 m^2) is between 3.2 – 5.6% (McCullough et al., 2012). The prevalence of impaired kidney function increases with age. Individuals above 69 years of age have a moderate reduction prevalence of 18% (Hallan et al., 2006).

Clinical consequences

The consequences of CKD are not only the progression to ESRD with a need for dialysis or transplantation. The reduced kidney function also elevates the risk of cardiovascular complications, leading to premature morbidity and mortality in affected patients. An American study showed that the risk of death based on the CKD stage increased with decreasing eGFR (Go et al., 2004). See Table 1. The underlying mechanisms are not entirely clear, but alterations in the lipoprotein metabolism, insulin resistance and low-grade inflammatory processes,

as well as deranged mineral metabolism and secondary hyperparathyroidism and hypertension have been proposed (Baigent et al., 2000). A Swedish study showed an increased risk of myocardial infarction in middle-aged men if the GFR was below 98mL/min/1.73m^2 (Soveri et al., 2009).

Progression of nephropathy

There seems to be a stage in the progression of CKD when the kidney function continues to deteriorate regardless of treatment, "the point of no return." When a patient reaches stage 4, with a GFR below 29 mL/min/1.73m^2, there is a significant risk of progression to ESRD. When the GFR drops below 15-20 mL/min/1.73m^2, the renal insufficiency becomes synonymous with development of the uraemic syndrome. This includes anaemia, metabolic, electrolytic and fluid disturbances, retention of toxic substances, oedema, neurological symptoms, and anorexia. With the GFR below 10 mL/min/1.73m^2, the patient has reached ESRD and the condition becomes life-threatening and renal replacement therapy then needs to be considered to save the patient's life.

Table 1 Levels of Chronic Kidney Disease (CKD) according to GFR (NKF, 2002) with mortality data.

Stage	Description	GFR ml/min/1,73m^2	Risk of death (Go et al, 2004)
1	Normal kidney function but abnormality, pathological urine findings or genetic disposition	>90	no data
2	Mildly reduced kidney function and other findings point to kidney disease.	60-89	no data
3	Moderately reduced kidney function	30-59	1.2-1.8
4	Severely reduced kidney function	15-29	3.2
5	Very severe or endstage kidney failure	<15	5.9

Renal Replacement therapy - RRT

Different methods have been developed to compensate for the defective kidney function in a patient with ESRD. These include various treatment modalities: haemodialysis, peritoneal dialysis or haemofiltration, together with kidney transplantation. All these methods are referred to as renal replacement therapy, RRT.

Dialysis

Haemodialysis is the most common form of dialysis, where the patient usually comes to an outpatient facility three times a week. The patient's blood is passed through a semipermeable membrane in a dialyser, where waste products, such as urea, potassium and phosphate, among others, diffuse into the dialysis solution.

Peritoneal dialysis works by introducing the dialysis fluid into the peritoneal cavity through a permanent catheter, and letting the peritoneum work as a semipermeable membrane. The dialysis fluid is then flushed out. The advantage, compared with haemodialysis, is that it the patient does not have to go to a dialysis facility, but the dialysis can be performed at the patient's discretion.

In 2012, 3026 patients in Sweden were treated with haemodialysis and 786 with peritoneal dialysis. There is an approx. 20% yearly mortality among dialysis patients (SRR, 2013). The mean age of patients beginning haemodialysis was 66 years.

Transplantation

In 2012, there were 5040 patients with a functioning kidney transplant in Sweden (SRR, 2013). A donor kidney may either come from a deceased donor or a living donor. The living donor may be a close relative or a non-relative. The complications of a kidney transplant include rejection of the donor kidney, infections, and side effects of the immunosuppressive medication. There is a 2.7% yearly mortality after transplantation (SRR, 2013). The mean age at transplantation was 54 years.

Lithium nephropathy

When starting lithium therapy, about 30-40% of the patients experience polyuria and polydipsia, symptoms of NDI. This it due to lithium inhibiting the effect of the antidiuretic hormone in the collecting ducts, causing less water reabsorption. This often becomes irreversible in long-term lithium use with permanent loss of the urine-concentrating ability. (Bendz and Aurell, 1999, Kishore and Ecelbarger, 2013). Patients show a reduction in urine-concentrating ability, also after lithium withdrawal (Bendz et al., 1994).

In some cases, lithium has also been associated with nephrotic syndrome, both due to minimal change disease and focal segmental glomerulosclerosis (Wood et al., 1989, Markowitz et al., 2000).

Lithium nephropathy is a chronic, progressive and insidious disease that may, in a few cases, result in ESRD (Bendz et al., 2010). Proteinurea is usually not present. Patients often have no apparent symptoms, except the symptoms of NDI. Serum creatinine tends to increase slowly as the GFR decreases. A French study found a decrease in the GFR by 0.57 mL/min/1.73m^2 per year in lithium-treated patients (Bassilios et al., 2008). The disease often takes decades to develop, and the creatinine level increases slowly, and often within the reference interval. It may therefore take many years before the renal impairment becomes evident.

The pathophysiological mechanism of lithium nephropathy is not clear. Lithium is freely filtered through the glomeruli and mostly reabsorbed in the proximal tubule, in parallell with sodium and water (Kishore and Ecelbarger, 2013). However, a smaller fraction passes through the distal tubule. One hypothesis is that it can reach toxic levels there, and cause damage to the distal tubule. The lithium passes to the collecting duct where it is reabsorbed in the principal cells through the epithelial sodium channels (ENaC). The ENaC have greater affinity (1.5-2) for lithium than for sodium. Lithium accumulates in the principal cells and inhibits the enzyme glycogen synthase kinase type 3β (GSK3β). This makes the principal cells less receptive to the actions of vasopressin and aldosterone. It is postulated that the accumulation of lithium in the principal cell can lead to cytotoxic effects and fibrosis that, in the long run, may damage the structure of the nephron and impair the glomerular filtration (Grunfeld and Rossier, 2009).

Histopathology

Lithium nephropathy is characterised by tubular atrophy and interstitial fibrosis that is disproportionate to the extent of the glomerular or vascular disease (Markowitz et al., 2000). The fibrotic changes are often cortical and focal, with

the glomeruli being less affected than the tubules, which are dilated. Microcysts are often present and have an abnormal epithelial lining. The distal tubule shows mitochondrial swelling and nuclear pyknosis (condensation of chromatin indicating necrosis)(Aurell et al., 1981, Hestbech et al., 1977). In an animal model, the changes seem to correlate with the time on lithium (Walker et al., 1986). See Figure 1 and 2.

Treatment

There is no specific treatment for lithium nephropathy, other than supportive treatment for nephropathy of any cause. Cessation of the lithium treatment seems to have a limited effect on the concentrating ability and the lithium therapy often has to continue due to the severity of the bipolar disease. Lithium treatment is often stopped or questioned when there are signs of renal damage with serum creatinine levels above the reference interval. It has not, however, been established whether there is a level of renal function below which continued treatment carries a significant risk of further progression; i.e., at what GFR level lithium should be discontinued.

There have been minor studies using the diuretic amiloride, in order to stop, theoretically, lithium from entering the principal cell through the ENaC. When this was given to patients with diabetes insipidus caused by lithium, only a minor effect was obtained (Grunfeld and Rossier, 2009); however, so far, no studies have been performed using amiloride as a prophylactic when commencing lithium treatment.

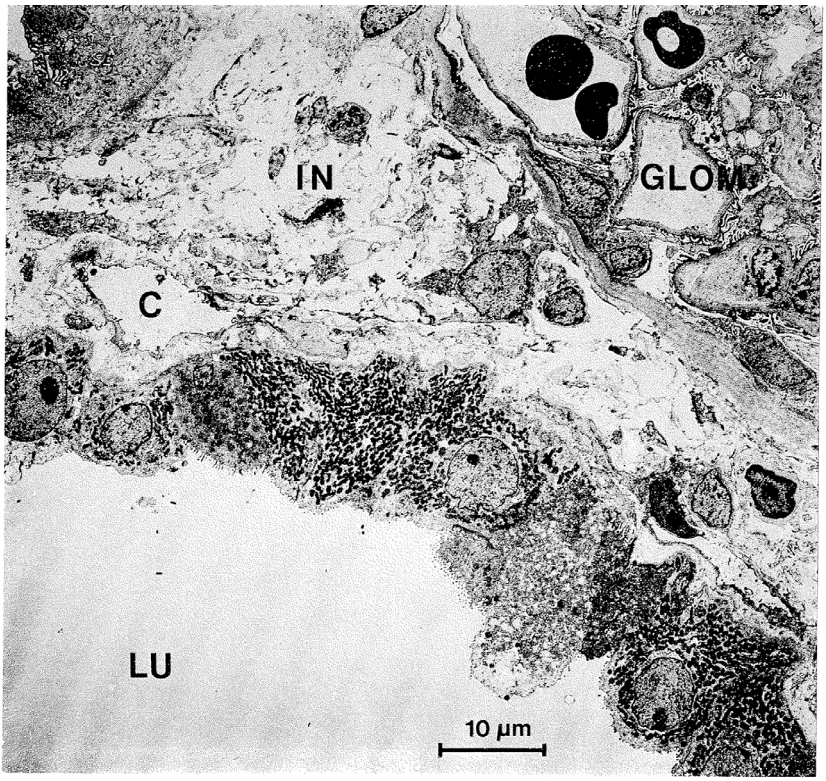


Fig 1 from (Aurell et al, 1981) with permission. Electron micrograph. Renal cortex is shown close to glomerulus (GLOM), with broadened interstitium (IN) containing profiles of fibroblasts and collagen fibres. Note small capillary (C) close to dilated tubule (LU) bordered by abnormal epithelial cells. Also note numerous mitochondria of variable density and small number of short villi on luminal surface. Tubular basement membrane is undulated. (Original magnification, x2500)

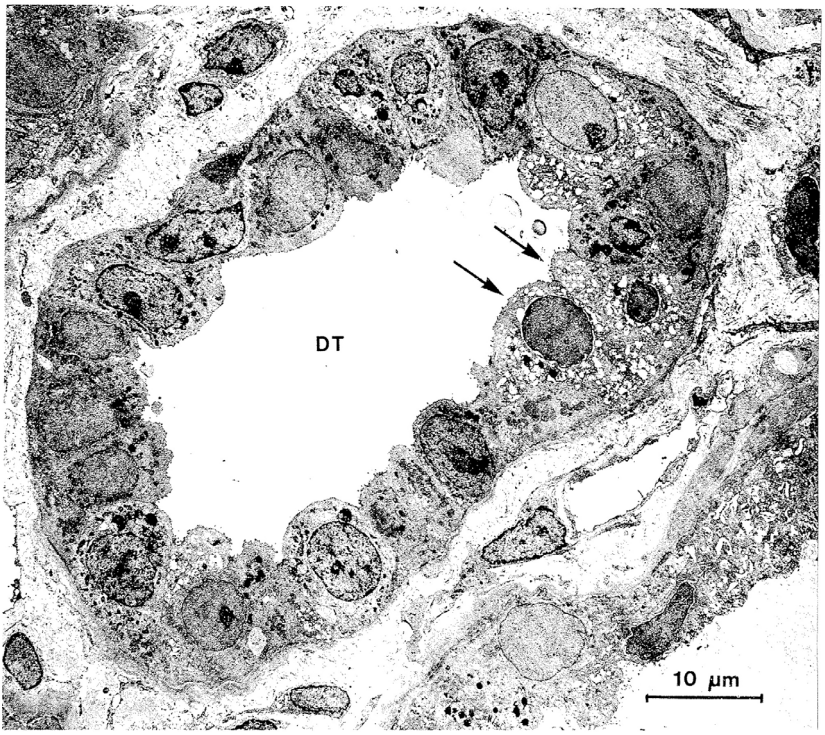


Fig 2 (Aurell et al, 1981) with permission. Electron micrograph showing inner strip of outer zone of medulla. Profile of pars recta of distal tubule (DT) with abnormal epithelium is shown. Note the numerous cytosegrosomes with variable density in the majority of the cells and the varying nuclear chromatin structure with prominent irregular nucleoli. Note mitochondrial swelling and nuclear pyknosis in two injured adjacent cells (arrows). (Original magnification, x3000)

Study background

Bipolar disorder is a devastating disease and lithium treatment is still important for its treatment. However, lithium has serious side effects, including chronic interstitial nephropathy that, in some cases, may lead to ESRD, as shown by (Bendz et al., 2010). The treatment regime was changed in the late seventies, due to reports of lithium nephrotoxicity in prophylactic lithium treatment. We wanted to investigate if "modern" lithium treatment had the intended effect on the prevalence of Li-ESRD. With the SRR and the contacts we had with the dialysis clinics, we saw the possibility of using this to measure the prevalence. We also wanted to investigate whether patients on modern lithium treatment developed renal impairment at a slower pace than earlier. The database at the Laboratory for Clinical Chemistry provided for a study on the development of renal function in a large urban population, in which patients on lithium treatment could be identified and followed retrospectively for decades.

AIMS OF THE THESIS

1. To estimate the prevalence of lithium-associated ESRD and to evaluate the role of lithium in the pathogenesis of ESRD.

2. To test the hypothesis that modern lithium treatment routines (i.e., after 1980) have eliminated the risk of Li-ESRD.

3. To study the prevalence and extent of kidney damage during the course of long-term (i.e., more than 10 years) lithium treatment in patients who started lithium treatment after 1980.

PATIENTS AND METHODS

PATIENT SELECTION Paper I & II

The methodology used in Paper I and II was different from that in Paper III. In Paper I and II, we used the Swedish Renal Registry, together with patient questionnaires and chart reviews. Paper III was based solely on laboratory database information.

Patient selection in Paper I

The study population for Paper I comprised patients who started RRT during the period 1991 through 2009, in the Västra Götaland Region(VGR) and Skåne, and who were alive at the prevalence date of December 31, 2010.

The Swedish Renal Registry retrieved all patients in VGR and Skåne who had RRT (dialysis or transplantation) on the prevalence date. We then contacted all dialysis and nephrology clinics in the two regions and asked the SRR nephrologist there to ask all patients at their next regular visit about past or present lithium use. If they replied that they had taken or were taking lithium at present, the SSR nephrologist asked for their written consent to let us review their charts.

Patient selection in Paper II

Paper I only included patients who were alive at the prevalence date to get an estimate of the point prevalence of lithium nephropathy in the two regions at a specific date. In Paper II, where we tested the hypothesis that modern lithium treatment (after 1980) could cause ESRD, we wanted to include as many patients as possible, thus making the ”risk” of detecting any patient who started lithium after 1980 as large as possible. We therefore added all patients from Paper I, together with the patients from the Bendz et al study (Bendz et al., 2010), and all patients with a diagnosis of lithium nephropathy or interstitial nephritis from the SRR, who had died between the two prevalence dates (2005-2010).

Chart review

We retrieved chart data from all patients who replied that they were using or previously had used lithium. Written consent was obtained from all but two

patients who refused further participation in the study. Since we could not ask the deceased patients about past or present lithium use, we used the registered renal diagnosis in the SRR. If this was either lithium nephropathy or interstitial nephropathy, we reviewed the charts of those patients as well. The ethical committee approved the review of the charts of deceased patients without written consent. The charts were reviewed for somatic and psychiatric diagnoses, history and development of renal disease and, if available, kidney biopsy. The lithium history was also reviewed: starting year of lithium treatment, duration, lithium levels during treatment, discontinuance of lithium treatment, available creatinine and clearance values, and other laboratory data.

Assessment of correlation between lithium and nephropathy

The entire group discussed the final assessment of the degree of association between the lithium treatment and the kidney disease for each case. The final decision rested with the three nephrologists in the research group.

The diagnosis of Li-ESRD was based on the following criteria:

- Confirmed history of lithium treatment;
- Absence of other renal diagnoses and post-renal obstruction;
- History of symptoms of diabetes insipidus;
- Renal biopsy findings—when available—of tubular and interstitial changes compatible with lithium nephropathy; six patients had had a kidney biopsy;
- No evidence of potentially toxic drug treatment;
- No evidence of hypertension, renal disease, or dysfunction prior to lithium treatment.
- Progressive increase in serum creatinine levels or decrease in the glomerular filtration rate;

We used three different levels of association between lithium and nephropathy (the same in both paper I and II):

1. Lithium is the sole cause of the ESRD—all criteria fulfilled;
2. lithium is the main cause of the ESRD—all criteria fulfilled, but with a history of concomitant disease that could possibly affect renal function;
3. Lithium is a minor contributing cause of the ESRD—criteria not fulfilled.

We used a conservative approach. If there was any doubt about the association between lithium and nephropathy we tended to grade the association lower to downgrade the association to reduce the risk of false positives.

Patients with ESRD with a history of lithium treatment are defined as lithium-associated ESRD. Patients with lithium as the sole or main cause of ESRD are defined in the following as lithium-induced ESRD (Li-ESRD).

Methodological discussion Paper I & II

Patient participation

We asked the SRR nephrologists at the different clinics to ask their patients about past or present lithium use. This is a sensitive subject, due to the stigma of psychiatric disorders, and patients may have denied lithium usage falsely. There is also the risk of negative recollection bias (Simon et al., 2012).

Patients who did not participate

In Paper I, two patients who answered that they had taken lithium but later refused to participate in the study. No chart reviews were made for these patients and we do not know whether they would have been classified as cases of lithium nephropathy. This would not have made a valid difference to the prevalence in Paper I. In paper 2, however, any patient that started lithium treatment after 1980 and then developed lithium nephropathy would have refuted the hypothesis.

Incomplete patient charts

For Paper I and II, it was sometimes hard to find complete charts. Some patients had recieved treatment at clinics that no longer existed and charts could not be found. One patient on long term treatment had a private doctor who refused to hand over the charts, even though we had permission from the patient. We used our best judgement when charts were incomplete, but there is always a risk of the wrong diagnosis.

The Swedish Renal Registry (SRR)

The Swedish Renal Registry in Jönköping (SRR), formerly the Swedish Registry for Active Treatment of Uraemia (SRAU), was founded in 1991. It includes all renal replacement therapy (RRT) centres in the country, now more than 60, located all over Sweden. Since January 1991, the registry covers more than 95% of all RRT patients in Sweden with end-stage renal disease (ESRD). The registry is located at the Jönköping County Hospital Ryhov. (Schön et al., 2004). The data has a high level of reliability, as the local clinics enter their own data into the system. The diagnosis is also entered in the register and we found the diagnosis of lithium nephropathy in the study patients to be correct. There is a risk that a patient with lithium nephropathy is classified with an unspecific diagnosis; hence, among the patients in Paper II, there may be some missed patients with lithium nephropathy. Since the SRR only covers patients with RRT, patients who chose not to receive RRT escaped detection.

The Swedish Prescribed Drug Register

We used the Swedish Prescribed Drug Register to estimate the number of lithium patients in the two regions. It comprises all purchases of personally identified prescribed medicine since 2005, and is maintained by the National Board of Health and Welfare (Socialstyrelsen). The estimate was the number of patients who had purchased lithium during the three-month period preceding the prevalence date in sufficient amounts to last through that date. The reason for using this method is that it is not possible to retrieve the number of lithium patients directly from the register, as it only keeps records of dispensed prescriptions, and not the number of patients taking the medication at a certain time. Since lithium medication in Sweden is generally prescribed on a three-month basis, we asked the register to search three months before the prevalence date to see how many prescriptions were dispensed that had enough medication to last through the prevalence date. This was an estimation of the number of lithium patients that we validated in a sub-region of the VGR.

Validation of the Swedish Prescribed Drug Register

To validate the data from the Swedish Prescribed Drug Register we performed a validation in the Skövde Hospital region in the VGR. We asked all psychiatric clinics for the number of lithium patients and compared that figure with the data from the register on the same date. In that study, the number of patients from the register was 414 and 436 from the psychiatric clinics, an underestimation of 5% in the register. The reason for this may be lack of compliance or patients withdrawing their whole annual prescription at the same time. What the true number of lithium patients is could also be discussed: the number

of patients at the different psychiatric facilities or the number of patients actually getting their medication from the pharmacy. Even though this study demonstrated a fair correlation, the risk of an under/overestimation of lithium patients can not be ruled out.

Statistics Sweden

The number of inhabitants in region the VGR and Skåne regions was retrieved from Statistics Sweden (SCB, 2013).

Age restricted lithium population

To control for the effect of age, comparisons between lithium users and non-lithium users were made after age-restricting the comparison groups (≥55 years), to accord with the age distribution of the lithium users with RRT.

Paper III

Patient selection

The database at the Department of Clinical Chemistry at Sahlgrenska University Hospital was established in the 1970s and keeps laboratory data from all laboratories serving the public hospitals and out-patient clinics in the greater Gothenburg area with a population of approximately 650 000 inhabitants. We retrieved the serum lithium and creatinine levels and the age and gender of all patients examined during a 30-year period (January 1, 1981 to December 31, 2010). We then excluded all patients who had only one lithium measurement, as we needed at least two measurements to establish a the treatment duration. Since we wanted to investigate the "modern" treatment regime, all patients who had at least one lithium measurement before January 1, 1981, were excluded. This was our "cut-off" for the modern lithium treatment. Patients younger than 18 years were excluded. Patients without creatinine measurements might have had their follow-up elsewhere and were excluded. Patients with an initial creatinine level above the laboratory reference value (adjusted for age and gender) were excluded, to avoid patients with disease processes affecting the kidneys already at the start of the lithium treatment. We used the laboratory reference value at the time of measurement.

Patients with less than ten years cumulative lithium treatment were also excluded, as our previous studies indicate that ESRD takes more than a decade to develop. It also made our patient group more consistent. We believe that patients with at least ten years of lithium treatment are the "core" of patients who benefit from the treatment, or else they would have ended it sooner.

In 2004, the serum creatinine measurement method was changed from a picrate method to a more specific enzymatic method. To enable correct comparisons between serum creatinine levels obtained before and after the change in methods, the earlier levels were subtracted by 25 umol/L.

If a patient had 365 days without any positive lithium measurements, we regarded this as a discontinuance of lithium treatment and that time period was subtracted from the total treatment duration. It is not uncommon for patients with bipolar disorder to interrupt their lithium treatment periodically for different reasons. The serum creatinine measurements closest (±6 months) to the first and last lithium measurement were regarded as the initial and final creatinine level, respectively. If initial and final serum creatinine measurements were not available, the patient was excluded. The reason for this is that it would be difficult to establish an association between lithium use and creatinine levels if the samples were not taken at the same time. The final sample consisted of 630 adult patients with at least ten years of cumulative lithium treatment and a normal or low serum creatinine level at the start of the lithium treatment. The selection of study patients is illustrated in Figure 3.

Data on lithium and creatinine concentrations were analysed using Microsoft Excel and SPSS. The glomerular filtration rate was estimated as the eGFR from the serum creatinine concentration, age and gender according to the Revised Lund-Malmö equation devised by Björk et al. (Bjork et al., 2011, SBU, 2013). The eGFR was used to categorise the level of renal function according to the KDOQI guidelines (NKF, 2002)

NORIP

We used data from the Nordic Reference Interval Project (NORIP, 2014) for reference regarding expected age-related changes in serum creatinine in a Nordic population. According to this database, the mean creatinine level in plasma for men increases from 77 μmol/L at the age of 18-29 to 81 μmol/L in patients above 70 years of age. In women, the corresponding values are 64 μmol/L to 67 μmol/L. This means that, on average, the creatinine level should only increase by 4 μmol/L over the whole lifespan of patients, both men and women. See Table 2.

We arbitrarily defined a clinically significant decrease in renal function as an increase in serum creatinine levels ≥30%. This difference is considerably greater than the intra-individual short-term variation in serum creatinine concentrations seen in patients with established renal disease (Reinhard et al., 2009).

Calculations of the eGFR

For estimation of the GFR in Paper III, we chose the Revised Lund-Malmö (LM-rev) equation for a number of reasons. In a Swedish population, the method is well validated, according to a national review performed by SBU, the Swedish Council on Health Technology Assessment (SBU, 2013). It also does not require knowledge about ethnicity, as is the case with the MDRD equation. It only uses age, gender and the creatinine level, data that we had access to via the lab database.

The validity of the LM-rev is good for kidney function above 30 mL/min/1.73m^2 compared with clearance measurements and with other eGFR Equations (e.g. MDRD, CKD-EPI), but for kidney function <30 mL/min/1.73m^2 the reliability is low, as with all eGFR equations (SBU, 2013). When interpreting the eGFR measurements in Paper III, this must be taken into consideration.

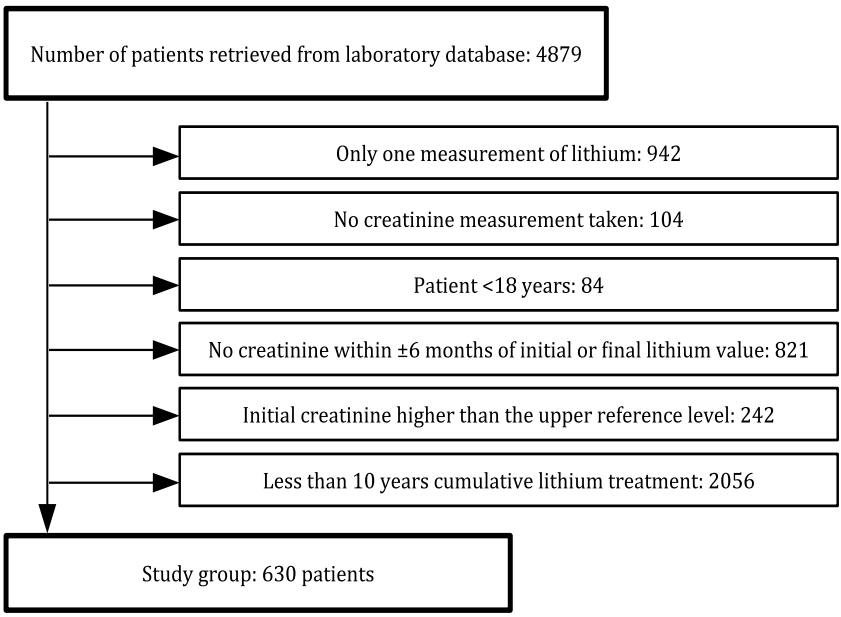


Figure 3. Flow chart of the final sample of patients with at least ten years of cumulative lithium treatment.

Table 2: Age related reference intervals for serum creatinine (µmol/L) from the NORIP database.

Men Age	**18-29**	**30-39**	**40-49**	**50-59**	**60-69**	**>=70**
97.5 centile	96	92	98	98	102	108
50 centile	77	76	78	77	78	81
2.5 centile	63	62	63	61	64	62
Women Age	**18-29**	**30-39**	**40-49**	**50-59**	**60-69**	**>=70**
97.5 centile	81	82	82	82	90	89
50 centile	71	70	70	70	74	73
2.5 centile	52	51	54	52	52	53

RESULTS

Paper I

We found 30 patients with previous or current lithium treatment who accepted to participate. Out of those, we found 24 patients with ESRD induced by lithium. We classified 14 cases with lithium nephropathy with all the criteria fulfilled and ten patients with lithium as the main cause, but also with some other concomitant disease. Six patients were classified as nephropathy where lithium only played a minor role in the disease progression. The average time on lithium before RRT was 27 years, although one patient only had 12 years of treatment time. Fifteen patients discontinued lithium treatment before the start of the RRT, while nine continued to use lithium during the RRT. The prevalence of lithium-induced nephropathy (n=24) was 12‰ and the relative risk 6.3. ESRD with RRT was significantly more prevalent among lithium users than among non-lithium users ($P<0.001$). The prevalence of ESRD with RRT (n=30) in the lithium user population was 15‰ (95% CI 9.7-20.3). The risk of ESRD in the lithium user group compared with the general population was 7.8 (95% CI 5.4-11.1).

Paper II

In total, we identified 32 patients (19 female and 13 male) with lithium as the sole or main contributing cause for ESRD (Li-ESRD). The study patients were collected from Paper I, the Bendz et al. (2010) paper, and from an analysis of deceased patients between 2005-2010 in the SRR. We found no patients who had started their lithium treatment after 1980. The hypothesis that we would find no patient with lithium nephropathy that started their lithium treatment after 1980 therefore remains to be refuted (Popper, 1969).

Paper III

We found 630 patients, 402 women and 228 men, who had at least ten years of cumulative lithium treatment. The mean age when starting lithium treatment was 46 years, with no significant difference between genders. We analysed the difference between the initial and final serum creatinine levels. An increase by at least 30% of the initial serum creatinine concentration was seen in 45% of the patients, after more than ten years on lithium. The initial creatinine level in the patients who had this significant increase was almost the same as in the

patients who did not have such a large increase (66 vs. 60 μmol/L). See Table 3 for the distribution of patients according to creatinine increase.

We calculated the change in the eGFR using the LM-Rev equation, and almost 5% of the patients developed stage 4 or 5 CKD after at least 10 years of lithium treatment. The final eGFR was below 60 mL/min/1.73m^2 in 32% of the patients.

Table 3. Increase in serum creatinine level during lithium treatment.

Creatinine increase	Male	%	Female	%	Total	%
< 30 %	123	53.9	222	55.2	345	54,8
30 - 100 %	85	37.3	144	35.8	229	36,3
100 - 200 %	15	6.6	28	7.0	43	6,8
200 - 300 %	3	1.3	7	1.7	10	1,6
> 300 %	2	0.9	1	0.2	3	0,5
Total	228	100	402	100	630	100

DISCUSSION

Paper I

The three studies look at the prevalence and occurrence of lithium-induced nephropathy from three different perspectives. In the first paper, we showed that the prevalence of lithium nephropathy is still a clinical concern, and that close to 1% of patients treated with dialysis or renal transplantation (RRT) had developed ESRD because of long-term lithium treatment. The risk of ESRD among lithium-treated patients was eight-fold higher than among the general population. Despite adequate RRT, these patients are at a greatly increased risk of premature morbidity and mortality, mainly from accelerating cardiovascular disease or complications from immunosuppressive therapy. We also confirmed that long-term treatment is an important factor for developing lithium-induced ESRD, as all patients had at least 12 years' treatment duration, and the mean treatment time was 25 years. Even though some of these patients stopped lithium treatment for different reasons many years before their kidney failure, they still developed ESRD after a "free interval." There seems to be a "point of no return" where lithium discontinuance has no effect on the clinical deterioration of the kidneys. Similar observations of progress to ESRD after lithium discontinuance have previously been reported by Presne et al. (2003), Lepkifker et al. (2004), and Bendz et al. (2010).

Six patients were not classified as having lithium as the sole or main cause of lithium nephropathy, but lithium may still have played a role in their kidney failure, as a comorbid factor. One would suspect that the combination of risk factors or disease of the kidneys and lithium therapy would increase the risk further.

The golden standard for diagnosing lithium nephropathy is a positive kidney biopsy. It is not possible to perform this in all patients with suspected lithium nephropathy, as the diagnosis in itself does not change the treatment or prognosis for the individual patient. In most of our clinical cases, the diagnosis of Li-ESRD had to rely on thoroughly scrutinised clinical information and stringent criteria for the identification of Li-ESRD patients. We eliminated false positive cases through our systematic chart review by three of the authors and it is unlikely that patients with non-Li-ESRD were included among patients judged to have Li-ESRD. However, there is a risk of false negatives, where lithium played a major part in the nephropathy, despite the occurrence of many strong comorbid factors. There is also a risk of missed patients in the SRR,

either due to recollection bias or unregistered patients. If patients with lithium nephropathy were too sick or rejected RRT, they were also "missed." The prevalence of lithium patients in the general population relied on the Swedish Prescribed Drug Register, which was validated against the number of outpatients retrieved from psychiatric clinics in a smaller region of the VGR.

When comparing the two regions of Skåne and the VGR, an interesting connection was found between the number of newly diagnosed patients with bipolar disorder in a registry (NBHW, 2011) and lithium usage and lithium nephropathy in that region; The larger the number of bipolar patients, the more lithium patients, and the more lithium patients, the more patients with lithium nephropathy.

Paper II

An interesting observation in previous studies, was that no patient who started treatment after 1980 was found to have lithium nephropathy. More thorough controls and follow-up, together with lower doses, were used after studies were published in the late seventies. We therefore tested the hypothesis that patients starting lithium treatment after 1980 would not develop Li-ESRD. Using the patient cohorts from Paper I, as well as all patients included in the study by Bendz et al. (2010) and deceased patients between 2005 and 2010 in the SRR with a diagnosis of lithium nephropathy or interstitial nephropathy, we found no patients who started lithium treatment after 1980. The hypothesis therefore remains to be refuted (Popper, 1969). These data should be interpreted with caution. Just because we found no new cases, it is not proven that it is impossible to develop lithium nephropathy today. Since lithium nephropathy in most cases take decades to develop, is an uncommon condition to begin with, and modern lithium treatment may have lowered that risk even further, the lack of any new cases in this study sample is merely an indication that something may have changed. Modern lithium treatment routines may have reduced the risk of lithium nephropathy to such a low level that larger catchment areas or longer follow-up periods are needed.

Paper III

To further investigate the finding in Paper II, we wanted to investigate whether patients with long-term treatment had reduced kidney function, but as yet undeveloped ESRD. To this end, we used the laboratory database at the Department of Clinical Chemistry at Sahlgrenska University Hospital. We identified patients on long-term treatment who began lithium treatment after 1980 as shown in figure 3. We found 4879 individual patients who had their first lithium measurement taken 1981 and after. There were 942 patients who had only one lithium measurent taken. The explanation for this might be early dropouts, patients with follow-up at other laboratories, and intoxications. In a some cases, creatinine values necessary for evaluation of kidney function were absent. Some patients had a creatinine value above reference value already at start of lithium treatment. We excluded those patients to reduce the risk of comorbid factors in the study population. A creatinine within reference value is not a guarantee of normal kidney function, however. The last exclusion criteria was treatment length. Since earlier studies have shown that lithium nephropathy takes years to develop, and the shortest duration of lithium nephropathy leading to ESRD is 12 years, we had a cut-off of 10 years. In future research we plan to also examine the patients with shorter treatment duration, to see if there is a difference in creatinine elevation between short-term and long-term treated patients.

It is important to recognise that a slight serum creatinine increase can have a much greater impact on the GFR, as the relationship is exponential. Patients can loose as much as 50% of kidney function and still be within reference interval. The serum creatinine level must be evaluated with regards to expected kidney function and muscle mass. As stated earlier, the level of serum creatinine between healthy individuals differs depending on age, muscle mass, protein ingestion. The intraindividual level however, should normally not change. This is due to the balance between loss of kidney function and the loss of muscle mass. If creatinine concentration does change, it could be a sign of decreasing GFR and kidney function. We chose a cut-off for clinical significant increment of creatinine concentration of 30%. For a twenty year old man, a 30% increase in creatinine between 90 mmol/L to 120 mmol/L is equal to a GFR loss from 84 to 63 mmol/min/1.73m^2 . For a seventy year old woman, this corresponds to a loss of GFR from 53 to 37 mmol/min/1.73m^2 . The eGFR is therefore an important tool to put the serum creatinine concentration into clinical context.

To estimate the GFR, we used the Lund-Malmö Revised Equation, which is shown to be the most accurate method in Swedish populations. The eGFR is a quick and non-invasive way to estimate kidney function. It is well validated except in very low GFR, where no eGFR formula is accurate.

To our surprise, 45% of those patients had at least a 30% increase of creatinine, and 5% of the patients had a CKD in stage 4 and 5, which is a severe kidney disease. This indicates that lithium, in some patients, is associated with a clinical significant reduction of kidney function, which could eventually lead to ESRD and the need for RRT.

This corroborates findings by Bassilios et al. (2008), who found an over-representation of CKD stage 3 and 4 in lithium-treated patients.

When studying the annual increase in creatinine levels in patients who were treated for more than ten years, we found that the mean creatinine increase started already the first year and then continued. See Figure 4. This was also found by Lepkifker et al. (2004), and was named "creeping creatinine."

As this is a laboratory study, there are several limitations to consider. The only data we have are gender, age, lithium use, and creatinine samples. We could not review any charts or look at other blood samples. This makes it impossible to determine if the increase in creatinine was only due to lithium (Li-ESRD) or some other comorbid factors in the individual patient. We can only conclude that lithium treatment was strongly associated with the increase in creatinine levels, compared with the normal reference values from the NORIP.

The majority of patients, however, did not have an significant increment in creatinine. It is unclear why some patients develop a clinically significant nephropathy and others are not affected. Since all of the studied patients had been on lithium for at least ten years, the lithium treatment time is not the only risk factor. It may be that a combination of other comorbid risk factors, together with individual sensibility, could explain the variation.

General discussion

These studies confirm findings from earlier studies (Bassilios et al., 2008, Bendz et al., 1994, Bendz et al., 2001, Lepkifker et al., 2004, McCann et al., 2008, Presne et al., 2003, Tredget et al., 2010), which show that lithium therapy in some cases leads to lithium nephropathy and, in the worst case, to Li-ESRD (paper I). To evaluate the effect of modern lithium treatment on prevalence of Li-ESRD we tested the hypothesis that no new cases of Li-ESRD would be found (paper II). We were unable to refute it (Popper, 1969). To see if patients who started lithium treatment developed loss of kidney function, we used a laboratory database. Paper III clearly indicates that a large proportion of patients with long-term lithium treatment develop clinically significant renal impairment.

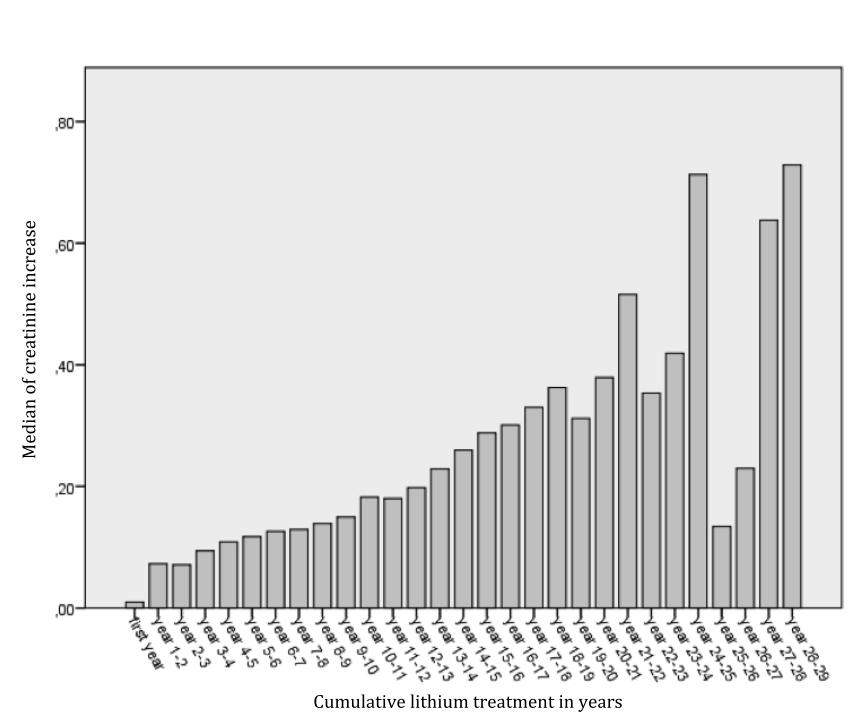


Figure 4. Median serum creatinine increase by cumulative lithium treatment in year 1 to 30.

There is reason to believe that these impairments could lead to ESRD in a few cases. However, since we cannot classify the individual patient and rule out comorbidity, lithium's etiological role can only be suspected but not proven. We found a high prevalence of patients with significant renal impairment, and it is safe to presume that lithium nephropathy is still is a clinical problem, and that lithium treatment must be closely monitored. If modern treatment regimes can cause Li-ESRD in a patient without comorbidity, remains to be shown.

One of the strengths of this study is the combination of retrospective prevalence data on an uncommon condition together with the clinical classification of causality. In Sweden, health care is freely accessible. When a patient develops Li-ESRD, it is highly probable that the patient is offered RRT and thus registered in the SRR. For this reason, we believe that the risk of underestimation of the problem is small. Using strict criteria for the diagnosis of Li-ESRD, we also believe that the risk of false positives is small.

The three studies rely on well-established registries with excellent coverage, and on the acknowledged Swedish individual identification system. These factors, together with competent scrutiny of available documents, provide for a complete follow-up of patients over time.

The Department of Clinical Chemistry at the Sahlgrenska University Hospital offers a unique possibility to investigate more than 30 years of lithium treatment in a large cohort of patients. The department is a certified laboratory of a university hospital in a large catchment area. In Paper III, we investigated the creatinine increment associated with lithium treatment, but the data could also be used for other purposes related to lithium therapy, such as the historic use of lithium and modes of lithium usage.

In bipolar disorder, the standard mortality ratio of cardiovascular disease is 1.9-2.6 compared with the general population (Osby et al., 2001). Bipolar disorder is associated with the metabolic syndrome, including obesity, diabetes mellitus and hypertension (Toalson et al., 2004). Depression is associated with hypercortisolaemia, which can lead to central obesity, vascular damage and development of insulin resistance. Emerging evidence also points to a direct connection between bipolar disorder and inflammation (Magalhaes et al., 2012), increasing the risk of vascular damage and diabetes. The relative importance of psychotropic medication in the development of metabolic risk factors remains to be evaluated. Prevention of relapses by prophylactic lithium treatment may improve the physical health in bipolar patients, who tend to exercise less, smoke more and not care for their physical health during depressive and manic episodes (Goodwin and Jamison, 2007). Lithium may, on the other hand, worsen their metabolic disturbances, with obesity, nephrotoxicity with increased cardiovascular risk and hypothyreosis.

The risks of lithium treatment must be weighed against the risk of not using the most evidence-based treatment of bipolar disorder, a devastating and crippling psychiatric disorder where lithium may be the only available option for many patients. In a decision analysis of long-term lithium treatment and the risk of renal failure (Werneke et al., 2012) the author concluded that the benefits of lithium exceed the risk of renal failure, both at the start of lithium treatment and after 20 years of lithium treatment. Although not specifically studied, lithium treatment is sometimes continued through dialysis or after transplantation, which shows how important lithium is to some patients.

If signs of lithium nephrotoxicity develop, the benefits of lithium treatment must be carefully weighed against the risk of ESRD together with the patient. If the prophylactic properties of lithium in the individual patient are strong, the reduced GFR may be the lesser evil. If discontinuing lithium is proven to

aggravate the bipolar disorder, this may have devastating effects on the patient's well-being, social and occupational functioning. If, however, the lithium treatment seems to have a lesser effect on the patient's suffering, switching to another mood stabiliser might be a possible option. The other available options for the treatment of bipolar disorder, including valproate, lamotrigine, and different antipsychotics, all have their side effects, including weight gain, teratogenic properties, sedation and extrapyramidal symptoms.

CLINICAL CONSEQUENCES

Our studies as well as those of others are important, both to the clinician and the patient, when considering lithium treatment. With regard to the risk of ESRD and significant kidney function loss, lithium treatment must be used with caution. Before starting lithium treatment, the patient's kidney function should be examined with serum creatinine and urine analyses for the presence of proteinuria. If the patient has any risk factors (hypertension, hereditary kidney disease, diabetes), a clearance measurement should be considered and used as the base level.

It is important to make informed decisions together with the patient with regard to the benefits and side effects of lithium treatment. One should not exaggerate the effects or underestimate the side effects, as this could lead to patients feeling misinformed, which could potentially impair compliance and trust. Since lithium treatment is generally a long-term therapy, the relationship with the doctor is crucial.

When the patient is on lithium treatment, it is important to follow creatinine concentrations on a regular basis and to compare with historic creatinine concentrations. As lithium nephropathy takes many years to develop, it is important to look at creatinine values over a long time period. If serum creatinine increases repeatedly, the patient should perform a measurement of renal function. Standard reporting by the clinical laboratory including present and previous eGFR calculations could increase the clinician's awareness. The awareness about lithium nephropathy should also be raised in psychiatric facilities, and designated staff should be responsible for the monitoring of lithium patients.

Patients should be educated about the side effects of lithium, and what to do with regard to dehydration to minimise the risk of lithium intoxication.

CONCLUSION

Our papers, together with earlier findings, show that lithium nephropathy is a clinical reality, and can sometimes lead to ESRD. It is therefore important to follow kidney function during lithium treatment, and weigh the benefits of lithium treatment against the risk of CKD and ESRD. In clinical reality, however, many patients with bipolar disease rely on lithium treatment to have a reasonable quality of life, and the risk of CKD and ESRD is the lesser evil than severe depression, mania or even suicide.

RECOMMENDATIONS FOR FUTURE RESEARCH

1. To establish why some patients develop "creeping creatinine" with nephrogenic diabetes insipidus and some are unaffected by lithium treatment.

2. To identify markers (e.g., creatinine level or other signs) early in the progression of lithium nephropathy to prevent further disease progress.

3. To establish the role of comorbidity in the development of lithium nephropathy.

4. To better understand the pathophysiology of lithium nephropathy to be able to develop more specific treatment and prevention programs.

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