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Screening for the markers of kidney damage in men and women on long-term lithium treatment

Authors' Contribution:

- A** Study Design
- B** Data Collection
- C** Statistical Analysis
- D** Data Interpretation
- E** Manuscript Preparation
- F** Literature Search
- G** Funds Collection

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Summary

Background:

Lithium is the most effective therapeutic modality for the prevention of recurrences in bipolar disorder. An important adverse effect of lithium, especially with long-term treatment, is a possibility of a toxic effect on kidney function. Therefore, the aim of the study was to assess kidney function in a group of long-term lithium-treated patients.

Material/Methods:

The study comprised 80 patients with bipolar mood disorder (26 male, 54 female), aged 60±11 years. They had been receiving lithium for 5–38 (16±9) years. Random urine sample was examined for albumin and creatinine excretion, and urinary albumin to creatinine ratio (UACR) was calculated. Specific gravity of the urine sample was recorded. Serum concentration of creatinine was measured and estimated glomerular filtration rate (eGFR) was calculated. Serum concentration of albumin was also measured.

Results:

Decreased eGFR values <60 ml/min/1.73 m² were found in 23% of patients, significantly more frequently in men than in women (38% vs. 16%, p=0.04). Elevated UACR values (>30 mg/g) were found in 25% of men and 12% of women, respectively. Serum albumin concentration >52 g/l was detected in 19% of patients (17% of men and 20% of women). Specific gravity of the urine, equal to or below 1.005, was recorded in 21% of men and 14% of women.

Conclusions:

The results confirm the opinion that screening for the markers of kidney damage should be performed in long-term lithium-treated patients for identification of persons with impaired kidney function. Male sex seems to be the risk factor for the development of kidney damage during long-term lithium treatment.

key words:

lithium • kidney • glomerular filtration rate • creatinine

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BACKGROUND

Lithium is the most effective therapeutic modality for the prevention of manic and depressive recurrences in bipolar disorder [1]. Since its introduction for such purpose in 1963 [2], considerable concerns have been aroused about a possible negative effect of lithium on kidney function. Such evidence has been substantiated with increasing experience with lithium-treated patients receiving lithium for 10 years or more. In recent years, most clinicians treating patients with lithium longitudinally have been of the opinion that in such patients, a systematic monitoring of kidney function is required and, in case of major disturbances, collaboration with nephrologists is needed.

The most frequent renal lithium effect is a decrease of urinary concentration ability, which clinically manifests itself by polyuria and polydipsia of various intensities. In lithium-treated patients, urinary concentrating capacity is diminished by about 10–30%, which results in the increase of urine volume by about 10–60% [3]. Extreme impairment of the lithium-induced urinary concentrating ability may lead to nephrogenic diabetes insipidus. A case of this complication occurred in our department and was reported 40 years ago [4]. In some patients receiving lithium for 10–20 years, chronic interstitial nephropathy may develop, first described in renal biopsy specimens 35 years ago [5]. The nephropathy results in increased serum creatinine and a reduction of glomerular filtration rate (GFR). Duration of lithium treatment is the main predisposing factor for nephropathy, which, in a small proportion of patients can result in end-stage renal disease [6]. An infrequent complication of lithium therapy may be nephrotic syndrome [7].

The results of studies performed in the last decade have confirmed that a substantial proportion of lithium-treated patients have a reduced GFR [8–10]. This is connected with the duration of lithium treatment, and is significantly more frequent in lithium-treated than in age-matched, non-lithium-treated subjects. The nephropathy can lead to renal failure, but this is uncommon [6,11]. The most recent review of lithium toxicity profile, including 30 studies of renal effects in long-term lithium patients, revealed a reduction in maximum urinary concentrating ability by about 15%, a mean reduction of GFR of 0.5 ml/min per year of lithium treatment, and a significantly lower GFR in lithium patients than that of age-matched controls. The risk of end-stage renal disease in lithium-treated patients was approximately 0.5% [12].

The aim of the study was to screen for some markers of kidney damage in a large group of men and women treated with lithium preparation, and to evaluate the sex-associated differences.

MATERIAL AND METHODS

Patients

The study comprised 80 patients with bipolar mood disorder, aged 36–82 (60±11) years. There were 26 men, aged 38–78 years; and 54 women, aged 38–82 years. Consensus diagnosis by at least 2 psychiatrists was made for each patient, according to DSM-IV criteria (SCID) [13]. The mean duration of bipolar illness was 6–50 (24±10) years. The

patients had been treated with lithium carbonate for 5–38 (16±9) years. In 20 patients (25%), lithium had been used as monotherapy, and in the remaining 60 it was administered with other psychotropic medications. Serum concentration of lithium had been maintained in the range of 0.5–0.8 mmol/l. Throughout the period of lithium treatment, the patients had been followed by the same outpatient clinic, the Department of Psychiatry, University of Medical Sciences in Poznan. If they needed hospitalization, they were hospitalized in the same institution (inpatient clinic, Department of Adult Psychiatry, University of Medical Sciences in Poznan).

A semi-structured questionnaire was used for registering patient clinical data, including concomitant medications and somatic conditions. Twenty-three patients had hypertension, 16 had thyroid dysfunction, and 6 had type 2 diabetes.

Table 1 presents clinical characteristics of all patients, divided into 2 subgroups by sex.

There were no differences between male and female lithium-treated patients in age, duration of illness, duration of lithium therapy, or mean serum lithium level.

Measures

The concentration of creatinine was measured in serum and urine by enzymatic method with creatininase. Estimated glomerular filtration rate (eGFR) was calculated according to the MDRD formula [14]. eGFR values <60 ml/min/1.73 m² were classified as moderately reduced [14,15]. The concentration of albumin in serum was measured by colorimetric method, and the concentration of microalbumin in urine was measured by the immuno-turbidimetric method. Urinary excretion rate of microalbumin was calculated in mg/g creatinine (UAER). Random urine samples were examined, with special attention to specific gravity.

The results are presented as the mean ±SD or median and range of the values, as appropriate. For comparative purposes, Student's t test and chi-square test were used where appropriate, and Pearson correlations were calculated.

The study was approved by the Bioethics Committee, Poznan University of Medical Sciences. After complete description of the study to the subjects, written informed consent was obtained from all of them.

RESULTS

The mean ±SD serum concentration of creatinine (Scr) in all patients was 1.0±0.2 mg/dl; in 29% of them the values exceeding the upper normal limit (1.2 mg/dl) were detected. Scr values were higher in men than in women (1.2±0.3 and 0.8±0.1 mg/dl, respectively), but did not differ markedly. However, men had 46% elevated Scr values, significantly higher than 21% in women (p=0.027).

The mean ±SD and range of values of eGFR in all patients and in the subgroups of men and women are shown in Table 2. The percent of moderately reduced eGFR values is also presented. The mean of eGFR for all patients averaged 70 ml/min/1.73 m². eGFR values <60 ml/min/1.73 m² were

Table 1. Clinical characteristic of lithium-treated patients.

	Total N=80 Mean ±SD (range)	Men\ N=26 Mean ±SD (range)	Women N=54 Mean ±SD (range)
Age (years)	60±11 (36–82)	58±10 (36–78)	61±11 (38–82)
Duration of illness (years)	24±10 (6–50)	25±11 (9–50)	23±10 (6–43)
Duration of lithium administration (years)	16±9 (5–38)	17±9 (5–38)	15±9 (5–38)
Serum lithium concentration (mmol/l)	0.65±0.14	0.65±0.11	0.65±0.16

Table 2. Estimated glomerular filtration rate (eGFR) in all patients studied and in the subgroups of men and women.

	eGFR (ml/min/1.73 m ²) Mean ±SD (range)	Percentage of patients with eGFR <60 ml/min/1.73 m ²
All patients (n=74)	70±14 (32–108)	23%
Men (n=24)	67±17 (32–99)	38%*
Women (n=50)	71±12 (48–108)	16%

* Significant difference vs. women, p=0.04.

Table 3. Urinary albumin to creatinine ratio (UACR) in all patients studied and in the subgroups of men and women with the percentage of persons with UAER >30 mg/g and UAER >300 mg/g.

	UAER (mg/g) Median (range)	% of patients with UAER >30 mg/g	% of patients with UAER >300 mg/g
All patients (n=49)	19.2±51.4 (0.02–349)	16%	2%
Men (n=16)	12.2±12.6 (0.04–37.4)	25%	0%
Women (n=33)	22.5±62.5 (0.02–349.4)	12%	3%

Table 4. Serum albumin (Salb) concentration in all patients studied and in the subgroups of men and women.

	Salb Mean ±SD (range)	Percentage of patients with Salb >52 g/l
All patients (n=75)	46.4±5.6 (32.8–62.0)	19%
Men (n=24)	45.9±6.1 (32.8–56.1)	17%
Women (n=51)	46.6±5.4 (36.7–62.0)	20%

found in 23% of them, significantly more frequently in men (38%) than in women (16%, p=0.022). The distribution of UAER values was not normal; the values ranged from 0.02 to 349 mg/g (median 5.9 mg/g) in all patients (Table 3). UACR values exceeding 30 mg/g were more frequent in men (25%) than in women (12%). There was only 1 UACR value in the macroalbuminuric range (1 female). The mean ±SD of serum albumin concentration (Salb) averaged 46 g/l in all patients

Table 5. Urine specific gravity (Usg) in all patients studied and in the subgroups of men and women.

	Usg of the urine sample Mean ±SD (range)	Percentage of patients with Usg ≤1.005
All patients (n=75)	1.013±0.007 (1.003–1.032)	16%
Men (n=24)	1.012±0.007 (1.003–1.025)	21%
Women (n=51)	1.013±0.007 (1.003–1.032)	14%

and in the subgroups of men and women (Table 4). Salb values exceeding 52 g/l were found in 17% of men and 20% of women. The specific gravity (Usg) of random urine sample in the patients was low, averaging 1.013 (Table 5). Usg values were equal or lower than 1.005 in 21% of men 14% of women.

A multivariate analysis of the 3 measures – serum creatinine (Scr), eGFR, and serum albumin (Salb) – was performed with such variables as sex, age, duration of lithium therapy, monotherapy vs combination therapy, lithium level, and co-existing medical conditions. In men, but not in women, a tendency toward positive correlation between the duration of lithium therapy and Scr values was observed ($r=0.33$, $p<0.1$). In men, but not in women, a significant negative correlation was found between the age of the patients and eGFR values ($r=-0.55$, $p<0.005$), but the negative correlation between duration of lithium therapy and eGFR ($r=-0.23$) did not reach statistical significance. Salb level was correlated with lithium levels in female patients (0.38 , $p=0.012$), but not in males. No significant correlations were found in any of the studied markers of kidney damage with lithium monotherapy vs. combination therapy, or with any somatic conditions such as hypertension, thyroid dysfunction, or diabetes.

DISCUSSION

The results of our screening examination indicate that in a proportion of long-term lithium-treated patients, the markers of kidney damage can be detected. They include increased serum creatinine levels, glomerular filtration rate reduced below $60 \text{ ml/min/1.73 m}^2$, and increased urinary albumin excretion. These results confirm those of other studies and meta-analyses. Generally, the percentages of patients showing particular abnormalities are similar to those described in the recent literature.

The mean value of serum creatinine level in our group of patients ($1.0 \text{ mg/dl}=88 \mu\text{mol/l}$) was similar to that McCann et al. [16] ($85 \mu\text{mol/l}$) obtained in 59 patients, with mean age of 55 years, and using lithium for a mean of 9.5 years. The authors demonstrated a positive association between duration of lithium use and serum creatinine levels; this association was found at the level of statistical trend ($p<0.1$) only in male patients,.

Calculated GFR values are considered to be better indicators of kidney function than are Scr values [14]. The mean value of eGFR in our study was similar to the GFR value reported by Tredget et al. [10] in their group of 61 patients using lithium for a mean of 15.6 years (70 vs. $66 \text{ ml/min/1.73 m}^2$, respectively). The percentage of patients showing eGFR $<60 \text{ ml/min/1.73 m}^2$ in our patients was slightly lower than in their study (23% vs. 34.4% , respectively), but it was similar to their's in our subgroup of male patients. Tredget et al. [10] did not compare GFR in men and women.

In our study, eGFR values negatively correlated with age in men, but not in women. It was established that GFR values decline with increasing age in the general population [18]. It is also known that male sex is a risk factor for progression of kidney function impairment. Therefore, it seems reasonable to assume that men are more susceptible than women to kidney injury associated with long-term lithium therapy. However, a significant association between the duration of lithium treatment and eGFR in men was not demonstrated in our cross-sectional screening study. This assumption is in agreement with the results of a recent study by Bendz et al. [11], performed in 3369 lithium-treated Swedish patients. The authors revealed that end-stage chronic kidney disease associated with long-term lithium therapy developed in about 1.2% of patients, mostly men [11].

The increase of albuminuria expressed as urinary albumin/creatinine ratio (UACR), mainly in the microalbuminuric range, was found in 16% of our patients. Danish investigators found a significant elevation of urinary albumin excretion in lithium-treated patients compared to control subjects [17], but they did not estimate the percentage of lithium-treated patients who had abnormal albuminuria. In our study, increased albuminuria was found twice as frequently in men than in women. It is known that increased albuminuria is an early marker of kidney damage [14].

An unexpected finding in our study was the fairly high percentage (19%) of patients with high serum albumin ($>52 \text{ g/l}$). In female patients, Salb significantly correlated with lithium level. Hyperalbuminemia is mainly associated with dehydration [14], but our patients did not show other signs of dehydration. It may be speculated that in lithium-treated patients demonstrating hyperalbuminemia, an impaired urine concentrating ability caused polyuria, which was not adequately corrected by increased fluid intake, and resulted in hemo-concentration. In 16% of our patients the specific gravity of the random urine sample was <1.005 , suggesting polyuria, but serum albumin concentration did not correlate with the specific gravity of the random urine sample ($r=0.09$, NS). The tendency to hyperalbuminemia in long-term lithium-treated patients has not yet been reported and needs further observation.

There have been few studies on the markers of kidney damage during long-term lithium administration in relation to sex.

The results of the present study indicate that male patients may be more vulnerable to a possible renal impairment connected with long-term lithium therapy. Therefore, while systematic monitoring of lithium function in all patients taking lithium for 10 years should be mandatory, male patients should be the subject of special attention in this respect.

CONCLUSIONS

The results confirm that screening for markers of kidney damage should be performed in long-term lithium-treated patients for identification of persons with impaired kidney function. Male sex seems to be a risk factor for the development of kidney damage during long-term lithium treatment.

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