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Reduced Relative Risk of Fractures Among Users of Lithium

P. Vestergaard, L. Rejnmark, L. Mosekilde

Department of Endocrinology and Metabolism C, Aarhus University Hospital, Aarhus Sygehus, Aarhus, Denmark

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Abstract. Lithium has been shown to inhibit bone resorption and to interact with Wnt signaling, potentially pointing to bone anabolic properties. We, therefore, studied the effects of lithium on fracture risk using a case–control study design. Cases were all subjects including children with any fracture sustained during the year 2000 (n = 124,655). For each case, three controls (n = 373,962) matched according to age and gender was randomly drawn from the background population. Adjustments were made for use of other psychotropic drugs (neuroleptics, antidepressants, and anxiolytics/sedatives), psychiatric disease (manic depressive states, schizophrenia, and other psychoses), and other confounders. The effect of dose was examined by stratifying for cumulated dose (DDD, defined daily dose). In the crude analysis, there was a decreasing relative risk of any fracture with increasing accumulated dose of lithium. After adjustment for psychotropic drug use, the risk of any fracture was decreased (odds ratio [OR] 0.74, 95% confidence interval [CI] 0.60–0.92 for 250–849 DDD, and OR 0.67, 95% CI 0.55–0.81 for ≥ 850 DDD of lithium). For Colles' fractures and spine fractures, a significant decrease was seen with ≥ 850 DDD (OR 0.57, 95% CI 0.35–0.94 for Colles' fracture and OR 0.32, 95% CI 0.11–0.95 for spine fractures). For hip fractures, a nonsignificant trend toward a decrease was seen; however, without a dose-response relationship. Adjustment for further confounders did not change the results. Lithium treatment was associated with a decreased risk of fractures potentially pointing at bone anabolic properties.

Key words: Fracture — Lithium — Epidemiology — Risk

Lithium can be used to treat manic-depressive states. In early studies, lithium was associated with a decreased bone mineral content (BMC) in the forearm [1–3] and bone mineral density (BMD) of the lumbar spine [4], possibly mediated through induction of hyperparathyroidism [2, 5–7]. However, these studies were in some cases performed in small groups [4, 5], and correction for use of other boneactive medications was not possible.

In contrast, more recent studies have demonstrated that the use of lithium is not a risk factor for osteoporosis [8, 9]. In fact, the BMD of the lumbar spine and femoral neck tended to be higher than that in normal controls [9].

The molecular effects of this may include an effect on Wnt signaling [10], inhibition of the effects of 1,25-dihydroxyvitamin D [11], and interference with the calcium-sensing receptor [12]. However, in humans exposed to lithium, many factors may interfere with the effects of lithium. The patients may be exposed to neuroleptics [13], antidepressants (selective serotonin reuptake inhibitors [14], tricyclic antidepressants and others [15, 16]), and anxiolytics and sedatives [17–19], all of which may contribute to decrease BMD or increase fracture risk by increasing the risk of falling. Depression *per se* may also be associated with decreased BMD [20, 21].

Furthermore, behavioral disturbances linked to the underlying disease may increase the risk of trauma, and socioeconomic deprivation [22] following the underlying disease may also be associated with an increased fracture risk.

We studied the risk of fractures in subjects exposed to lithium in a population-based setting, adjusting for the use of other psychotropic drugs, the underlying disease, and other confounders, to examine if the fracture risk was decreased in users of lithium compared to the background population.

Subjects and Methods

Study Designs

The study was designed as a case–control study. All subjects of all ages including children sustaining a fracture during the year 2000 in Denmark were included as cases (n = 124,655), and, for each case, three subjects of the same age (same birth year)

Correspondence to: P. Vestergaard; E-mail: p-vest@post4.tele.dk

and gender were randomly selected from the background population as controls (n = 373,962). Both high- and low-energy fractures were included.

Endpoints

The study endpoints were occurrence of any fracture (International Classification of Diseases 10th edition [ICD10] codes: S02.0–S02.9, S07.0–S07.9, S12.0–S12.9, S22.0–S22.9, S32.0–S32.8, S42.0–S42.9, S52.0–S52.9, S62.0–S62.9, S72.0–S72.9, S82.0–S82.9, and S92.0–S92.9) between January 1, 2000, and December 31, 2000. In Denmark, almost all patients with fractures are managed in the hospital system (also including the emergency rooms) [23]; even fractures sustained abroad are registered upon return for insurance reasons. The capture of fractures is therefore very high.

Exposure Variables

The primary exposure variable was use of lithium (Anatomical Chemical Classification [ATC] code: N05AN01). Ever use of lithium was defined as having at least one prescription of lithium during the period from January 1, 1996, to the date of fracture, or the dummy date corresponding to this among the controls in the year 2000. The total dose of lithium was calculated as number of defined daily dose (DDD) purchased in the period specified.

The secondary exposure variables were (A) use of (1) neuroleptics, (2) antidepressants, or (3) anxiolytics or sedatives, and (B) presence of (1) manic-depressive states, (2) schizophrenia, or (3) other psychoses. Confounders were (1) a diagnosis of alcoholism, (2) a prior fracture [24], (3) use of corticosteroids [25], and (4) use of antiepileptic drugs [26]. The latter is important as some antiepileptic drugs may be used to treat psychoses because epilepsy and psychoses may coexist, and because antiepileptic drugs may increase fracture risk [26]. Ever use of other drugs was defined in the same way as for lithium, that is, as having had at least one prescription of the drug in question from January 1, 1996, to the date of fracture, or the corresponding dummy date among the controls.

The presence of psychiatric diseases was defined from the Psychiatric Central Register as at least one occurrence of the diagnosis in question from January 1, 1968, to the date of fracture or the corresponding dummy date among the controls.

Adjustment for comorbidity was done using the Charlson index, which is a validated index of 19 items of comorbid conditions (acute myocardial infarction, cancer, liver disease, kidney disease, and chronic obstructive pulmonary disease, among others) [27]. The data for the Charlson index were retrieved from the National Hospital Discharge Register for the period of 1977 to 2000.

The proxy variables for disease severity were (1) number of bed days in hospital the year before the fractures and (2) number of contacts to general practitioner or practicing specialist. The variables for socio economic deprivation were (1) working or not, (2) income in the year of the fracture (dichotomized by average income), and (3) living alone or together with another person.

Registers Used

The information on fracture occurrence and occurrence of other diseases, prior fractures, alcoholism, etc., came from two registers: (1) The National Hospital Discharge Register [28], and (2) The Psychiatric Central Register [29]. The study was subject to control by the National Board of Health and the Danish Data Protection Agency.

The National Hospital Discharge Register was founded in 1977 [28]. It covers all in-patient contacts from 1977 to 1994, and from 1995 also all outpatient visits to hospitals, outpatient clinics, and emergency rooms [28]. Upon discharge, the physician codes the reason for the contact by using the ICD system. The code used is at the discretion of the individual physician. The register has a nationwide coverage, and an almost 100% capture of contacts [28]. In general, the validity of registrations is high [30], especially for fractures, for which a precision of 97% has been reported for fractures treated both on an inpatient basis and for fractures treated on an outpatient basis via emergency rooms (e.g., a forearm fracture) [31]. The cases occurred only once in the analyses, with the first occurrence of an incident fracture during the year 2000.

The Psychiatric Central Register was founded in 1968 and covers all in- and outpatient contacts to Danish mental hospitals [29]. It has a nationwide coverage, and a high validity of diagnoses has been reported [23]. This register also uses the ICD system for coding contacts. The National Health Service keeps a register of all contacts to general practitioners for reimbursement purposes. The register does not contain ICD codes for the contacts but codes for the nature of the contact (regular check-up visit, routine vaccination in children, etc.). The Danish Medicines Agency keeps a nationwide register of all drugs sold at pharmacies throughout the country from 1996 and onward (The National Pharmacological Database run by the Danish Medicines Agency—http://www.dkma.dk). Any drugs bought are registered with ATC code, dosage sold, and date of sale for the period January 1, 1996 to December 31, 2000. Because all sales are registered to the individual who redeemed the prescription, the capture and validity is high. Information on income was obtained from the tax authorities, and information on working status and marital status from the National Bureau of Statistics (Statistics Denmark).

It is possible to link these sources of information through the Central Person Register Number which is a unique registration code given to every inhabitant—to some degree similar to the American social security number—that allows registration on an individual basis.

Statistical Analyses

Median, range, and 95% percentiles were used as descriptive statistics. Crude and adjusted odds ratios (ORs), and 95% confidence intervals (CIs) were calculated. A conditional logistic regression analysis was used to assess the association between any fracture and the exposure variable.

In the analysis plan, crude ORs for use of lithium were first calculated. In the second step adjustments for use of neuroleptics, antidepressants, and anxiolytics/sedatives were made; in the third step, presence of psychiatric comorbidity (manic depressive disease, schizophrenia, or other psychoses), and use of corticosteroids and antiepileptic drugs were introduced. In the final step, number of bed days in 1999, number of contacts to general practitioners or specialists in 1999, Charlson index, working or not, income in 1999, and living with another person versus living alone were introduced as confounders. Because lithium may introduce hyperparathyroidism, adjustments for occurrence of hyperparathyroidism were also made.

The dose–response analysis was performed for cumulated dose (DDD — one DDD equals 24 mmol of lithium) for lithium from January 1, 1996, to date of censoring. The average daily dose was calculated as total number of DDDs divided by the time interval from first prescription to date of censoring. It did not change the results to change from the cumulated dose to the average number of DDDs per day.

Age ($\geq$ 60 years vs. $<$60, and $\geq$?50 years vs. $<$ 50) and gender-stratified analyses were also performed. A separate analysis including cumulated DDDs for lithium, as a continuous variable was also performed.

Analyses were performed using STATA 8.1 (STATA Corp., College Station, TX, USA) and SPSS 10.1.0 (SPSS Inc., Chicago IL, USA), both in the UNIX version.

Table 1. Characteristics of patients and controls — any fracture

Variable	Cases (n = 124,655)	Controls (n = 373,962)	P
Age (yr, median and range)	42 (1–100)	42 (1–100)	—
Gender			—
Men	60,107 (48.2%)	180,321 (48.2%)	
Women	64,548 (51.8%)	193,641 (51.8%)	
Annual income (DKR)[a]	125,665 (7,519–368,193)	132,743 (6,889–402,080)	< 0.01
Marital status			< 0.01
Widowed	18,365 (14.8%)	52,550 (14.2%)	
Divorced	10,423 (8.4%)	23,239 (6.3%)	
Married	35,859 (28.9%)	123,719 (33.3%)	
Unmarried	59,335 (47.8%)	171,349 (46.2%)	
Other	90 (0.1%)	264 (0.1%)	
Occupational status			< 0.01
Independent	3,374 (3.3%)	11,816 (3.9%)	
Assisting wife	209 (0.2%)	951 (0.3%)	
Working	37,797 (36.9%)	124,984 (40.8%)	
Retired	40,201 (39.3%)	109,447 (35.7%)	
Other	20,752 (20.3%)	59,278 (19.3%)	
Charlson index[b]			< 0.01
0	97,256 (78.0%)	314,099 (84.0%)	
1–2	19,634 (16.8%)	47,745 (12.8%)	
3–4	5,450 (4.4%)	9,132 (2.4%)	
≥5	2,315 (1.9%)	2,986 (0.8%)	
Previous fracture	41,315 (33.1%)	56,200 (15.0%)	< 0.01
Number of bed days in hospital in 1999[a]	0 (0–45)	0 (0–19)	< 0.01
Contacts to GP or specialists in 1999[a]	11 (0–86)	9 (0–64)	< 0.01
Alcoholism	8,863 (7.1%)	9,473 (2.5%)	< 0.01
Antiepileptic drugs	7,091 (5.7%)	10,974 (2.9%)	< 0.01
Sedatives, anxiolytics, and hypnotics	35,840 (28.8%)	82,766 (22.1%)	< 0.01
Neuroleptics	9,738 (7.8%)	17,243 (4.6%)	< 0.01
Antidepressants	18,511 (14.8%)	34,521 (9.2%)	< 0.01
Inhaled β-agonists	23,898 (19.2%)	60,943 (16.3%)	< 0.01
Other inhaled bronchodilators	1,756 (1.4%)	3,440 (0.9%)	< 0.01
Schizophrenia	765 (0.6%)	1,580 (0.4%)	< 0.01
Manic-depressive states	3,702 (3.0%)	6,939 (1.9%)	< 0.01
Other psychoses	2,565 (2.1%)	4,594 (1.2%)	< 0.01
Ever use of lithium	440 (0.4%)	963 (0.3%)	< 0.01
Age of lithium users (yr, median and range)	65 (17–93)	65 (18–97)	0.22
Gender distribution of lithium users			0.69
Men	126 (28.6%)	266 (27.6%)	
Women	314 (71.4%)	697 (72.4%)	

[a] Median and 95% percentile
[b] A composite index of 19 comorbid conditions (see text)
DKR, Danish Kronor; GP, general practitioner

Results

Table 1 shows baseline characteristics of the cases and controls. The cases and controls were well matched concerning age and gender. The fracture cases more often were retired individuals and thus had a lower income. In addition, the cases were more often unmarried. The comorbidity and use of drugs in general was higher among cases than among controls. The age and gender distribution among lithium users was similar in cases and controls. However, the lithium users were older and fewer were men than in the entire population.

Table 2 shows the age and gender characteristics according to the individual fractures.

Table 3 shows the risk of any fracture associated with use of lithium. In the crude analysis, there was an increased fracture risk among users of low accumulated doses of lithium compared to never users. However, the relative fracture risk decreased with increasing dose ($2P < 0.01$ by test for trend). Upon adjustment for concomitant use of other psychotropic drugs (antidepressants, neuroleptics, and anxiolytics/sedatives), the increased fracture risk disappeared and use of lithium was associated with a decreased fracture risk. The introduction of further confounders did not change the risk estimates by much.

The increased fracture risk associated with neuroleptics, antidepressants, and anxiolytics/sedatives was

Table 2. Age and sender characteristics of the individual fractures

Characteristic	Hip	Colles'	Spine
Age (yr, median and range)	81 (1–100)	38 (1–100)	64 (1–99)
Gender			
Men	2,975 (28.3%)	7,684 (38.4)	1,506 (44.8%)
Women	7,555 (71.7%)	12,351 (61.2%)	1,858 (55.2%)
Ever use of lithium			
Cases	73 (0.7%)	63 (0.3%)	16 (0.5%)
Controls	149 (0.5%)	144 (0.2%)	34 (0.3%)

Table 3. Risk of any fracture

Variable	Crude OR	Drug adjusted[a]	Disease and drug adjusted[b]	Multiply adjusted[c]
Lithium use				
<250 DDD	1.84 (1.52–12.22)	1.03 (0.85–1.24)	0.88 (0.72–1.07)	0.96 (0.78–1.18)
250–849 DDD	1.33 (1.08–1.63)	0.74 (0.60–0.92)	0.64 (0.51–0.79)	0.71 (0.57–0.89)
≥850 DDD	1.08 (0.89–1.31)	0.67 (0.55–0.81)	0.58 (0.47–0.70)	0.72 (0.59–0.89)
Alcoholism	2.95 (2.86–3.03)	—	—	2.10 (2.03–2.17)
Prior fracture	2.69 (2.44–2.97)	—	—	2.41 (2.37–2.45)
Corticosteroid use	1.16 (1.14–1.17)	—	1.08 (1.07–1.09)	1.02 (1.00–1.04)
Antepileptic drug	2.45 (2.09–2.87)	—	1.59 (1.54–1.64)	1.31 (1.27–1.36)
Anxiolytics and sedatives	1.91 (1.74–2.09)	1.21 (1.19–1.23)	1.16 (1.14–1.18)	1.04 (1.02–1.06)
Neuroleptics	1.99 (1.75–2.26)	1.36 (1.32–1.40)	1.29 (1.25–1.32)	1.14 (1.10–1.18)
Antidepressants	2.33 (2.10–2.58)	1.43 (1.40–1.46)	1.37 (1.34–1.40)	1.23 (1.20–1.26)
Schizophrenia	1.46 (1.34–1.59)	—	0.88 (0.78–0.96)	0.90 (0.82–1.00)
Manic-depressive states	1.62 (1.56–1.69)	—	1.04 (1.00–1.09)	0.99 (0.94–1.03)
Other psychoses	1.69 (1.61–1.77)	—	1.17 (1.10–1.23)	1.02 (0.97–1.09)

[a] Adjusted for use of anxiolytics/sedatives, neuroleptics, and antidepressants
[b] Adjusted for use of anxiolytics/sedatives, neuroleptics, and antidepressants, schizophrenia, manic-depressive states, other psychoses, use of corticosteroids, and use of antiepileptic drugs
[c] Adjusted for use of anxiolytics/sedatives, neuroleptics, and antidepressants, schizophrenia, manic-depressive states, other psychoses, use of corticosteroids, and use of antiepileptic drugs, number of bed days in 1999, number of contacts to general practitioners or specialists in 1999, Charlson index, working or not, income in 1999, living with another person versus living alone
DDD, defined daily dose; OR, odd ratio

attenuated upon adjustment for confounders but did not disappear completely.

The increased fracture risk associated with schizophrenia, manic-depressive states, and other psychoses also disappeared after introduction of confounders. Restricting the analysis to any fracture excluding hip, Colles' and spine fractures did not change the results.

Table 4 shows the fracture risk associated with lithium at various skeletal sites. In these analyses, the same trends as for any fracture were present for Colles' fractures and for spine fractures. At high-accumulated doses a decreased fracture risk was seen in users of lithium. At low doses an increased fracture risk was present for Colles' fractures, and a trend was seen for spine fractures. For hip fractures a nonsignificant risk reduction was seen with use of lithium, but no trend with doses was present (Fig. 1). Changing the analysis from cumulated to average daily dose did not significantly change the results. In this analysis, the reduction in overall fracture risk was seen from a daily dose of 0.25 DDD/day (equal to 6 mmol lithium per day).

The results did not change by adjusting for the occurrence of hyperparathyroidism. Age and gender stratification did not change the results. In particular did exclusion of childhood. Including lithium use as a continuous variable showed a significantly decreasing trend for the risk of fractures with increasing dose of lithium for any fracture and for the spine, but not for the hip and for Colles' fractures.

Discussion

In this study we have demonstrated a decreased fracture risk among users of lithium for any fracture with a trend toward a decrease for Colles' fracture and spine fracture. No significant decrease was present for hip fractures. To our knowledge this is the first study with fracture risk as end-point among subjects exposed to lithium.

One prior study reported a decreased forearm BMC in bipolar patients, but not in unipolar patients [1]. However, the daily lithium dose tended to be higher in bipolar (mean ± SD 28.8 ± 8.3 mmol/day) than in

Table 4. Risk of fractures at various skeletal sites

Skeletal site	Variable	Crude OR	Drug adjusted[a]	Multiple adjusted[b]
Hip fracture	Lithium use			
	<250 DDD	1.35 (0.77–2.36)	0.59 (0.34–1.04)	0.75 (0.42–1.36)
	250–849 DDD	1.50 (0.94–2.40)	0.71 (0.44–1.14)	0.78 (0.47–1.30)
	≥850 DDD	1.53 (0.98–2.39)	0.81 (0.51–1.28)	0.85 (0.52–1.40)
	Alcoholism	4.61 (4.10–5.19)	—	3.05 (2.69–3.46)
	Prior fracture	2.56 (2.44–2.68)	—	2.07 (1.97–2.17)
	Anxiolytics and sedatives	1.74 (1.66–1.82)	1.33 (1.27–1.40)	1.14 (1.08–1.20)
	Neuroleptics	2.24 (2.12–2.38)	1.69 (1.59–1.80)	1.50 (1.41–1.61)
	Antidepressants	2.38 (2.27–2.50)	1.93 (1.83–2.03)	1.68 (1.58–1.78)
	Schizophrenia	2.42 (1.79–3.26)	—	1.50 (1.07–2.08)
	Manic-depressive states	1.75 (1.59–1.93)	—	0.88 (0.79–0.99)
	Other psychoses	2.09 (1.84–2.38)	—	1.09 (0.95–1.27)
Colles' fracture	Lithium use			
	<250 DDD	2.90 (1.74–4.83)	1.84 (1.10–3.08)	1.61 (0.94–2.75)
	250–849 DDD	1.02 (0.56–1.88)	0.66 (0.36–1.22)	0.61 (0.33–1.16)
	≥850 DDD	0.82 (0.50–1.35)	0.57 (0.35–0.94)	0.58 (0.34–0.99)
	Alcoholism	2.69 (2.45–2.95)	—	2.10 (1.90–2.31)
	Prior fracture	2.11 (2.03–2.19)	—	1.91 (1.82–2.01)
	Anxiolytics and sedatives	1.22 (1.18–1.27)	1.06 (1.02–1.11)	1.03 (0.98–1.08)
	Neuroleptics	1.49 (1.39–1.59)	1.24 (1.15–1.33)	1.11 (1.02–1.20)
	Antidepressants	1.52 (1.44–1.60)	1.39 (1.31–1.47)	1.28 (1.20–1.36)
	Schizophrenia	1.25 (0.96–1.63)	—	0.85 (0.64–1.14)
	Manic-depressive states	1.46 (1.31–1.63)	—	1.02 (0.90–1.15)
	Other psychoses	1.44 (1.26–1.64)	—	0.95 (0.82–1.11)
Spine fracture	Lithium use			
	<250 DDD	4.00 (1.39–11.5)	1.98 (0.67–5.84)	2.32 (0.75–7.17)
	250–849 DDD	1.71 (0.50–5.86)	0.80 (0.23–2.76)	0.90 (0.25–3.26)
	≥850 DDD	0.57 (0.20–1.67)	0.32 (0.11–0.95)	0.31 (0.10–1.02)
	Alcoholism	3.09 (2.62–3.65)	—	2.02 (1.68–2.41)
	Prior fracture	2.80 (2.57–3.06)	—	2.34 (2.13–2.56)
	Anxiolytics and sedatives	1.83 (1.69–1.98)	1.44 (1.32–1.57)	1.20 (1.09–1.32)
	Neuroleptics	1.97 (1.74–2.23)	1.36 (1.19–1.55)	1.19 (1.03–1.38)
	Antidepressants	2.32 (2.10–2.55)	1.82 (1.63–2.02)	1.55 (1.38–1.74)
	Schizophrenia	1.79 (1.09–2.94)	—	1.32 (0.74–2.35)
	Manic-depressive states	1.79 (1.47–2.18)	—	0.90 (0.71–1.14)
	Other psychoses	1.77 (1.38–2.27)	—	0.93 (0.69–1.24)

[a] Adjusted for use of anxiolytics/sedatives, neuroleptics, and antidepressants, schizophrenia, manic-depressive states, other psychoses, use of corticosteroids, and use of antiepileptic drugs
[b] Adjusted for use of anxiolytics/sedatives, neuroleptics, and antidepressants, schizophrenia, manic-depressive states, other psychoses, use of corticosteroids, and use of antiepileptic drugs, number of bed days in 1999, number of contacts to general practitioners or specialists in 1999, Charlson index, working or not, income in 1999, living with another person versus living alone.
DDD, define daily dose; OR, odds ratio

unipolar patients (26.0 ± 5.0 mmol/day, $P = 0.06$). The BMC in unipolar patients was a little higher than in normal controls (102%, nonsignificant), whereas the BMC of the bipolar patients was significantly reduced (88% of normal, $P < 0.01$) [1]. Similarly, Cohen et al. [8] reported normal BMD in the lumbar spine and femoral neck both in patients who had used lithium for less than 12 months (daily dose 22.3 mmol/day), and in patients treated for more than 3 years (daily dose 26.8 mmol/day). This could support the bimodal effect of lithium on mesenchymal stem-cell growth observed by De Boer et al. [10] with a stimulatory effect al low concentrations and an inhibitory effect at high concentrations.

On the cellular level, lithium has been shown to affect Wnt signaling in a bimodal manner—at low concentrations lithium increases the proliferation of human mesenchymal stem cells, whereas it inhibits the proliferation in high concentrations [10]. At low concentrations lithium may therefore possess bone-anabolic properties.

Lithium has also been shown to inhibit bone resorption by inhibiting the effects of 1,25-dihydroxy vitamin D [11, 32].

Lithium also interferes with the calcium-sensing receptor (CaSR) by decreasing the sensitivity to calcium, that is the "set-point" is increased, and parathyroid hormone (PTH) secretion is increased [12, 33]. The increase in PTH secretion following administration of lithium [12] may theoretically mimic the anabolic effects of PTH [34].

A negative correlation between duration of lithium treatment and femoral neck BMD [4] has been reported.

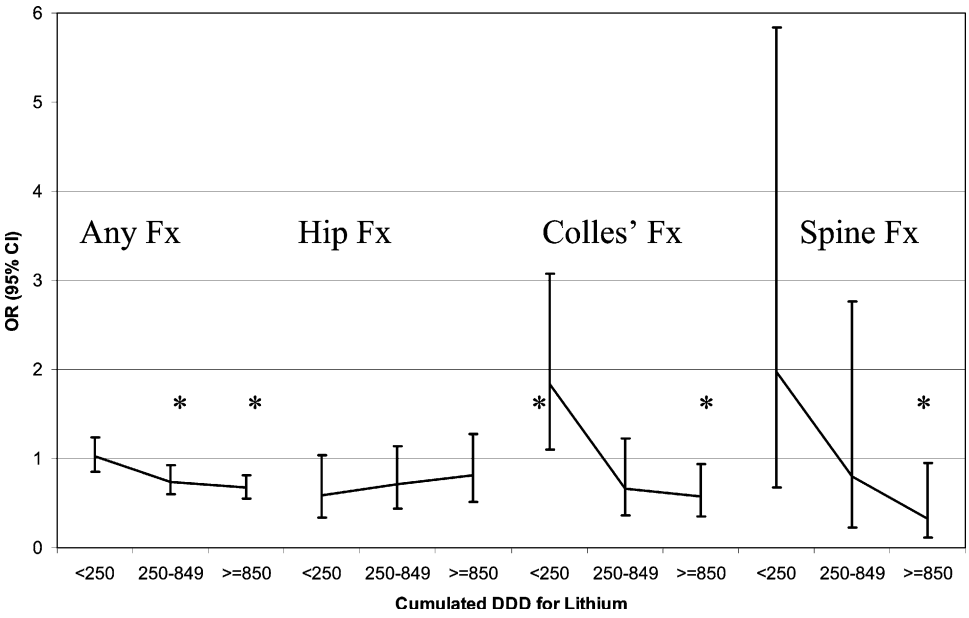

Fig. 1. Fracture risk (odds ratio–OR and 95% confidence intervals [CIs]) in users of lithium adjusted for concomitant use of neuroleptics, antidepressants, and anxiolytics/sedatives. *$2P < 0.01$ for comparison with the general population.

However, no correlation between forearm BMC, and daily dose of lithium, duration of lithium treatment, total lithium dose, and serum lithium could be found in another study [3]. Eren et al. also failed to show a correlation between serum lithium and spine or femoral neck BMD [4]. The absence of a correlation with serum lithium may be due to the fact that in most patients, serum lithium was aimed at being in therapeutical levels, that is, within a narrow interval.

In our study the positive effects were observed at average dosages well below 1 DDD (24 mmol/day or 889 mg of lithium carbonate per day), that is, below the dosage of 28 mmol/day reported by Baastrup et al. [1] to be associated with a decreased BMC of the forearm. Baastrup et al. [1], and Cohen et al. [8] failed to show a decrease in BMC or BMD at a dosage of 26 mmol/day. The positive effects of lithium may therefore be seen in dose intervals of 6 to 26 mmol/day (222–963 mg of lithium carbonate per day), that is, at low-to-average daily doses, whereas detrimental effects may be seen at concentrations just a little above the average daily dose.

In this context it must be remembered that lithium has a narrow therapeutic window and that adverse effects are severe and that treatment needs to be closely monitored by plasma concentration measurements. The dose of lithium needed to maintain therapeutic effects may also vary considerably between patients.

A single dose of lithium raises PTH levels acutely in humans [12], which may mimic the effects of intermittent PTH administration, which has been shown to possess strong bone-anabolic effects [34]. A study in patients on lithium also showed that although PTH levels were increased, urinary calcium excretion was reduced, suggesting a reduced bone resorption and perhaps a positive calcium balance [35]. However, at high doses administered for a long period a more constantly elevated PTH level may be induced, mimicking primary hyperparathyroidism leading to detrimental effects on bone [2, 5].

In our study, a decrease in overall relative fracture risk was seen with a cumulated dose of lithium of greater than 250 DDD, and for Colles, and spine fractures a statistically significant reduction was seen above a dose of 850 DDD. The reason that the statistically significant reduction was first seen at higher doses for spine and Colles' fractures may be the lower number of these fractures, that is, statistical significance could not be reached owing to wide confidence intervals, despite a reduction in relative risk. The reason that no significant reduction was present for hip fractures was not completely clear. It may be related to differences in bone architecture, the spine and forearm being more dominated by trabecular bone, whereas cortical bone constitutes a larger part of the hip, and the differential effects of PTH on cortical and trabecular bone.

The advantages of our study are that it is population based and includes almost all fracture cases. Almost all fracture cases are included as the register has nationwide coverage with a high capture rate [28], which limits selection bias. Information bias is limited because of the relatively high validity of fracture diagnoses [31] and the use of data from prescription databases. Furthermore, our data allow adjustment for multiple potential confounders.

The drawbacks are that we do not have BMD data, or data on serum calcium, serum PTH, and weight and height of the patients. The data on spine fractures may also be incomplete, as many cases of spine fractures are asymptomatic and therefore do not come to the attention of the health care system [36]. However, because

patients who are prescribed lithium and have psychiatric disorders are more likely to come into contacts with doctors, they may undergo spine X-rays more frequently and consequently may be more likely to have diagnosed otherwise asymptomatic spine fractures. This should theoretically have resulted in an excess risk of spine fractures. However, in fact, a reduction was seen, making it likely that lithium does in fact have a fracture–reducing potential. Our study was a case–control study. It is thus an observational study, and definitive evidence for a positive effect on bone mineral and fracture risk may come only from randomized controlled trials. Experiments on animal of cell cultures may also give important imformation. In the case–control study one of the fundamental problems is selecting an appropriate control group. In our study the control group came from the general population, and exposure date was sampled in the same way in cases and controls. As mentioned, psychiatric patients may be more likely to be diagnosed with fractures, especially of the spine, owing to the more intense monitoring while being under the care of health professionals, but this should tend to give more fractures among patients and not less. Because the data in our study came from public registers, recall bias was limited.

Almost no children in our study were exposed to lithium, and only few fractures of the spine and hip occurred in children. The results did not change upon exclusion of children. In our study alcoholism; a prior fracture; and use of anxiolytics/sedatives, neuroleptics, and antidepressants were associated with an increased fracture risk in most skeletal sites, the association being most pronounced for alcoholism and a prior fracture. Even after adjustment for these potential confounders, lithium treatment seemed associated with a decrease in relative fracture risk. These confounders were the reason that lithium users had an increased fracture risk in the crude analysis.

In conclusion use of lithium seems to be associated with a decreased risk of fractures after adjustment for use of other psychotropic drugs, possibly indicating a fracture-reducing potential of lithium. This may point to an anabolic effect of lithium through its interaction with Wnt signaling and effects on CaSR.

Future studies to corroborate the effects of lithium on bone mineral may include randomized controlled trials in osteoporotic subjects on the effects of lithium on bone mineral and perhaps fracture risk. Studies in animal and cell models on the effects lithium are also needed.

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