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ORIGINAL SCIENTIFIC REPORT

Characterization of Calcium Homeostasis in Lithium-Treated Patients Reveals Both Hypercalcaemia and Hypocalcaemia

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Abstract

Introduction Prevalence studies demonstrate that a significant proportion of lithium-treated patients develop hypercalcaemia (3–30%). Lithium-associated hyperparathyroidism (LHPT) is poorly defined, and calcium homeostasis may be affected in a more complicated fashion than purely by elevated PTH secretion. The current study aims to examine in detail calcium homeostasis principally with regard to lithium duration.

Methods Medical records of 297 lithium-treated patients (193 women, 104 men; median age 58 years) were examined, and information on gender, age, lithium treatment duration and calcium homeostasis was obtained. The median treatment duration with lithium was 16 (1.5–45) years.

Results A total of 8504 calcium values were retrieved. Before initiation of lithium treatment, serum calcium was on average 2.33 mmol/l (2.02–2.60). During the treatment period, 178 patients (60%) remained normocalcaemic, 102 (34%) developed hypercalcaemia or were strongly suspected of LHPT, 17 (6%) had 3 or more intermittent episodes of hypocalcaemia. Forty-one per cent of patients with suspected or confirmed LHPT had low (<4 mmol) 24-h urine calcium levels. The success rate after 33 parathyroidectomies was 35%, hyperplasia being diagnosed in 75% of extirpated glands.

Conclusions The prevalence of hypercalcaemia during lithium treatment is very high. In addition, hypocalcaemic episodes appear to occur frequently, possibly reflecting a more complicated parathyroid dysfunction than previously known. Long-term surgical results are unsatisfactory. LHPT biochemical profile is different from that of primary hyperparathyroidism and is in some ways similar to familial hypocalciuric hypercalcaemia.

Abbreviations

BD	Bipolar disorder
BNE	Bilateral neck exploration
FHH	Familial hypocalciuric hypercalcaemia
iCa	Serum ionized calcium concentration
IOPTH	Intraoperative parathyroid hormone
HPT	Hyperparathyroidism
LHPT	Lithium-associated hyperparathyroidism
MGD	Multiglandular disease
NCHPT	Normocalcaemic hyperparathyroidism
pHPT	Primary hyperparathyroidism
PTH	Parathyroid hormone
TCa	Serum total calcium concentration

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Introduction

Lithium remains a central therapeutic alternative in the pharmacological treatment of bipolar disorder (BD) and in suicide prevention [1]. Though lithium-associated hyperparathyroidism (LHPT) was first documented by Garfinkel et al. [2] in 1973, the endocrinopathy remains ill-defined. The prevalence of LHPT has been reported to be in the range of 3–30% [3–5]. The hitherto largest prevalence study has estimated the prevalence to be 18% [6], in stark contrast to the prevalence of primary hyperparathyroidism (pHPT) in the general population of approximately 0.5% [7]. While a plethora of theoretical models exist regarding lithium's role in the development of hypercalcaemia, the predominant conceptual model suggests that lithium affects the "set-point" of parathyroid glands by way of calcium sensing receptors [8, 9]. It is also purported that lithium may stimulate the nascent development or "de-masking" of parathyroid adenoma or hyperplasia [10, 11]. Thus, controversy still surrounds the histopathological background of LHPT [12, 13] and the appropriate management of the condition has yet to be fully demonstrated, with the risk of persistent or recurrent disease after routine parathyroidectomy alarming [14].

In previous studies, we have frequently noted a tendency of considerable inter- and intraindividual variation in calcium values in lithium-treated patients. Additionally, we have also noted that hypocalcaemia frequently occurs. The reason for these changes seems unclear, and any clinical significance remains to be properly detected and explained. The aim of the current study was therefore to describe, through a comprehensive retrospective examination of medical records, calcium homeostasis in a well-defined population. Further, we report the collective findings of a total of 33 parathyroidectomies in 29 lithium-treated patients between 1993 and 2017.

Materials and methods

On 1 January 2017, 314 lithium-treated patients were attending the Affective Disorders Out-patient Unit in Jönköping, Sweden. Jönköping is situated in the south of Sweden, and the municipality has approximately 135,000 inhabitants, where the prevalence of BD is comparable to other parts of Sweden. For inclusion in the study, all participants were 18 years old or older and had been medicated with lithium at least one year. This study enrolled 297 patients [193 women, 104 men; median age 58 years (range 21–92 years)] with a median lithium treatment duration of 16 years (1.5–45). In Jönköping, lithium-treated patients attending the Affective Disorder Out-patient Unit receive regular monitoring of blood chemistry, normally 3–4 times annually. Calcium monitoring has occurred here regularly, though not consistently, from 1999 with the introduction of computerized medical journals, but before this year determination of serum calcium was made only sporadically. Retrieval of medical records of those 29 individuals who had undergone parathyroidectomies was done in collaboration with the Department of Surgery at Ryhov Hospital in Jönköping.

Data collection

Data were collected from all hospital and primary healthcare charts from the start of each patient's lithium medication until the inspection period between January and April 2017. Verbal informed consent was obtained from all patients, and consent was witnessed and formally recorded. Demographic details including age, gender, lithium duration, thyroxine medication, principal psychiatric diagnosis and laboratory findings were recorded.

Calcium homeostasis was assessed on all available calcium values, predominantly total serum calcium concentration (TCa); when only ionized serum calcium concentration (iCa) values were available, the TCa was estimated arithmetically according to validated formulae [15]. Hypocalcaemia and hypercalcaemia were defined, respectively, according to national recommendations [16], where the agreed reference value for TCa = 2.15–2.50 mmol/l and for iCa 1.15–1.33 mmol/l. All calcium determinations were performed using the same biochemical assay and reference range. Every attempt was made to retrieve calcium values before the initiation of lithium treatment and was successful in 196 individuals (66%). Of those 101 individuals where calcium values were not retrieved, six had elevated calcium determinations in the first three-year period of lithium medication (6%), and it cannot be completely rejected that these patients had pHPT already at the start of lithium medication. On the other hand, 17 of the 188 patients with normocalcaemia before the start showed elevated calcium levels during the first 3 years (9%). Since the general belief is that the development of LHPT accumulates with time, we chose time periods of 3 years to be clinically relevant in the monitoring and assessment of any disturbances in calcium homeostasis. For each three-year period, all available calcium values were retrieved per patient and the lowest, highest and mean values were registered. In addition, the number of calcium values which were below or above the reference value was also noted. Further, all currently available laboratory parameters (including TCa, iCa, PTH, vitamin D as well as creatinine and phosphate), and any information concerning thyroid and/or parathyroid surgery were documented. In 66 cases (22%), in whom LHPT was established or highly suspected, additional biochemistry

was retrieved further to understand antecedent calcium disturbances or with a diagnostic aim. This included the assessment of 24-h urine calcium levels in 29 cases.

Indications for surgery and surgical performance

Fifty-one of the 66 patients with strongly suspected LHPT were referred to the team of endocrine surgery at Ryhov Hospital for operative evaluation. The indication for surgery was primarily intermittent hypercalcaemia in combination with an inappropriate increase in serum PTH concentration; however, preoperative investigations revealed that three individuals (all women) had osteopenia. Twenty-two were considered unsuitable for surgery due to high age, additional chronic diseases, marginally elevated calcium and/or the reluctance to be operated.

A total of 29 patients underwent parathyroidectomy performed by four separate surgeons experienced in endocrine surgery. Ten were investigated preoperatively with Sestamibi scintigraphy which revealed large adenomas in three patients (two remained cured at last follow-up), though there were indeterminate findings in seven cases. Focused parathyroidectomy was performed in the three cases with adenomas, and in the remaining 26 patients, the intention was to carry out a traditional four-gland exploration. All macroscopically enlarged parathyroid glands, as judged by the individual surgeon, were removed, and when doubt arose, a biopsy was conducted. Biopsy revealed normal parathyroid tissue in seven patients. Intraoperative PTH determinations were not used. No patient was subject for autotransplantation.

Definitions of normal and pathological calcaemic states

The normocalcaemic group was defined as patients having all calcium values within the normal range or, at most, two hypocalcaemic and/or two hypercalcaemic determinations during the complete period of lithium medication.

The hypocalcaemic group was defined as patients with three or more hypocalcaemic values during the study period. A maximum of two hypercalcaemic determinations were accepted.

The hypercalcaemic group consisted of patients with three or more hypercalcaemic values during the study period. Once again, a maximum of two hypocalcaemic determinations were accepted.

Established LHPT was defined as patients with hypercalcaemia and elevated PTH levels, in whom neck surgery had removed pathological parathyroid tissue.

Suspected LHPT was defined as patients with 5 or more increased calcium levels during lithium treatment, in the majority of cases combined with elevated PTH values.

Of those patients who had undergone surgery, cure was defined as normal calcium and PTH at the latest follow-up. Aberrant calcium and/or PTH suggested surgical failure and was further classified as persistent (elevated calcium 6 months postoperatively), recurrent (normal calcium at 6 months postoperatively but elevated values at the later follow-up), and Normocalcaemic Hyperparathyroidism (NCHPT, normal calcium but elevated PTH at the follow-up).

Ethics

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving patients were approved by the Central Ethics Review Board at The University of Uppsala, Sweden (Dnr 2014/435). Any additional laboratory tests were performed on a voluntary basis with full consent of participants.

Statistical analysis

Descriptive statistics included frequencies (percentages) and median values (ranges). Regression analysis was used to identify any correlation between calcium values and treatment duration. Normocalcaemic patients were compared to the two groups with pathological calcium values using Chi-squared test for categorical variables and from a median test for continuous variables. Two-tailed Student's unpaired t test was also utilized. Statistical significance was set at $p < 0.05$. Data were processed using SPSS (version 22).

Results

Seventy-five per cent of patients were diagnosed with BD. The dosage of lithium was prescribed and monitored by the patient's psychiatrist and adjusted according to the patient's psychological well-being and tolerance of the drug, irrespective of the current TCa or serum PTH concentrations. Median dosage of lithium for the whole group was 210 mg daily (range 42 – 420 mg) at the time for this investigation. A majority of patients used other psychiatric drugs such as antidepressants (181 individuals, 61%), whereas thiazide diuretics (three patients, 1%) and calcium supplementation (five patients, 2%) were used sparingly.

Before initiation of lithium treatment, the median TCa for the whole group was 2.33 (2.02–2.60) mmol/l. At the follow-up, after a median lithium treatment duration of 16 years (range 1.5–45), the median TCa was 2.34 (range

2.04–2.75) mmol/l. Four female patients were hypocalcaemic at treatment start, ranging in values from 2.02 to 2.14 mmol/l, but all patients were normalized with time. An additional four patients (two men and two women) had hypercalcaemia before lithium treatment: one patient normalized, one normalized but developed hypocalcaemia intermittently, one remained moderately hypercalcaemic even after 20 years of observation and, lastly, one patient underwent parathyroidectomy resulting in persistent disease.

A total of 8504 calcium values were retrieved during inspection of medical records, though 234 determinations were retrieved before lithium medication was started. Altogether, there were 6975 (82%) normocalcaemic values, though 147 (1.7%) values were below and 1148 (13.5%) values were above the normal range (2.15–2.50 mmol/l). The median time length between the start of lithium medication and the first hypercalcaemic value was 1.5 (range 1.5–44) years. Table 1 shows an analysis comparing the normocalcaemic group with the two categorized groups with pathological calcium values (see "Methods" section). All groups were predominantly female. In comparison with the normocalcaemic lithium-treated group, the two other groups showed statistical difference in age, calcium values, and lithium duration. Twenty-four of the 102 patients in the hypercalcaemic group had creatinine levels above the normal range but stable renal function, and none had end-stage renal dysfunction; this explains the significantly increased creatinine value in comparison with the normocalcaemic group (Table 1).

In the hypercalcaemic group, the median number of calcium determinations per participant was 36 (range 7–65), of which 20 (range 5.5–98.3)% were hypercalcaemic. Considerable variation in calcium levels existed in general, though particularly in patients belonging to the hypercalcaemic group (Fig. 1a), as witnessed continually over time, while the normocalcaemic group had a relatively stable calcium homeostasis (Fig. 1b).

Further, biochemistry was analysed in 66 patients with surgically confirmed or strongly suspected LHPT (Table 2). These data were collected before eight patients had undergone parathyroid surgery and after seven patients had undergone surgery. (We report a further 14 surgical cases; seven had either moved address or ended with lithium at the follow-up, while a further seven had died.) The finding that several calcium and PTH values were normal at the end of the study period can be explained by the fact that patients with suspected LHPT continued to display fluctuations in TCa. Collectively, the group was once again predominantly women, with a median lithium treatment duration of 24 years. Calcium levels were slightly elevated, as was PTH. Serum phosphate, creatinine, and vitamin D levels were generally normal. Urinary calcium excretion was low or very low in most patients. (Nine patients (31%) had values below 1.2 mmol/24 h.)

A total of 29 lithium-treated patients (21 women and 8 men; median age 59 years) were identified having undergone parathyroidectomy on a total of 33 occasions (Table 3). The ten patients who at the follow-up were considered cured (Group A) had been subject to slightly more radical surgery than the remaining 19 patients (Group B), though this was not statistically significant. The follow-up was significantly shorter in Group A in comparison with that in Group B. Five patients had persistent disease, nine recurrent, and five had NCHPT at the follow-up. Success rate was thus 35%. Seventy-five per cent of all

Table 1 Intergroup analysis comparing the three groups categorized according to general trends in calcium homeostasis during the study period, i.e. normocalcaemia, hypocalcaemia, and hypercalcaemia

Variables	Normocalcaemic group (n = 178)	Hypocalcaemic group (n = 17)	Hypercalcaemic group (n = 102)	p value[§]
Age, median (range), years	52 (22–89)	66 (43–92)	64 (21–91)	<0.000
Female (%)	113 (63)	10 (59)	69 (68)	0.720
Average calcium values, median (range), mmol/l (ref. 2.15–2.50)	2.33 (2.02–2.86[a])	2.24 (1.86–2.59[a])	2.45 (2.03–3.09[a])	<0.000
Lithium duration, median (range), yrs	11.5 (1.5–40)	17.0 (1.5–40)	23.0 (3–45)	<0.000
Creatinine at the last follow-up, median (range), μmol/l (ref. 45–90)[b]	75 (42–173)	81 (59–115)	80 (49–205)	<0.000

[§]P values are derived from Chi-square tests for categorical variables and from a median test for continuous variables

[a]Two pathological values in either direction (hypo- or hypercalcaemia) were accepted as a normal occurrence. Categorization was based on the occurrence of at least three pathological values during the study period

[b]Reference values for women are 45–90 μmol/l and for men 60–105 μmol/l

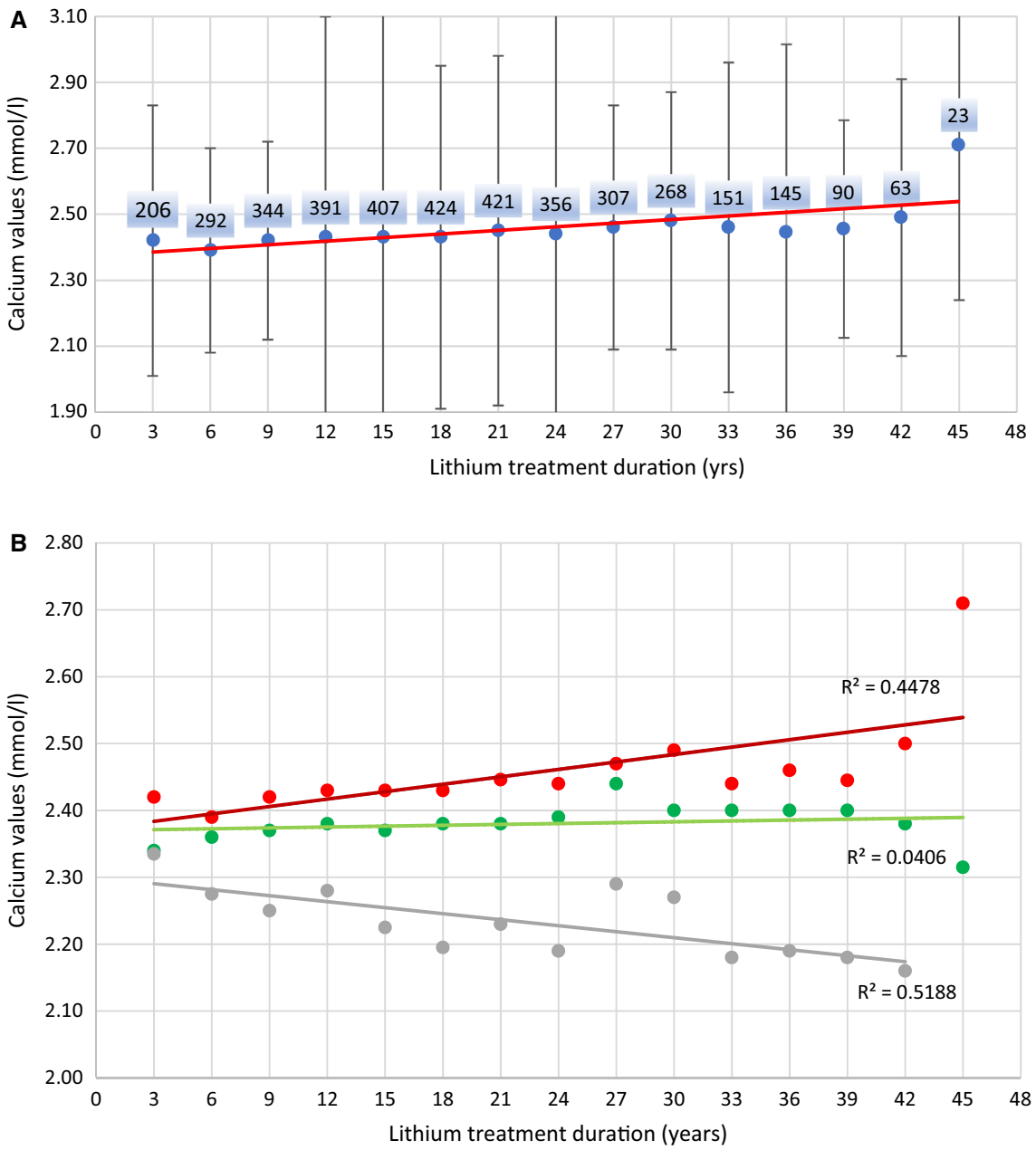

Fig. 1 **a** Plot of median total serum calcium (TCa) values and ranges for 102 patients monitored with at least three hypercalcaemic values during the follow-up. The diagram illustrates the considerable variance in calcium determinations for each three-year period. The numbers beside each median point provide the exact number of calcium observations retrieved from medical records for that period. **b** Plot of median total serum calcium (TCa) determinations in 297 patients with lithium treatment duration varying from 1.5 to 45 years. Linear correlation was calculated for 102 hypercalcaemic patients (red line, R^2 = 0.448), 178 normocalcaemic patients (green line, R^2 = 0.041), and 17 hypocalcaemic patients (grey line, R^2 = 0.519)

histopathological diagnoses revealed hyperplasia. Two patients had discontinued with lithium at the latest follow-up. No permanent complications to surgery could be discerned.

Discussion

This descriptive study has aimed to characterize calcium homeostasis in lithium-treated patients. The results confirm previous findings that hypercalcaemia is very common, and that surgically confirmed, or biochemically suspected, HPT

Table 2 Current demographic and biochemical profile at the latest follow-up of 66 patients (48 women, 18 men) with confirmed or strongly suspected LHPT

Variable	No. of available patients	Reference value	Median value (range)
Age	66	Years	66 (29–92)
Lithium duration, years	66	Years	24 (10.5–44)
Total Ca	66	2.15–2.50 mmol/l	2.55 (2.32–3.1)
Ionized Ca	64	1.15–1.33 mmol/l	1.37 (1.18–1.85)
PTH	60	1.6–6.0 pmol/l	9.8 (3.3–39)
Phosphate	49	0.80–1.5 mmol/l[a]	1.1 (0.68–1.91)
Urinary calcium	29	1.3–6.5 mmol/24 h	2.9 (0.8–10.7)
Creatinine	66	45–90 μmol/l[b]	96 (46–359)
25-OH-D	59	nmol/l[c]	64 (20–162)

[a]Reference values for women are 0.80–1.5 mmol/l and for men 0.7–1.6

[b]Reference values for women are 45–90 μmol/l and for men 60–105 μmol/l

[c]Values over 50 nmol/l are most often considered as adequate

Table 3 A summary of pre- and postoperative data[a] for 29 lithium-treated patients having undergone 33 parathyroidectomies, including four reoperations. The patients were classified according to surgical and biochemical results (Group A = cured and Group B[b] = not cured)

Characteristics/values	Preoperative results		Postoperative results (at the latest follow-up)	
	Group A	Group B	Group A	Group B
No.	10	19	10	19
Gender (%)	*F* = 6 (20), *M* = 4 (14)	*F* = 15 (52), *M* = 4 (14)	–	–
Age, *yrs*	58 (39–73)	60 (46–71)	–	–
Lithium duration, *yrs*	22 (12–28)	21 (6–44)	–	–
Calcium (ref. 2.15–2.50 mmol/l)	2.69 (2.54–3.12)	2.71 (2.41–3.46)	2.35 (2.11–2.46)	2.45 (2.05–2.86)
PTH (ref. 1.6–6.0 pmol/l)	10.2 (8.1–31.0)	11.5 (6.6–39.5)	5.3 (4.0–5.6)*	9.5 (3.9–26)*
No. of glands identified peroperatively	–	–	3 (1–4)	3 (2–4)
No. of glands extirpated, total = 70[c]	–	–	3 (1–3)	2 (1–3)
Histopathological diagnosis, total = 67[d]	–	–	Normal = 5	Normal = 3
			Hyperplasia = 15	Hyperplasia = 32
			Nodular hyperplasia = 1	Nodular hyperplasia = 3
			Adenoma = 4	Adenoma = 4
Follow-up, *mths*	–	–	35 (24–308)*	148 (24–312)*

*Significantly different PTH values could be detected between Group A and Group B at the follow-up, p=0.002; statistically significant different follow-up values were also detected, p=0.05

F female, *M* male, *yrs* years, *mths* months

[a]Median values with ranges in parentheses are presented, unless otherwise specified

[b]Group B consists of five patients with persistent disease, nine with recurrent disease and five with NCHPT

[c]This number includes seven half glands that were extirpated

[d]Three histopathological diagnoses could not be recovered from medical records

is more prevalent than in the general population. The present study illustrates both the extensive inter- and intraindividual variability in calcium levels over time, with approximately 20% of all calcium determinations being pathological. A tendency towards hypocalcaemia frequently occurred, though its significance is yet to be divulged.

Is LHPT a separate endocrinopathy: What do we know?

While pHPT remains the third most common endocrinopathy, LHPT as a form of parathyroid pathology is by far more prevalent. Typically, pHPT is characterized by moderate-to-high serum calcium and PTH,

hypercalciuria and reduced levels of phosphate, though other variants exist such as normocalcaemic hyperparathyroidism [7, 17]. Biochemically, LHPT is somewhat different: serum calcium can range from normal to moderately elevated, PTH ranges from normal to high (and often inappropriately high in relation to serum calcium), phosphate is normal to moderately elevated, and lastly, urinary secretion of calcium is low or very low (Table 2) [5, 9, 18, 19]. Many individuals with pHPT have osteopenia or even osteoporosis, while it is suggested that lithium may have a protective effect on the skeleton [20]. While fatigue may be the most common symptom of pHPT, in Western countries nephrolithiasis is still the most prevalent complication of pHPT demanding medical care, with prevalence rates ranging from 7 to 15% [21]. No occurrences of lithiatic medical conditions were detected through retrospective inspection of the present patient material, as observed in other studies [5, 22]. The current study is the first, to our knowledge, to report the occurrence of hypocalcaemia as a possible side-effect of lithium treatment. Seventeen patients (5.7%) met the arbitrary requirement of having at least three hypocalcaemic values during the follow-up, and though small, the population did differ significantly from the normocalcaemic group (Table 1, Fig. 1b). No ascertainable explanation for hypocalcaemia was apparent from the inspection of medical records (e.g. use of diuretics), and unfortunately no PTH was taken coincidentally. Considering that normal physiological conditions are elegantly attuned to limited changes in inter- and extracellular calcium, larger fluctuations might have clinical implications for individuals [23]. Hypothetically, it may reflect a general parathyroid dysfunction due to chronic lithium medication.

However, there are similarities in these parathyroid pathologies (pHPT vs LHPT). Both conditions predominantly affect females, particularly post-menopausal women (Tables 1 and 2) [24, 25], and both are caused by either parathyroid adenomas or hyperplasia, although multiglandular disease (MGD) is more frequent in LHPT [14, 26, 27]. Both conditions are difficult to diagnose, with pHPT and LHPT typically debuting with diffuse symptoms, which in the case of LHPT can be clinically challenging to differentiate from the lithium-treated patients' affective condition [25, 28]. Existing anomalies may suggest other mechanisms in the development of LHPT, possibly necessitating another medical approach.

Surgical results

The present study confirms that surgical results in LHPT are poor and distinct from the admirable results obtained in pHPT [8, 11, 17, 29]. The cure rate in this study was found to be 35%, a rate that potentially may decrease with time since the follow-up was relatively short in cured patients (Group A). There may be several reasons for this. Preoperative imaging gave accurate results in only 30%, allowing for focused surgery in few cases. Norlén et al. [30] and Marti et al. [31] report levels of accuracy with Sestamibi in over 50%, and better results with concordant ultrasound assessment, in particular regarding adenomas. In addition, Carchman et al. [12] present preoperative imaging that could predict ten adenomas in a case material of 16 patients, though two were later found to have MGD. Largely, the role of imaging is contentious, possibly because of the high proportion of MGD [11, 17], and Skandarajah et al. [27] actually argue, "the sole indication for preoperative imaging…is to exclude concomitant thyroid disease". While most centres now use intraoperative PTH (IOPTH) monitoring, that was not the case at the current centre during most of the time period studied. Its utility in LHPT is questionable. While Carchman et al. [12] contend satisfactory correlation between IOPTH and subsequent cure, Hundley et al. [26] dispute its reliability and predictive value in lithium-treated patients, where six of 12 patients had MGD, concluding IOPTH could not "supplant good surgical judgement". It is also interesting to note that in this study, preoperative PTH values were not useful in establishing suitable surgical management. An important explanation to the discrepancy in cure rate in our study is possibly due to the histopathological background of LHPT and subsequent surgical strategy. Once again, dichotomous evidence emerges in the literature where some surgical studies present incidences of adenomas comparable to pHPT [12, 26, 32], while others report higher incidences of MGD (Table 3) [10, 14, 27, 33]. Another contributing factor to the exceptionable results of surgery in LHPT might be the inappropriate surgical strategy performed at the primary operation, as in the present study [14, 32, 34]. Macroscopic assessment of parathyroid gross morphology can be difficult, leading to insufficient excision of parathyroid tissue. Bilateral neck exploration (BNE) has found wide support as the appropriate surgical strategy [8, 11, 13, 35], though Saunders et al. [8] stress that sufficient evidence is lacking to fully endorse this method universally. These are questions we are attempting to address in our ongoing randomized study comparing surgery with watchful waiting.

LHPT's biochemical similarity to familial hypocalciuric hypercalcaemia (FHH) raises the question as to what the correct management of suspected LHPT might be: active observation, medication with calcimimetics or surgery, and, if surgery is deemed appropriate, what degree of surgical radicality should be implemented.

Strengths and limitations

The strengths of this study consist in the homogeneity of the patient material from a well-defined geographical area. The Swedish Social and Health Care system, through identification numbers, registers and computerized medical records, allow for clear identification of individual patients, facilitating the follow-up. The same researchers (JJ & AM) collaborated closely in data collection according to a predetermined protocol. The manual collection of data is in itself a self-generating mark of quality. The study also has some limitations. The study is retrospective and cannot, therefore, guarantee the absence of any unforeseen bias. The absence of PTH and vitamin D at synchronous periods of calcium fluctuations would have greatly facilitated the understanding of these disturbances, making any conclusions more reliable. While the authors only found calcium values for 66% of patients before lithium-treatment initiation, the coverage rate for the follow-up was an admirable 88%.

Conclusion

The prevalence of hypercalcaemia during lithium treatment is very high, with 34% of patients having displayed at least three hypercalcaemic episodes. In addition, hypocalcaemic episodes frequently occur, possibly reflecting a more complicated parathyroid dysfunction than previously known. LHPT biochemical profile is different from that in pHPT and is in some ways similar to FHH. Prospective studies are required to illuminate the clinical relevance of these chronic, biochemical disturbances, to clarify further appropriate medical management and would allow for a robust assessment as to whether surgery should remain the golden standard in patients with HPT and concomitant lithium treatment.

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Authors contributions The article reflects a collaborative effort from all the authors. The original idea for the study was derived by JJ. The study theme was further developed by ADM. JJ and ADM were responsible for the collection of all raw data. All authors contributed to the analysis of the material and the drafting of the manuscript. All authors read and approved the revision of the final manuscript.

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Compliance with ethical standards

Conflict of interest AM, GW, and JJ have nothing to declare. The authors have judged that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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