Alterations in Parathyroid Dynamics in Lithium-Treated Subjects*

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ABSTRACT

Chronic lithium (Li) therapy, used extensively in the treatment of bipolar affective disorders, is one of psychiatry's most effective treatments. The data on the effects of Li on baseline PTH and calcium (Ca) levels are conflicting. A clear resetting of the PTH set-point to the right was documented *in vitro*; however, the effect of Li on the Ca-PTH axis has not been rigorously studied *in vivo*. In this study, we used a Ca and citrate infusion protocol to fully characterize PTH dynamics in seven female patients, 40 ± 11 yr old, on chronic Li therapy for 5.23 ± 4.0 yr, compared with seven controls, 41 ± 16 yr old (mean $\pm$ SD). Baseline ionized Ca (Ca_i) and intact PTH levels were 5.2 ± 0.06 mg/dL and 38.4 ± 5.7 pg/mL in the Li group and 4.9 ± 0.06 mg/dL and 21.2 ± 5.0 pg/mL in the controls, (mean $\pm$ SEM) $P = 0.008$ and 0.042,

respectively. We defined an inverse sigmoidal curve between Ca_i and the intact biologically active PTH molecule (iPTH) for the two study groups and demonstrated a significant shift in the iPTH set-point to the right in the Li-treated patients, compared with controls. The set-point was 5.08 ± 0.04 for the former group and 4.88 ± 0.04 mg/dL for the latter, $P = 0.004$. Patients on Li had significantly higher Ca_i levels during citrate and Ca infusions, $P = 0.0008$ and 0.012, respectively; however, iPTH levels were not significantly different between the two study groups during either infusion. The shift in the iPTH set-point to the right in the Li-treated patients and the similar iPTH levels, despite higher serum Ca_i levels during both infusions, establish the presence of a clear alteration in PTH dynamics in patients on chronic Li therapy. (*J Clin Endocrinol Metab* **82:** 2844–2848, 1997)

L ITHIUM (Li) is widely used in the treatment of bipolar affective disorders. This monovalent cation is one of psychiatry's most effective drugs, not only for acute episodes of mania, but also for reducing the number and intensity of recurrent episodes, thereby reducing the overall morbidity and mortality of the illness (1, 2). It is estimated that in many developed countries, 0.1% of the population is receiving Li treatment (3). A variety of complications of Li therapy have been described, including nephrogenic diabetes insipidus, hypothyroidism, and hyperparathyroidism (4–7). A longitudinal study suggested that chronic Li administration increases PTH and/or calcium (Ca) levels (8). Yet, in many studies, these parameters stay within the normal range in the majority of subjects (4, 8). Cross-sectional studies of patients on Li reveal that serum Ca and PTH levels were elevated above the normal range in anywhere from 12–25% of patients (4, 5). The conflicting results regarding PTH levels in Li-treated patients may be attributable to the fact that many studies failed to measure ionized Ca (Ca_i) levels, the primary modulator of PTH secretion; lacked concomitant measurements of Ca_i and PTH; or used older assays that lack the

sensitivity and specificity needed to measure the intact biologically active PTH molecule (iPTH) (4–11).

Mallette *et al.* demonstrated increments from baseline in Ca_i levels at 3 months and in Ca_i and PTH levels and parathyroid gland volume at 103 months of Li therapy (12). In addition, administration of 600 mg Li to normal healthy volunteers was shown to increase iPTH levels acutely from 22–32 pg/mL without any change in Ca_i levels (13). These results suggest that Li may indeed exert a direct effect on the parathyroid gland.

In vitro, Li stimulates the release of iPTH from bovine and human parathyroid cells (14, 15) and increases the set-point for PTH release in response to Ca (14). *In vivo*, the administration of a graded Ca infusion to six healthy men, before and 5 days after Li, resulted in no changes in PTH suppressibility in response to Ca (16). However, a full characterization of the Ca-PTH axis was not possible because of the lack of a citrate infusion (16).

In this study, we have fully characterized the Ca_i-iPTH axis in patients taking Li and in control subjects to test the hypothesis that Li induces alterations in PTH dynamics that may not always be apparent under baseline conditions.

Materials and Methods

Subjects

Seven women taking chronic Li therapy for the treatment of bipolar affective disorder and seven age-matched control subjects were studied over 2 days. In both groups, four subjects received a Ca infusion on the first day, followed by the citrate infusion on the second day, whereas three subjects received the citrate infusion on the first day, followed by the Ca infusion on the second day. Because of the effect of the menstrual cycle on PTH levels (17), young women had to have spontaneous,

regular cycles of 28–35 days, as documented by a three-month diary, to be eligible for the study. All premenopausal women (five in each study group) were studied during the early follicular phase of their menstrual cycle. In addition, two postmenopausal women, not taking hormone replacement therapy, were studied in each group. The subjects were on no other medication known to affect Ca and bone metabolism. Before enrollment, each subject underwent a physical examination and a laboratory evaluation that included a multichannel serum chemistry analysis and complete blood count with differential, an iPTH level, a TSH level, and a 25 hydroxyvitamin D [25(OH)D] level. Subjects with 25(OH)D levels below 15 ng/mL were excluded. To avoid any confounding effect of obesity on the PTH axis (18), all subjects had a body mass index (weight in kilograms divided by height in meters squared) of less than 30. The mean dietary Ca intake of all study subjects was evaluated with a Ca questionnaire generated by the General Clinical Research Center dietitian. The study was reviewed and approved by the Committee for the Protection of Human Subjects of the Brigham and Women's Hospital. Informed written consent was obtained from each subject before participation.

Study design

The design of the protocol has been described in detail in previous publications examining PTH dynamics in healthy volunteers (19, 20). The protocol required two visits to the Ambulatory Clinical Center, one for a citrate and the other for a Ca infusion. For each visit, the subject arrived at 0800 h in a fasting state. An iv catheter was placed in a vein of each antecubital fossa and kept open with 5% dextrose in water. One iv line was used for blood sampling and the other for infusion of Ca or citrate. Samples for serum 1,25 dihydroxyvitamin D [1,25(OH)$_2$ D] levels and chemistries, including blood urea nitrogen and creatinine (Cr), were obtained before the infusion started and on completion of the infusion. Serum 25 (OH)D levels were measured at the beginning of the infusion on the first day only.

Citrate infusion

Citrate (anticoagulant-citrate-dextrose USP Formula A [ACD-A], containing per 100 mL: 2.45 g dextrose, 2.2 g sodium citrate, and 0.7 g citric acid; Fenway Laboratories, Deerfield, IL) mixed in 5% dextrose water was administered via an IV infusion pump (Travenol, Deerfield, IL). Throughout the course of the infusion, blood pressure was monitored by an automated blood pressure recorder (adult/pediatric vital sign monitor, Critikon, Inc., Tampa, FL), and an EKG was obtained from a cardiac monitor (Physio Control Lifepak 7, Rowayton, CT) at each step before the infusion rate was increased. The study consisted of four 30-min pulse-step intervals of citrate infusion. In brief, a rapid 5-min infusion of citrate was followed by a slower infusion for 25 min. Progressively increasing rates of both the fast and slow infusions were used for three additional 30-min periods. The citrate dose was 42 mg citrate/mg/kg/hr, followed by 20 mg citrate/mg/kg/hr for the first 30-min interval; dosages for subsequent intervals were 70/33, 96/44, and 130/60 mg citrate/mg/kg/hr, respectively. iPTH levels, measured at 5 min of each step, reflect the effect of change in Ca$_i$ on iPTH release, whereas the 30-min points, when Ca$_i$ is more stable, reflect the effect of Ca$_i$ concentration *per se* on iPTH dynamics (19). Samples for serum Ca$_i$ and iPTH levels were collected anaerobically at 0, 5, 10, 20, and 30 min for each step of the infusion.

Ca infusion

Ca gluconate (Astra, Westboro, MA) was infused over three 30-min pulse-step intervals via an IV infusion pump by the same procedure as that used for the citrate. The doses for Ca for the fast/slow infusions were 2.4 mg/kg/hr followed by 0.75 mg/kg/hr in step 1; 3.4 mg/kg/hr followed by 1.25 mg/kg/hr in step 2; and 4.4 mg/kg/hr followed by 1.75 mg/kg/hr in step 3. Samples for serum Ca$_i$ and iPTH levels were collected anaerobically at 0, 5, 10, 20, and 30 min for each step of the infusion.

Characterization of the Ca$_i$-iPTH axis

The following indices of parathyroid function were used to evaluate the relationship of iPTH to Ca$_i$: the maximal iPTH response to hypocal-cemia, the minimal iPTH level after induced hypercalcemia, the set-point for iPTH, and the slope of the curve at the set-point. The set-point is defined as the serum Ca$_i$ concentration at which the iPTH level is half maximal (21). Samples obtained at the 30-min time points of both the Ca and citrate infusions, when Ca$_i$ levels were stable, were used to characterize the Ca$_i$-iPTH axis. We used GraphPad Prism software 1.0 (GraphPad Software, San Diego, CA) to fit sigmoidal curves to our data. This computer program generated the four variables mentioned above. In addition, data obtained from all time points of the Ca and citrate infusions also were compared between the two groups to further evaluate the effect of Li on Ca$_i$-iPTH dynamics.

Laboratory tests

Serum levels of Ca, phosphate, magnesium, and Cr were determined by the clinical chemistry laboratory by a calorimetric method with an Olympus AU-5061 analyzer (Olympus Corporation, Lake Success, NY). Blood for Ca$_i$ was collected anaerobically and measured with an AVL 987-S electrolyte analyzer (AVL Scientific Corporation, Roswell, GA), which has a precision of 0.39% and an interassay precision of 1.7–2.5% for Ca$_i$ levels between 1.12 and 1.48 mmol/L (normal range: 1.15–1.33 mmol/L, N = 57). Fasting urinary Ca and Cr levels were measured on both days before administration of the infusion. Fasting urinary Ca/Cr clearance ratios were calculated for both groups using the following formula: [UCa × SCr]/[SCa × UCr].

Serum iPTH was measured by the Allegro immunoradiometric assay [Nichols Institute, San Juan Capistrano, CA (22)]. The detection limit of the assay is 1.0 pg/mL (normal range 10–65 pg/mL) and the intra- and interassay CV percents are 1.7 and 6.5% at iPTH concentrations of 37.7 and 44.1 pg/mL, respectively. Serum 25(OH)D was measured by a competitive protein-binding assay (Incstar, Stillwater, MN) with the normal range 10–55 ng/mL. A radioreceptor assay kit (Nichols Institute Diagnostics), with the 1,25(OH)$_2$D receptor from calf thymus, was used for the 1,25(OH)$_2$D assay (normal range 15–65 pg/mL). For 25(OH)D, the intraassay CV% is between 8.7 and 8.9% at serum concentrations of 12 and 53 ng/mL, respectively, and the interassay CV% is 12% at a serum concentration of 49 ng/mL. For 1,25(OH)$_2$D, the intraassay CV% is 8.7% at a concentration of 34 pg/mL, and the interassay CV% is 13.2% at a concentration of 43 pg/mL. Except for serum Ca$_i$ samples, which were measured on the same day, all other serum samples were stored at −70 C. All samples from each patient (except for Ca$_i$) were run in duplicate and in the same assay.

Because of the controversial effect of Li on bone mass (8, 23, 24), bone mineral density (BMD) of the spine (L1-L4), hip (femoral neck, trochanter), and forearm (distal ⅓ radius) was measured in all subjects, with dual-energy X-ray absorptiometry, QDR 2000 (quantitative digital radiography, Hologic, Inc, Waltham, MA). BMD was expressed in both groups as Z scores, that is, the number of SD, compared with an age-matched normative database supplied by the bone densitometer software.

Statistical methods

Baseline demographics were analyzed with a two-tailed *t* test. Summary measures for both study groups, including functions of the maximal responsiveness, minimal responsiveness, set-point, and slope derived from the sigmoidal curve, were compared by *t* test. Data from both infusions included multiple measures (*i.e.*, Ca$_i$ and iPTH) sampled repeatedly, over time, that were analyzed with use of repeated-measure ANOVA. The results were expressed as mean ± SEM, unless otherwise indicated. Significance was indicated for $P < 0.05$.

Results

Baseline characteristics

As shown in Table 1, there was no significant difference in the average age, body mass index, or dietary Ca intake between the two study groups. The average duration of Li use was 5.23 ± 4.0 yr (mean ± SD). The mean Li level for six patients, obtained within 3 months of the study and while on a stable Li dose for at least 6 months, was 0.63 ± 0.08 mmol/L

TABLE 1. Baseline characteristics of study subjects

	Lithium (N = 7)	Controls (N = 7)	*P*
Age (yr ± SD)	40 ± 11	41 ± 16	NS
Lithium use (yr ± SD)	5.23 ± 4.0	–	–
Body mass index (kg/m^2)	25.0 ± 1.5	24.1 ± 1.0	NS
Dietary calcium (mg/day)	1150 ± 275	1036 ± 203	NS
Serum calcium (mg/dl)	9.6 ± 0.1	9.5 ± 0.1	NS
Serum creatinine (mg/dl)	1.03 ± 0.03	0.93 ± 0.03	0.029
Ionized calcium (mg/dl)	5.2 ± 0.06	4.9 ± 0.06	0.008
Intact parathyroid hormone (pg/ml)	38.4 ± 5.7	21.2 ± 5.0	0.042
25 (OH) vitamin D (ng/ml)	20.0 ± 2.0	25.2 ± 4.2	NS
1,25 (OH)$_2$ vitamin D (pg/ml)	26.4 ± 4.1	35.7 ± 6.4	NS
Urinary calcium (mg/dl)	4.8 ± 0.9	9.8 ± 2.1	0.046
Urinary creatinine (mg/dl)	47.3 ± 9.1	122.0 ± 31.2	0.041
Urinary Ca/Cr clearance ratio^a	0.011 ± 0.001	0.010 ± 0.002	NS

Measurements expressed as mean ± SEM, unless otherwise stated.
–, Not applicable; NS, not significant.
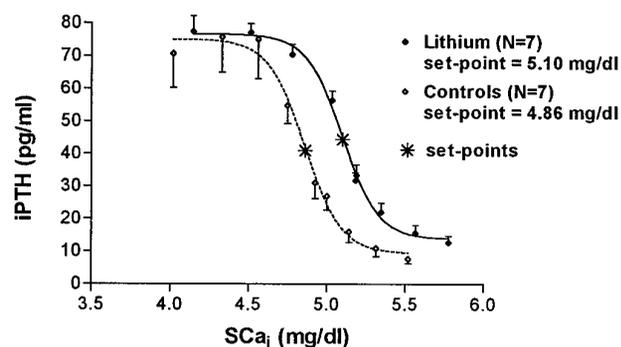^{a} Ca/Cr clearance ratio = [UCa × SCr]/[SCa × UCr].

FIG. 1. PTH dynamics in the Li-treated and control groups. Sigmoidal curves are generated from the 30-min data points when Ca$_i$ levels are stable during the citrate and the Ca infusions.

(normal range is 0.5 to 1.3 mmol/L). Mean baseline serum Ca, 25(OH)D, and 1,25(OH)$_2$D levels were not significantly different between the two groups. However, serum Ca$_i$ and iPTH levels were slightly, but significantly, higher in the Li-treated group (Table 1). Fasting urinary Ca levels, but not urinary Ca/Cr clearance ratios, were significantly lower in the Li-treated patients, compared with the controls, $P = 0.046$ (Table 1).

Sigmoidal curve characteristics

The set-point is defined as the Ca$_i$ concentration at which iPTH levels are half-maximally inhibited. Rapid changes in serum Ca$_i$ levels can shift the sigmoidal curve, relating Ca$_i$ to iPTH levels, to the right, thereby elevating the set-point (19). Therefore, to evaluate the effect of changing Ca$_i$ concentration *per se* rather than the effect of the rate of change in Ca$_i$ on iPTH levels, we used the 30-min points from both the citrate and Ca infusions to plot the sigmoidal curve. The 30-min time points reflect stable Ca$_i$ levels following the increases in infusion rates. The set-points were calculated using two methods. In the first method, the 30-min time points for both the citrate and Ca infusions were averaged for each study group, and two separate sigmoidal curves were fitted to the average data points for each study group, as shown in Fig. 1. The set-points derived from this method were 5.10 ± 0.01 mg/dL for the Li-treated patients and 4.86 ± 0.02 mg/dL for the controls. In the second method, a sig-
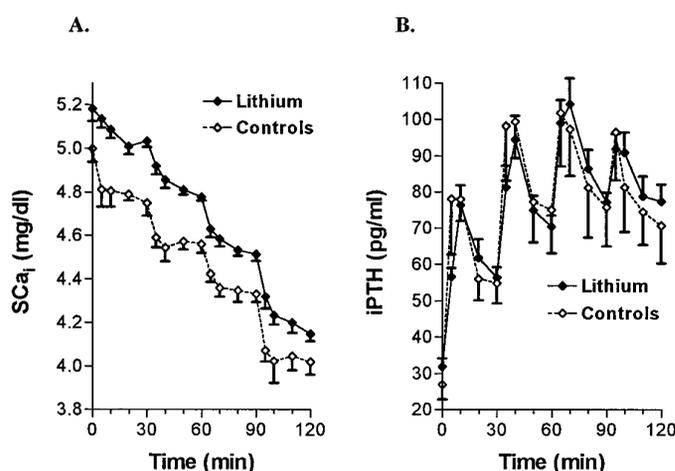

FIG. 2. Levels of Ca$_i$ (A) and iPTH (B), obtained during the 120-min citrate infusion in the Li and control groups. For each time point, the Li-treated patients had higher Ca$_i$ levels, whereas both groups demonstrated similar iPTH levels.

moidal curve was fitted to each individual's data to derive an individual set-point. The individuals' set-points were then averaged to calculate a mean set-point for each study group. The set-point with this second method was 5.08 ± 0.04 mg/dL for the Li-treated patients and 4.88 ± 0.04 mg/dL for the normal subjects, $P = 0.004$. According to the second method, the average slopes of the sigmoidal curves in the Li group and the control group were −12.9 ± 1.9 and −12.2 ± 1.5, respectively, $P = 0.768$. The maximal and minimal iPTH responses derived from the sigmoidal curves did not differ between the two study groups; they were 80.4 ± 5.0 pg/mL and 11 ± 2.12 pg/mL in the Li-treated group, compared with 79.9 ± 12.2 pg/mL and 6.2 ± 3.3 pg/mL in the control group, respectively.

PTH responsiveness to hypocalcemic stimuli: data from the citrate infusion

An evaluation of the data obtained from all time-points revealed that the Ca$_i$ levels were higher in the Li-treated patients than in the controls throughout the citrate infusion, $P = 0.0008$ (two-way ANOVA, Fig. 2A). Both study groups
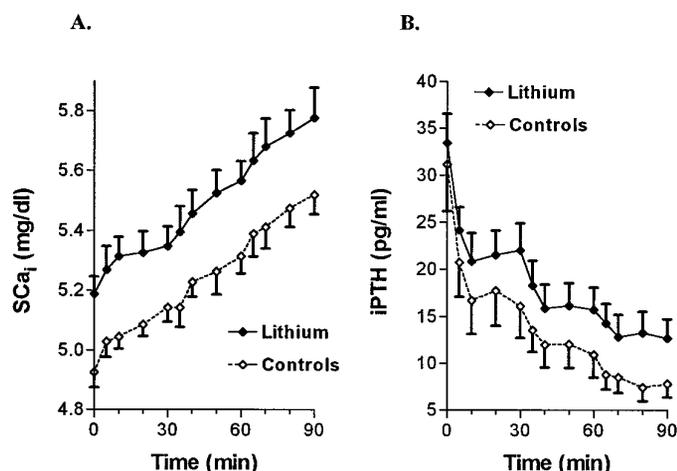
A.

B.

FIG. 3. Levels of Ca_i (A) and iPTH (B), obtained during the 90-min Ca infusion in the Li and control groups. For each time point, the Li-treated patients had higher Ca_i levels, whereas both groups demonstrated similar iPTH levels.

had sharp increments in iPTH levels within the first 10 min of each step that were not significantly different between the two groups (two-way ANOVA, Fig. 2B).

PTH suppressibility: data from the Ca infusion

As in the citrate infusion, an evaluation of the data obtained from all time-points revealed that Li-treated patients had significantly higher serum Ca_i levels than the controls, $P = 0.018$ (two-way ANOVA, Fig. 3A). However, iPTH levels did not differ significantly between the two study groups in response to the Ca infusion, (Fig. 3B). However, our study did not have the power to detect differences in PTH suppressibility of the magnitude observed.

Bone density

The BMD, expressed as Z scores, of the lumbar spine in the Li-treated patients was slightly higher than that of the controls (Z = 0.73 ± 0.4 and Z = -0.32 ± 0.3 respectively, $P = 0.08$). In the Li and the control group, the Z scores for the femoral neck were -0.09 ± 0.4 and -0.19 ± 0.6, respectively; for the trochanter, -0.13 ± 0.4 and -0.14 ± 0.4, respectively; and for the distal ⅓ radius, 0.42 ± 0.3 and -0.15 ± 0.21, respectively. There were no differences between the two study groups.

Discussion

In this study, we were able to demonstrate a clear shift in the iPTH set-point to the right in Li-treated patients. Moreover, the comparable iPTH levels in the two study groups, despite higher Ca_i levels achieved in the Li-treated patients during both the Ca and the citrate infusions, further confirm nonsuppressibility of iPTH levels and altered Ca sensing in patients on chronic Li therapy.

Stimuli for elevated iPTH levels include low serum Ca, 25(OH)D levels, and/or 1,25(OH)$_2$D levels. Despite comparable baseline total Ca and vitamin D metabolite levels in the two study groups, serum Ca_i was higher in patients on Li. If parathyroid dynamics were entirely normal, such elevations

in Ca_i levels would be expected to result in lower, rather than higher, iPTH levels as observed in our study. Other conditions leading to elevated iPTH levels include mild renal failure or renal hypercalciuria (25, 26). Renal function in the Li-treated patients, as determined by serum Cr levels, was normal, and fasting urinary Ca/Cr clearance ratios were comparable with the ratio calculated in the control group. However, the lower urinary Ca, but not Ca/Cr clearance ratio, in the Li-treated subjects, despite comparable serum Ca between the two groups, raises the possibility of an effect of Li on renal function (5, 27).

The Li-induced shift in the iPTH set-point to the right that has previously been demonstrated *in vitro* (14) and is now documented *in vivo* in our studies suggests a direct effect of this cation on the parathyroid gland. This hypothesis is further confirmed by the acute increase in PTH levels in response to Li administration, both *in vitro* and *in vivo* (13–15). The mechanisms of Li-induced changes at the cellular level have been studied extensively (28). Considerable evidence has accumulated over the last few years, identifying key components of signal transduction pathways (G proteins, adenyl cyclase, protein kinase C) and gene expression in the central nervous system as targets for the molecular effects of Li (28). Racke *et al.* evaluated the locus of action of Li in parathyroid cells and demonstrated that Li blunted cation (Ca and magnesium)-induced changes in cytosolic Ca but had no effect on Ca-induced hydrolysis of inositol phosphates (29, 30). These findings suggest that the locus of action of Li is distal to the calcium receptor (CaR), although its precise site remains unclear. The observed alteration in PTH dynamics and the reduction in Ca excretion in patients on Li therapy could be caused by an effect of Li on the CaR signal transduction system of the parathyroid gland and kidney and can be likened to familial hypocalciuric hypercalcemia (FHH) (31). Using a Ca infusion, Khosla *et al.* suggested a shift in the Ca/PTH curve to the right in patients with FHH. However, because a hypocalcemic stimulus was not applied, a full characterization of the PTH/Ca axis was not possible (32).

The above-proposed Li-induced alterations in Ca sensing, and therefore PTH dynamics, could conceivably result in hyperparathyroidism with four-gland hyperplasia. However, two reviews evaluating the pathology of the parathyroid glands in patients with hyperparathyroidism have yielded conflicting results (4, 33). In the review of Mallette *et al.*, the pathology was predominantly that of adenomas (4). A more recent histopathologic retrospective study demonstrated that the predominant pathology was that of parathyroid hyperplasia in five out of six patients treated with Li, whereas an adenoma was found in ten out of eleven patients on tricylic antidepressant medication (33). It would seem that Li unmasks frank hyperparathyroidism in only a subset of patients predisposed for that condition, apriori.

The effect of the Li-induced hyperparathyroidism on the skeleton remains controversial (8, 23, 24). Spine, hip, and distal ⅓ radius Z scores in both the Li-treated patients and the controls were within the range expected for age in all sites studied. These results are, however, based on a small number of subjects studied cross-sectionally. Yet, similarly to FHH (34, 35), patients on Li may have normal bone density despite

slightly higher iPTH levels, possibly caused by a lowering of urinary Ca excretion (4, 23).

In conclusion, our study documents a clear alteration in PTH dynamics in patients on chronic Li therapy, even though their baseline total Ca and iPTH levels were well within the normal range. This may reflect generalized altered Ca sensing, not only at the level of the parathyroid gland, but also of the kidney.

Acknowledgments

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