Lithium-associated hyperparathyroidism
To my great-aunt Elisabeth Campbell
(1901-1986)

"Hold fast to dreams,
for if dreams die,
life is a broken-winged bird
that cannot fly!"
Langston Hughes (1902-1967)
Lithium-associated hyperparathyroidism: Prevalence, Pathophysiology, Management
Abstract

Lithium has been used in the treatment of bipolar disorder, formerly called manic depression, for nearly seven decades. Lithium-associated hyperparathyroidism (LHPT) is an ill-defined and less well known possible side-effect of chronic lithium therapy and was first described in 1973. The condition has been considered to be rare, though there exists conflicting evidence as to its prevalence, its pathophysiological background, and, if and when identified, what the appropriate medical or surgical treatment should be. The principal aim of this thesis was to understand and more comprehensively characterise this condition through studying a large patient cohort, with regards its prevalence, development, and additionally by providing an evaluation of surgical management up until now.

In Study I a population of 423 lithium-treated out-patients (251 women, 172 men) were recruited from Jönköping and Örebro County. We found that 18% met the criteria for hyperparathyroidism (HPT) and that a further 21% had intermittent episodes of hypercalcaemia. We then examined, in Study II, the effects of lithium only in patients with bipolar disorder and compared them, firstly, to patients with bipolar disorder without lithium and, secondly, to a control population. In total, 563 individuals participated in the study. Hypercalcaemia was found to be strongly associated to lithium therapy (adjusted OR 13.45; 95% CI 3.09, 58.55; \( p = 0.001 \)). Study III is a descriptive study of calcium homeostasis in 297 lithium-treated patients from Jönköping where three main groups could be discerned: 178 were normocalcaemic (60%), 102 hypercalcaemic (34%), and 17 hypocalcaemic (6%). Many patients demonstrate robust fluctuations in serum calcium intermittently. Of those with suspected LHPT, 31% had urinary calcium excretion values below 1.2 mmol/24hrs. Study IV analysed surgical results of 78 parathyroidectomies in 71 patients with concurrent lithium therapy. In strong contrast to surgical outcomes in those with primary HPT, the overall cure-rate was lower (58%) and the predominant histological diagnosis was hyperplasia (52%). Two patients had double adenomas.

Factors which should be particularly taken into consideration while monitoring lithium-treated patients are age, gender and lithium-duration.

Keywords: Lithium, hypercalcaemia, hyperparathyroidism, hypocalcaemia, hyperplasia, adenoma

Adrian Meehan, School of Health and Medical Sciences, Örebro University, SE-701 82 Örebro, Sweden, adrian.meehan@regionorebrolan.se
Table of Contents

ORIGINAL PAPERS ................................................................................................. 7

ABBREVIATIONS ................................................................................................... 9

LITHIUM-ASSOCIATED HYPERPARATHYROIDISM ......................................... 11
Lithium – one of our oldest ions ........................................................................... 11
John Cade & lithium – “mysterious intruder” .................................................... 12
Mogen Schou consolidates lithium’s role .............................................................. 14
Lithium’s side-effects – hypercalcaemia amongst others ...................................... 14
The development of hypercalcaemia ................................................................. 15
Lithium-associated hypercalcaemia – possible mechanisms .............................. 16
Single Glandular Disease vs Multiglandular Disease .......................................... 17
Clinical management of pHPT and LHPT ......................................................... 18

AIMS OF THE THESIS ...................................................................................... 20

PATIENTS AND METHODS .............................................................................. 21
Patients .......................................................................................................................... 21
Definitions .................................................................................................................. 21
Methods ...................................................................................................................... 22
Statistics ..................................................................................................................... 24
Ethics ......................................................................................................................... 24

RESULTS .................................................................................................................. 25
Paper I: Prevalence of LHPT .................................................................................. 25
Paper II: Lithium-associated hypercalcaemia in BD .............................................. 26
Paper III: Hypercalcaemia and hypocalcaemia? ................................................... 28
Paper IV: Long-term surgical results ..................................................................... 31

DISCUSSION .......................................................................................................... 33
Paper I ......................................................................................................................... 33
Paper II ......................................................................................................................... 35
Paper III ......................................................................................................................... 36
Paper IV ......................................................................................................................... 38
General Conclusions ............................................................................................... 39

FORTHCOMING STUDIES ................................................................................. 41
Randomized study – surgery vs watchful waiting ................................................ 41
Ethics ......................................................................................................................... 41
Materials and methods .......................................................................................... 41
Original Papers

This thesis is based on the following four papers, which will be referred to in the text by their roman numerals:

I. The prevalence of lithium-associated hyperparathyroidism in a large Swedish population attending psychiatric outpatient units.


II. Lithium-Associated Hypercalcemia: Pathophysiology, Prevalence, Management.


III. Characterisation of Calcium Homeostasis in Lithium-treated Patients: Disturbances Reveal Both Hypercalcemia and Hypocalcemia.

Meehan AD, Wallin G, Järhult J submitted

IV. Long-term results of surgery for lithium-associated hyperparathyroidism.


Reprints were made with the permission of the publishers.
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALP</td>
<td>Alkaline phosphatase</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine transaminase</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate transaminase</td>
</tr>
<tr>
<td>AS-18</td>
<td>Affective disorder rating scale -18 (Swedish)</td>
</tr>
<tr>
<td>BD</td>
<td>Bipolar disorder</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>BNE</td>
<td>Bilateral neck exploration</td>
</tr>
<tr>
<td>cAMP</td>
<td>Cyclic adenosine monophosphate</td>
</tr>
<tr>
<td>CaSR</td>
<td>Calcium-sensing receptor</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>DEXA</td>
<td>Dual energy x-ray absorptiometry</td>
</tr>
<tr>
<td>eGFR</td>
<td>Estimated glomerular filtration rate</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiography</td>
</tr>
<tr>
<td>FHH</td>
<td>Familial hypocalciuric hypercalcaemia</td>
</tr>
<tr>
<td>FRAX</td>
<td>Diagnostic tool to estimate bone fracture risk</td>
</tr>
<tr>
<td>GAF</td>
<td>Global assessment of function</td>
</tr>
<tr>
<td>GSK-3</td>
<td>Glycogen synthase kinase</td>
</tr>
<tr>
<td>HPT</td>
<td>Hyperparathyroidism</td>
</tr>
<tr>
<td>iCa</td>
<td>Ionised calcium</td>
</tr>
<tr>
<td>IMPase</td>
<td>Inositol monophosphatase</td>
</tr>
<tr>
<td>IOPTH</td>
<td>Intra-operative parathyroid hormone</td>
</tr>
<tr>
<td>IQR</td>
<td>Inter-quartile range</td>
</tr>
<tr>
<td>LHPT</td>
<td>Lithium-associated hyperparathyroidism</td>
</tr>
<tr>
<td>MADR-S</td>
<td>Montgomery-Asberg depression scale</td>
</tr>
<tr>
<td>Mg</td>
<td>Magnesium</td>
</tr>
<tr>
<td>MGD</td>
<td>Multiglandular disease</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>pHPT</td>
<td>Primary hyperparathyroidism</td>
</tr>
<tr>
<td>PTH</td>
<td>Parathyroid hormone</td>
</tr>
<tr>
<td>PTX</td>
<td>Parathyroidectomy</td>
</tr>
<tr>
<td>QoL</td>
<td>Quality of life</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SF-36</td>
<td>Short form (36) health survey</td>
</tr>
<tr>
<td>SGD</td>
<td>Single gland disease</td>
</tr>
<tr>
<td>S-PO4</td>
<td>Serum phosphate</td>
</tr>
<tr>
<td>TCa</td>
<td>Total calcium</td>
</tr>
<tr>
<td>TSH</td>
<td>Thyroid stimulating hormone</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
</tr>
<tr>
<td>----------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>tU-Ca</td>
<td>24-hour urine excretion of calcium</td>
</tr>
<tr>
<td>UNE</td>
<td>Unilateral neck exploration</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual analogue scale</td>
</tr>
<tr>
<td>VDR</td>
<td>Vitamin-D receptor</td>
</tr>
<tr>
<td>1,25(OH)-2D</td>
<td>1,25 dihydroxyvitamin D (calcitriol)</td>
</tr>
<tr>
<td>25-OH-D</td>
<td>25-hydroxyvitamin D (calcidiol)</td>
</tr>
</tbody>
</table>
Lithium-associated hyperparathyroidism

Lithium-associated hyperparathyroidism (LHPT) is an ill-defined and somewhat indistinct endocrinopathy. Despite an ever increasing, though currently relatively limited, body of descriptive literature there remains a good deal of controversy as to its prevalence and pathohistological background, thereby leading to clear difficulties in establishing recommendations for adequate management of the condition. The studies in this dissertation aimed at addressing these issues. Furthermore, preliminary results are provided at the end of the introductory section of the dissertation of our ongoing prospective randomised study aimed at evaluating the efficacy of surgery versus controlled monitoring.

Lithium – one of our oldest ions

It is thought that lithium has probably existed as a separate element since shortly after the Big Bang and as such is one of the oldest known metals (1). The salutary effects of lithium have been experienced since at least the times of the ancient Greeks, and it is suggested that the waters at Delphi were rich in lithium salts and gave alleviation to those with mental disorders (2). Lithium was not, however, discovered until 1800 by a young Brazilian naturalist, and later leading statesman, José Bonifácio de Andrade e Silva, who discovered two new minerals on an expedition on the island of Utö in Stockholm’s archipelago (3). Initially it was termed petalite but subsequently, when the metal was properly extracted by Johan August Arwerdson working in the laboratory of Berzelius, it was named lithium in 1817 (4). Later, in the nineteenth century, lithium water was bottled on an industrial scale and sold for the treatment of an array of ailments primarily thought to be caused by gout (Figure 1). Once again today, lithium-enriched waters are bottled and vigorously marketed. There continues to exist an almost mysterious aura surrounding lithium based on its presumed alimental properties.

Gout is one of the oldest conditions described in medical history (2, 3). The word gout derives from the Latin gutta, meaning dropping, illustrating the belief that pathological “droppings”, because of a surplus of uric acid, secreted from the blood leading to problems in the joints (5). This in turn was believed to give rise to a plethora of mood disorders, and even as early

---

1 Santo-Li (a bottled water enriched with minerals including lithium) was the official sports drink of the Nordea Tour 2014.
as 1707 the term *melancholia arthritica* was derived, clearly expounding the strong assumption of a correlation between gout and psychiatric conditions (3).

Figure 1. A typical advertisement from the nineteenth century for the sale of lithium-enriched water extolling its ability to treat a range of conditions, including gout, and to lead to improved health.

It must be accredited above all the English doctor Alfred Baring Garrod that lithium became a treatment for gout, through his widely-read treatise in 1859 which powerfully argued for a connection between uric acid diathesis and to various affective disorders (3, 6). He also ascertained that tremors, dyspepsia and polyuria were side-effects of lithium usage (2). Periodic depression as a seeming complication to gout was claimed to be particularly manifest in Denmark, and it was there that the brothers Carl and Frederik Lange in the late 1880’s launched lithium as a prophylactic treatment for recurrent depression and that continual medication was important (3, 6). They even made observations about the efficacy of lithium in the treatment of mania. All these observations by and large dissipated until the father of modern psychopharmacology emerged onto the scene.

**John Cade & lithium – “mysterious intruder”**

John Cade, a young Australian resident psychiatrist at the Bundoora Repatriation Hospital in Melbourne, spent many hours observing patients with severe affective disorders, many of whom had been institutionalised for many years. He had even spent time observing fellow prisoners of war while imprisoned at Changi Prison 1942-1945 (7). Based on these observations
and the continued idea that uric acid was connected to affective dysfunction, Cade injected urine from manic patients into guinea pigs, but in order to compensate for uric acid’s limited solubility, Cade added lithium urate. He noticed the guinea pigs became calm. Cade was at that time unaware that lithium had previously been used in the treatment of mania but fully aware of its use for gouty conditions. He, however, applied his findings on ten patients with recurrent mania and six patients with *dementia praecox*. A remarkable improvement was observed in almost all patients with mania, so much so, that several could be discharged and return to work (3, 6, 7). Patients with *dementia praecox* did not fundamentally improve but became “more amenable”. Cade published his seminal work in 1949 (8)². Sadly, two factors did not work in his favour. Firstly, Cade was unknown and published in a relatively obscure journal. Secondly, a paper published in the JAMA reported accounts of lithium intoxication in patients with congestive heart disease (9). Nevertheless, Cade’s findings did not go unnoticed, and lithium, or as he later called it the “mysterious intruder”, would soon gain wide acceptance (10).

Figure 2. John Cade (1912-1980) was the first to specifically treat manic patients with lithium and noted lithium’s role as a mood stabilizer. He is regarded by many as the father of modern psychopharmacology.

² The Medical Journal of Australia in 2004 stated that Dr. Cade’s article was its most cited article during the previous period of fifty years with nearly 900 citations (https://www.mja.com.au/journal/2004/181/1/jewels-crown-medical-journal-australias-10-most-cited-articles). It was also in this journal that Dr. Barry Marshall reported Helicobacter Pylori’s role in GI disease, with over 700 citations, for which he was later awarded the Nobel Prize in Medicine.
Mogen Schou consolidates lithium’s role

Despite fierce scepticism in the US, the use of lithium did gain interest slowly but progressively, for example in England and France (6, 11). A major break-through was achieved with the publication in 1954 by a Danish psychiatrist, Mogen Schou, in what may have been the first double-blinded, randomly controlled pharmacological study in psychiatry (6, 12). The rigorous scientific methodology employed in this study convincingly proved the efficacy of lithium in the treatment of manic-depressive patients and demonstrated lithium to be a “useful alternative” to barbiturates and electroconvulsive treatment (12, 13). Schou’s research was instrumental in disseminating the observations of Cade (14). Since then, lithium became and still is today the gold standard in the long-term management of what has become known as bipolar disorder (BD) (15-17), remaining the best documented treatment for BD, and multiple studies have also shown lithium to be an efficacious drug in the reduction of suicide behaviour (18, 19). It is of some significance that it took until 1970 in the US before lithium salts were permitted to be used in the treatment of manic depression (20). Despite the prodigious body of evidence supporting lithium’s long-term effects, the prescribing of this drug has fallen in recent years, particularly in the US, possibly because of the known side-effects, the demands of monitoring, and the alternatives available (21-23).

Lithium’s side-effects – hypercalcaemia amongst others

Bipolar Disorder describes a spectrum of affective conditions where the lifetime estimated incidence for BD-type I is 0.8% and BD-type II is 3%, though estimations vary widely (24-27). BD is the primary pharmaceutical indication for lithium, which can be used as monotherapy or in combination with other drugs (28). Currently in Sweden there are approximately 15,000 individuals who medicate with lithium, though a clear clinical problem is that BD is underdiagnosed and many individuals receive the diagnosis after many years (29). Before starting with lithium, a series of tests are carried out, including an electrolyte status, according to international recommendations (30, 31). In the last decades, the biochemical indices which have been monitored regularly in lithium-treated patients have primarily been lithium concentration, thyroid and kidney function. Interestingly, the inclusion of the monitoring of calcium has only recently been added to recommendations which has meant that there have existed considerable disparities nationally and internationally as to how parathyroid function has been
monitored actively (32-34). Parker et al. have underlined the “considerable inconsistencies” between the multiple guidelines (35).

As mentioned above, Sir Alfred Barring Garrod noted that lithium had a number of side-effects, and among the most common are hand tremor (27%, most often transient), cognitive disturbances (28%), thyroid abnormalities (25%), and tubular renal dysfunction (15%)(36, 37). Some studies report that hypercalcaemia or hyperparathyroidism are rare adverse effects of lithium medication (38), whereas McKnight et al. purport the absolute risk to be 10% (37).

The first publication to claim that lithium may lead to hypercalcaemia was written by Garfinkel et al. in 1973, illustrated through a single case vignette (39). However, it was a further seventeen years before this endocrinopathy was first described in surgical literature (40). Since then, an estimated 300 cases have been described in the English literature; Appendix 1 gives an overview of the majority of these studies and some of their most important findings.

The development of hypercalcaemia

Hypercalcaemia may arise from a multitude of various causes. The majority of cases are related to primary or sporadic hyperparathyroidism (pHPT) or malignancy (41, 42). Hypercalcaemia can be divided into two main groups: PTH-dependent and PTH-independent (43). Lithium affects parathyroid hormone (PTH) secretion and thereby causes PTH-dependent hypercalcaemia, whereas the use of drugs such as thiazides (not uncommon in the elderly) and vitamin D, as well as inflammatory conditions such as Sarcoidosis and malignancies, can cause PTH-independent hypercalcaemia. Moreover, a series of incremental changes occur with the development of chronic kidney disease, including the decrease of 1,25 dihydroxyvitamin D and the retention of phosphate, which in turn leads to the increased secretion of PTH - a condition referred to secondary hyperparathyroidism.

PTH and 1,25-dihydroxyvitamin D (1,25(OH)2D) are the primary regulators of extracellular calcium in the body (44). Serum calcium is strongly and very precisely regulated in humans and any changes in calcium concentration are detected by calcium-sensing receptor (CaSR) in the parathyroid chief cells, which in turn swiftly regulate secretion of PTH (45, 46). PTH reacts to hypocalcaemia in three principal, separate ways: 1. increased bone turnover and thereby releasing calcium and phosphorus, 2. reabsorption of calcium from the kidneys and the elimination of phosphorus, and lastly, 3.
increased absorption of both calcium and phosphorus from the gastrointestinal canal by effecting the synthesis of 1,25(OH)2D (47). Although in clinical praxis it is 25-OH-D which is monitored, it is when vitamin D is in its biologically active form of 1,25(OH)2D that it exerts its regulatory effects on calcium homeostasis via the ubiquitous vitamin D receptor (VDR). It does this by enhancing absorption from the gut, reducing excretion via the kidneys, and suppressing bone resorption (48). It is postulated that low levels of vitamin D may have multiple detrimental effects, including on an individual’s psychiatric well-being (49-52). Substitution therapy with vitamin D rarely leads to hypercalcaemia.

Lithium-associated hypercalcaemia – possible mechanisms

Lithium is described as a mood stabilizer but the exact biochemical mechanism of action has yet to be fully elucidated. The lithium ion is thought to be active particularly in signal transduction pathways and at multiple sites. Two main pathways of mood stabilizing action are proposed, namely, the inhibition of inositol monophosphatase, IMPase, (important for cell regulatory functions such as cell growth and apoptosis) and the inhibition of glycogen synthase kinase, GSK-3 (important in the process of apoptosis) (53-55). By inhibiting GSK-3, long-term plasticity and neurocellular protection and stability may be achieved. Inhibition is probably accomplished through lithium functioning antagonistically in the displacement of magnesium (56).

These mechanisms may also have some bearing on lithium’s implicated role in the development of hypercalcaemia. Szalat et al. (57) explains lithium’s involvement in the cascade leading to the inhibition of IMPase in parathyroid chief cells resulting in intracellular changes in calcium levels and thereby PTH secretion. The classic theory is that of lithium’s interaction with CaSR, a widely expressed transmembrane G-protein-coupled cell surface receptor, which seems to lead to a so-called right-shift or set-point elevation of calcium concentrations in relation to PTH (58, 59). Chief cells then react as if the extracellular concentration of calcium has decreased. How exactly lithium interacts with CaSR is difficult to determine, as is the phenomenon of CaSR stimulation and subsequent PTH secretion (60). Furthermore, increased direct secretion of PTH is thought to occur through the development of hyperplasia, occasionally adenoma (47). Hypocalciuria likely arises through the inhibition of renal cyclic adenosine monophosphate (cAMP) (61, 62).

To summarise thus far, lithium is principally used in the treatment of BD, but the exact mechanism leading to mood stabilisation is not yet known.
Lithium may have multiple cellular roles, affecting - among other organs - both the parathyroid glands and kidneys, and through its interaction with CaSR, it is thought to induce PTH-dependent hypercalcaemia. The clinical consequences of hypercalcaemia, alternatively HPT, for the individual medicating with lithium are largely unknown.

**Single Glandular Disease vs Multiglandular Disease**

In pHPT a single adenoma explains calcium disturbances in approximately 85% of cases, with hyperplasia in 10-15%, while parathyroid carcinoma is uncommon (<1%) (63). Until relatively recently, one of the histopathological diagnostic criteria for parathyroid adenoma was the fact that the lesion was solitary. Pre-operative imaging and identification of pathological parathyroid glands has not always proven to be sufficiently sensitive, particularly in patients with mildly elevated calcium levels (63, 64). Other histopathological criteria characterising adenomas include the existence of a capsule, the predominance of a single cell type and the scarcity of fat cells (65). However, differentiating between adenoma and hyperplasia can prove a major challenge for the pathologist (66).

The pathoanatomical diagnostic background to LHPT is a matter of some contention. Lithium, through GSK-3 inhibition, contributes to irregular Wnt/β-catenin signalling, believed to be significant for the development of parathyroid adenomas and hyperplasia (44). Theoretically lithium should exert an equal effect on all parathyroid glands (67). Carchman et al., however, states there to be no significant increased risk for multiglandular disease (MGD) in the sixteen lithium-treated patients who had undergone focused parathyroid exploration (68). Other studies indicate the continued predominance of SGD in cases of LHPT, though also displaying increased frequency of MGD in comparison to pHPT (69-73). On the other hand, numerous studies present higher frequencies of MGD ranging from 25-83% (57, 74-80) (Appendix 1). The equivocation of lithium’s particular role in the development of HPT is often reflected in the use of language to describe this endocrinopathy: lithium-associated versus lithium-induced, with the latter indicating a more certain relationship.

Up until the turn of the twentieth century, LHPT was largely viewed as being almost indistinguishable from pHPT. Saunders et al. in a review article summarises how LHPT was considered that, “it is not entirely understood whether lithium causes hyperparathyroidism directly or somehow potentiates hyperparathyroidism in patients with early parathyroid dysfunction” (59). This is also the view proposed by Szalat et al. who believe lithium
leads to an exacerbation in patients with a “pre-existing HPT state” (57). Most cases described in the literature were, as in pHPT, postmenopausal females. The first documented case descriptions confirmed the existence of adenoma, but only reported very short or no follow-up, making it difficult to assess curative claims (39, 71, 81, 82). As early as 1976, Dr. Tony Christensson in the Lancet suggests the routine monitoring of serum calcium during lithium therapy, a theme that runs through all studies on this subject (71). This has, as yet, not fully been put into clinical practice. Another frequently described phenomenon is the belief that lithium withdrawal will result in the normalisation of elevated calcium values (20, 40), though in our material we have not witnessed this in the few cases we know of where lithium was withdrawn because of hypercalcaemia. This may have to do with lithium duration.

**Clinical management of pHPT and LHPT**

If there is one classic dictum from my medical education that has stayed with me it is the mnemonic “stones, bones, moans and groans”, illustrating the traditional symptomatology of pHPT, where renal stones, bone loss, psychiatric disabilities (particularly in the elderly), and lastly muscular fatigue have all been the hallmarks of this disease. The condition *Hyperparathyroidism* first gained its name in 1927 from the Viennese surgeon, E. Gold, who understood that the parathyroid glands were overactive and, thereby, followed the example of his colleague, Dr. Felix Mandl, the first surgeon to perform a parathyroidectomy in 1925 (83). At that time, patients with the disease had gravely debilitating symptoms that may have resulted in them being bed-ridden or in need of electro-convulsive therapy! In recent decades, with the introduction of efficient and affordable blood tests, as many as 80% of patients are detected at an “asymptomatic” stage (63). The only cure for pHPT is surgery, and since the majority of cases are caused through SGD i.e. adenoma, unilateral neck exploration (UNE) or focused surgery with adenomectomy is most often utilised. The operation can be successfully performed in local anaesthesia, with most patients being discharged the same day (though praxis in Sweden often allows for one night of observation in hospital) and up to 98% being considered cured at follow-up (63, 84). Indications for surgery are predominantly to reduce bone loss, especially in younger individuals (i.e. < 50 yrs old), but good results have also been well-documented in older individuals, particularly with regards quality of life (85, 86). Primary HPT has also been proposed to be associ-
ated with cardiovascular disease, diabetes, and the development of malignant disorders (87, 88). The treatment of pHPT is, therefore, socially and health-economically cost-effective, and surgery seldom gives rise to complications (89). The curative results of surgery in patients with LHPT have, however, not been as good.

This fact that so many studies reported MGD in patients with concurrent lithium therapy could have ramifications for the treatment and management of LHPT. Most authors support BNE (bilateral neck exploration) as an appropriate surgical strategy that should be considered (72, 74, 80, 90), but this has not meant a unified approach to surgical outcome, with Nordenström et al. (80) reporting that 1-2 parathyroid glands left in situ. Available follow-up times varied from a few to 31 months, somewhat limiting assessment of long-term results of surgery. Surgical series are based on small cohorts, but that given, many authors reported persistent or recurrent disease. Awad et al. reported that 14/15 had adenomas (of these, three had double adenomas!) and at 2-year follow-up one person had recurrent disease (72). Interestingly, while Abdullah et al. (90) and Hundley et al. (74) both report cases of recurrence, they also describe a total of five cases of normocalcaemic hyperparathormonemia, possibly indicating a suboptimal first operation which progressively leads to a subclinical form of LHPT at latest follow-up. The predictive value of intraoperative PTH measurement (IOPTH) is also disputed in LHPT (74).
Aims of the thesis

At the outset of the studies presented in this thesis, little was known about the true prevalence of hypercalcaemia, or LHPT, in patients with concurrent lithium therapy, considerable controversy existed as to lithium’s role in calcium disturbances, and the largest surgical study examining LHPT consisted of 26 patients. The principal aim of this thesis was to understand and more comprehensively characterise, in a larger patient cohort, the condition referred to as lithium-associated hyperparathyroidism (LHPT). The studies presented herewith have attempted to bring new insights to an otherwise slightly impoverished area of medical knowledge.

Paper I To calculate the prevalence of hypercalcaemia and LHPT, based on biochemical indices, in a well-defined population of lithium-treated adults attending psychiatric out-patient units.

Paper II To determine the prevalence of hypercalcaemia in bipolar patients with concurrent lithium treatment and compare this firstly to bipolar patients without lithium treatment and secondly to a randomly selected control population.

Paper III To examine in detail, through a retrospective examination of medical records, calcium homeostasis in a well-defined lithium-treated population.

Paper IV To evaluate the results of surgery in a large series of patients with LHPT treated during a 16-year interval.
Patients and methods

Patients
The series of studies in this thesis are not presented in chronological order but rather in a more thematic order, which I think has a pedagogical point where I am aiming to describe how common the disorder is, what the pathological background may be, and lastly, how best to manage those that have the condition. Inevitably, these themes are touched upon in all the studies.

For Paper I, a total of 423 individuals (251 women, 172 men) with concurrent lithium therapy were recruited from Affective Psychiatric Outpatient Units in Örebro County (Örebro, Lindesberg, Hallsberg; in total 247) and from Jönköping Municipality. They were aged between 19 and 92 years old (mean age 57 yrs) and had medicated with lithium on average 13.5 years (SD±9.5yrs). Seventy-five percent had BD as the principal diagnosis. The bipolar patients in this population also became the focus for our attention in Paper II. In total, 313 individuals (188 women, 125 men) with BD with lithium therapy were identified from Paper I. These individuals were compared to 148 individuals (88 women, 60 women) with BD without concomitant lithium therapy as well as to a control population consisting 102 individuals (62 women, 40 men) without any known psychiatric diagnosis. The individuals in Paper III consisted of all patients in Jönköping Municipality who had received lithium medication for a minimum of 1.5 years. This meant the enrolment of 297 individuals (193 women, 104 men), with a minimum age of 18 years. A majority of these patients were also enrolled in Paper I.

In Paper IV, seventy-one individuals (55 women, 16 men) with lithium therapy and who had undergone parathyroid surgery were identified through an inspection of surgical records at six centres in Sweden. These included the surgical departments at the district hospitals in Eksjö, Jönköping, and Vänersborg-Trollhättan, and even at the university hospitals in Gothenburg, Umeå and Stockholm.

Definitions
Hypercalcaemia was defined in Papers I-IV as being an average total calcium TCa≥2.50 mmol/l, in accordance with national guidelines. Hypocalcaemia was additionally defined as TCa<2.15 mmol/l or iCa<1.15 mmol/l. Furthermore, polypharmacy was defined as having 5 or more pre-
scribed drugs simultaneously (91). A working definition of LHPT was proposed in Paper I with the purpose of doing an initial screening of the defined population (Figure 3). The formation of the definition was based on clinical experience but also with careful consideration of the literature.

**Figure 3. Proposed working definition of lithium-associated hyperparathyroidism (LHPT).**

\[
i\text{Ca} > 1.30/\ T\text{Ca} > 2.45/\ T\text{Ca}_{\text{corr}} > 2.45 + \text{PTH} > 65 + 25(\text{OH})\text{-vit D} > 25 \\
\text{or} \\
i\text{Ca} > 1.34/\ T\text{Ca} > 2.50/\ T\text{Ca}_{\text{corr}} > 2.50 + \text{PTH} > 65, \text{independent of} \\
25(\text{OH})\text{-vit D} \\
i\text{Ca} = \text{ionised calcium; } T\text{Ca} = \text{total calcium; } T\text{Ca}_{\text{corr}} = \text{”corrected” total calcium; } 25(\text{OH})\text{-vit D} = 25\text{-hydroxyvitamin D}
\]

In Paper IV, persistent disease after operation was defined as having elevated serum calcium at six months follow-up. Recurrent disease was defined as having elevated serum calcium at follow-up in an individual who was otherwise normocalcaemic at 6 months after the operation.

**Methods**

The areas for recruitment in Papers I-III were Örebro County and Jönköping Municipality. These two socio-economically similar areas, located in central Sweden, have approximately 450,000 residents, which is roughly 4.5% of Sweden’s population. For Paper I all relevant clinical and laboratory data was collected according to a protocol the authors had constructed. Collected data included, apart from demographic details, treatment duration, blood tests reflecting calcium homeostasis and parathyroid function, and information as to whether patients had undergone neck-surgery. Details were documented between October 2012 and March 2014.

The patients from Paper I with diagnosis BD were then investigated further with regards risk for development of hypercalcaemia. These patients were compared to a second population, patients with BD without concomitant lithium treatment, and who were recruited as part of a research project called the St.Göran’s Bipolar Project led by psychiatrist Professor Michael
Landén (co-author Paper II)(92). The project is an interdisciplinary longitudinal study aimed at further understanding the neurobiological mechanisms of mood disorders with specific attention to the clinical setting. The project started in October 2005 and regular follow-ups have occurred and continue to occur annually. Patients were recruited from the Bipolar Out-patient Unit at the Northern Stockholm Psychiatric Clinic, Stockholm, Sweden, with a catchment of approximately 300,000 residents. A third population-based control group was randomly selected by Statistics Sweden (SCB) (93). Individuals were contacted by post and 14% of those contacted agreed to participate as volunteers, and this level of participation is, according to SCB, comparable to similar studies. Assessment of symptomatology and daily function was assessed according to Global Assessment of Function (GAF) and ascertained for 403 participants (94). Concerning these latter two populations, appropriate data for assessment of parathyroid function was limited, though details concerning calcium, creatinine and current medications were available. Medications were categorised according to whether they were mood-stabilisers, central stimulants, antidepressants, antipsychotics, anxiolytics, “non-psychiatric” medications – most often for the treatment of hypertension or diabetes, and lastly whether Levothyroxine was prescribed. Surgical details were available for 7 patients with lithium therapy.

In Paper III calcium homeostasis in lithium-treated patients was characterised, whereby every effort was made to retrieve all available calcium determinations for all included patients. The introduction of computerised medical journals in 1999 has definitely facilitated data collection, and while calcium monitoring has occurred regularly though not consistently since then, before this year, the determination of serum calcium occurred sporadically. Serum calcium values were retrieved in 66% of participants before lithium initiation. Data was collected between January and April 2017. Three-year intervals were deemed to be clinically relevant for the assessment of calcium homeostasis since lithium associated hypercalcaemia is thought to be slightly progressive and relatively stable (61, 95). For each three-year period, mean calcium was calculated and the lowest and highest determination noted, along with the number of determinations which were pathological. Participants were grouped according to whether they had normocalcaemia (though, at most, 2 hypocalcaemic and/or 2 hypercalcaemic values were accepted), hypercalcaemia (2 hypocalcaemic values accepted), or hypocalcaemic (2 hypercalcaemic values accepted). Sixty-six patients, with 5 or more elevated serum calcium values, were considered to have suspected...
LHPT and further tests were carried out including 24-hour urine calcium levels in 29 cases. Surgical results of 16 parathyroidectomies were presented.

For Paper IV, inspection of surgical records took place in 2008 regarding all parathyroidectomies at the six surgical centres between 1991-2006. All operations were performed by experienced surgeons. All specimens were analysed at the local pathology department. Extirpated specimens were either weighed or measured. When the specimens were measured, weight was calculated according to an accepted formula by Parfitt et al (96). Histopathological evaluations were carried out according to recommended pathological criteria (97).

Statistics
Descriptive statistics were used in all four papers which included the presentation of frequencies, percentages, means and standard deviations, and when appropriate, median values and ranges. In Papers I-III, Chi-squared test (for categorical measures), Student’s t test (for normally distributed continuous measures) and Wilcoxon rank sum test (non-parametric distributed continuous measures) were used. In Paper I a multivariate analysis was performed with data from 154 participants using the parameters lithium duration, levothyroxine usage, eGFR and vitamin-D levels and its association with HPT, adjusted for age and sex. A further multivariate analysis was performed in Paper II comparing hypercalcaemia in bipolar patients with and without lithium and the control population with regards age, sex, kidney function, pathological TSH, medications. Statistical differences were calculated in Paper IV by means of Mann-Whitney U test.

The statistical software used was Stat version 12/SE for Windows (StatCorp, College Station, Texas), Excel® 2016, SPSS (version 22). P-values less than 0.05 were considered significant.

Ethics
All studies in this thesis were conducted according to the principles of the Helsinki Declaration. Permission for the execution of Papers I-III was granted by the Regional Ethical Review Board, Uppsala, Sweden in 2011. The study in Paper IV was approved after communication with the Regional Ethical Review Board, Linköping, Sweden in 2007.
Results

Paper I: Prevalence of LHPT

One third of the entire group had mean TCa > 2.45mmol/l. According to our working definition of LHPT (Figure 3), 77 patients (18%) fulfilled the criteria, having a median TCa= 2.55mmol/l (2.45-2.86) and PTH=90 ng/l (65-305), while a further 21% of patients had had at least one elevated calcium determination during the study period (Table 1).

Table 1. Basic parameters of HPT status in 77 patients treated with lithium.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Reference value</th>
<th>HPT, n=77</th>
<th>Non-HPT, n=246</th>
<th>P value</th>
<th>Total, n=323</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs, mean (SD)</td>
<td>65 (±12.00)</td>
<td>55 (±15.04)</td>
<td>57 (±14.97)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>55 (71)</td>
<td>142 (58)</td>
<td></td>
<td>0.031†</td>
<td>197 (61)</td>
</tr>
<tr>
<td>Creatinine, µmol/l</td>
<td>60-105</td>
<td>93 (65-171)</td>
<td>86 (60-155)</td>
<td>0.082‡</td>
<td>86 (60-171)</td>
</tr>
<tr>
<td>Males, median (range)</td>
<td>45-90</td>
<td>80 (58-130)</td>
<td>70 (46-101)</td>
<td>&lt;0.001‡</td>
<td>72 (46-130)</td>
</tr>
<tr>
<td>Females, median (range)</td>
<td>2.10 – 2.55</td>
<td>2.55 (2.35-2.86)</td>
<td>2.42 (2.17-2.73)</td>
<td>&lt;0.001‡</td>
<td>2.44 (2.17-2.86)</td>
</tr>
<tr>
<td>Total Calcium, mmol/l, median (range)</td>
<td>10 – 73</td>
<td>90 (65-305)</td>
<td>58 (22-206)</td>
<td>&lt;0.001‡</td>
<td>66 (22-305)</td>
</tr>
<tr>
<td>PTH, ng/l, median (range)</td>
<td>48 (17-103)</td>
<td>53 (9-146)</td>
<td></td>
<td>0.192‡</td>
<td>52 (9-146)</td>
</tr>
<tr>
<td>Vitamin D, nmol/l, median (range)</td>
<td>23 (3-40)</td>
<td>9 (2-44)</td>
<td></td>
<td>&lt;0.001‡</td>
<td>11.5 (2-44)</td>
</tr>
<tr>
<td>Duration of lithium therapy, yrs, median (range)††</td>
<td>3.67 (1.80 – 7.00)</td>
<td>4 (1.83 – 7.13)</td>
<td>0.520‡</td>
<td>3.98 (1.80 -7.13)</td>
<td></td>
</tr>
<tr>
<td>Average number of lithium tablets per day, median (range)††</td>
<td>70 (±15.21)</td>
<td>87 (±16.08)</td>
<td>&lt;0.001*</td>
<td>81 (±17.80)</td>
<td></td>
</tr>
<tr>
<td>Levothyroxine use, n (%) ††</td>
<td>21 (39.62)</td>
<td>17 (16.83)</td>
<td></td>
<td>0.002†</td>
<td>38 (24.68)</td>
</tr>
<tr>
<td>GFR, estimated according to the MDRD formula, ml/min/1.73 m², mean (SD) ††</td>
<td>70 (±15.21)</td>
<td>87 (±16.08)</td>
<td>&lt;0.001*</td>
<td>81 (±17.80)</td>
<td></td>
</tr>
</tbody>
</table>

* P value from t-test
† P value from Chi square test
‡ P value from Mann-Whitney (Wilcoxon rank-sum) test
** Information was available for 68 individuals with HPT and 200 non-HPT individuals; 75nmol/l is the recommended optimal value for patients
†† Information was available for 154 (45%) individuals: 53 with HPT and 101 without HPT
SD = standard deviation; PTH = parathyroid hormone; GFR = Glomerular Filtration Rate, MDRD = Modification of Diet in Renal Disease formula (available at: www.mdrd.com)
The LHPT group was constituted predominantly of women (71%) and older individuals (median age 65 yrs) compared to the non-LHPT group which was significantly younger (median age 55 yrs). Vitamin D was determined in 287 patients (68%) at various seasons of the year and no statistical difference could be detected between the two groups. No patient had end-stage renal failure, though 7 patients had lithium withdrawn because of detrimental effects on renal function. In the multivariate analysis completed with data from 154 patients, lithium duration, levothyroxine usage (as an indirect sign of thyroid pathology), and kidney dysfunction all proved to be significant factors in distinguishing the groups. Only five patients (≈1%) had undergone parathyroidectomy (PTX).

**Paper II: Lithium-associated hypercalcaemia in BD**

Bipolar patients with lithium (BWL) were compared to Bipolar patients without lithium (BWOL) and a control population with regards calcium homeostasis. Of all individuals with BD (BWL + BWOL), 87 (16%) had hypercalcaemia with a median TCa = 2.57 mmol/L (range 2.50 – 2.86) (Figure 4). A majority of them (94%) belonged to the BWL group (p=0.001). Creatinine was not shown to be significantly different between these groups. Once again, those who were hypercalcaemic were predominantly women (67%) and older, with a median age of 64 (range 24-90) years.
Figure 4. The distribution of calcium values for the three separate study groups. The available values included bipolar with lithium treatment (n=313), bipolar without lithium (n=148), population-based control group (n=102). The median calcium value for the group as a whole was 2.37 mmol/l (illustrated with red line). Eighty-seven patients had P-Ca > 2.5 mmol/l; of those, eighty-two (94%) were bipolar patients with lithium treatment.

Patients with BD generally scored lower in the symptom scale GAF (values available for 403 individuals) compared to the control population, and though there were indications that those with hypercalcaemia scored lower, these did not prove statistically significant. BWL had much more polypharmacy, possibly indicating a greater level of psychiatric morbidity. In a multivariate analysis (Table 2), comparing BWL and the control population with BWOL (regarded as the reference population), concomitant lithium therapy (adjusted OR 13.45; 95% CI 3.09, 58.55; \( p = 0.001 \)) was very strongly associated with hypercalcaemia, as was age and gender.
Table 2. Multivariable analysis comparing hypercalcemia in bipolar patients without concomitant lithium treatment with bipolar patients with lithium and to a control population.

<table>
<thead>
<tr>
<th>Study groups*</th>
<th>Unadjusted OR (95% CI)</th>
<th>P value</th>
<th>Adjusted OR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bipolar without lithium</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
<td>23.96 (5.80,99.00)</td>
<td>≤0.001</td>
</tr>
<tr>
<td>Control population</td>
<td>2.05 (0.36,12.47)</td>
<td>0.438</td>
<td>2.40 (0.38,15.41)</td>
<td>0.355</td>
</tr>
<tr>
<td>Age</td>
<td>-</td>
<td>1.04 (1.02,1.06)</td>
<td>≤0.001</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>-</td>
<td>0.38 (0.19,0.77)</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>-</td>
<td>1.01 (0.99,1.03)</td>
<td>0.489</td>
<td></td>
</tr>
<tr>
<td>Pathological TSH</td>
<td>-</td>
<td>1.30 (0.63,2.69)</td>
<td>0.477</td>
<td></td>
</tr>
<tr>
<td>Levothyroxine</td>
<td>-</td>
<td>1.03 (0.46,2.28)</td>
<td>0.945</td>
<td></td>
</tr>
<tr>
<td>Antidepressants</td>
<td>-</td>
<td>0.38 (0.21,0.67)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>-</td>
<td>1.88 (1.04,3.04)</td>
<td>0.036</td>
<td></td>
</tr>
<tr>
<td>Anxiolytics</td>
<td>-</td>
<td>1.66 (0.80,3.45)</td>
<td>0.174</td>
<td></td>
</tr>
<tr>
<td>“Non-psychiatric” medications</td>
<td>-</td>
<td>1.45 (0.75,2.79)</td>
<td>0.273</td>
<td></td>
</tr>
</tbody>
</table>

* Complete values were available for 552 individuals.

Surgical results were presented in seven cases of PTX, performed due to suspected LHPT in four women and three men with a median age of 60 (range 46-74) years, with lithium duration a median of 29 (range 14-34yrs) years. Four patients had parathyroid hyperplasia (a median of two glands extirpated), one was deemed to have normal parathyroid glands (1 gland extirpated, a half taken for biopsy), one patient had lipoadenoma in the one extirpated gland (but later re-operated with a further 2 hyperplastic parathyroid glands extirpated), and lastly one patient had an adenoma. Six patients had recurrent disease after the initial operation, with a median follow-up of 11(range 5-12) years. The patient who underwent a second operation was normocalcaemic at one-year follow-up.

Paper III: Hypercalcaemia and hypocalcaemia?
Three groups of patients with concurrent lithium therapy were identified based on calcium homeostasis: 178 were normocalcaemic (60%), 102 hypercalcaemic (34%), and 17 hypocalcaemic (6%). Before starting with lithium, four female patients were hypocalcemic, ranging in values from 2.02-
2.14 mmol/l, but all patients normalized with time. An additional four patients (two men, two women) had hypercalcemia 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 PTX resulting in persistent disease.

Table 3. Intergroup analysis comparing the three categorized groups with pathological calcium values (hypo grp= hypocalcaemic group (n=17); hyper grp= hypercalcaemic group (n=102)) with the normocalcaemic group (n=178).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group values</th>
<th>Normocalcemic lithium-treated patients</th>
<th>p-value§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range), yrs</td>
<td>Hypo grp= 66 (43-92)</td>
<td>52 (22-89)</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td></td>
<td>Hyper grp= 64 (21-91)</td>
<td></td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>Female (%)</td>
<td>Hypo grp= 10 (59)</td>
<td>113 (63)</td>
<td>0.720</td>
</tr>
<tr>
<td></td>
<td>Hyper grp= 69 (68)</td>
<td></td>
<td>0.480</td>
</tr>
<tr>
<td>Average calcium values, median (range), mmol/l (ref.2.15-2.50)</td>
<td>Hypo grp= 2.24 (1.86-2.59*)</td>
<td>2.33 (2.02-2.86*)</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td></td>
<td>Hyper grp=2.45 (2.03-3.09*)</td>
<td></td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>Lithium duration, median (range), yrs</td>
<td>Hypo grp= 17.0 (1.5-40)</td>
<td>11.5 (1.5-40)</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td></td>
<td>Hyper grp= 23.0 (3-45)</td>
<td></td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>Creatinine at last follow-up, median (range), μmol/l (ref.45-90)#</td>
<td>Hypo grp= 81 (59-115)</td>
<td>75 (42-173)</td>
<td>0.218</td>
</tr>
<tr>
<td></td>
<td>Hyper grp= 80 (49-205)</td>
<td></td>
<td>&lt;0.000</td>
</tr>
</tbody>
</table>

§ P-value from t-test.
*Two pathological values in either direction (hypo-or hypercalcemia) were accepted as a normal occurrence. Categorization was based on the occurrence of at least three pathological values.
# Reference values for women are 45-90 μmol/l and for men 60-105 μmol/l.

A total of 8504 calcium determinations were retrieved, 234 before lithium therapy initiation. The median therapy duration before the first elevated calcium determination was 10.5 (range 1.5-44) years. Both the hypercalcaemic and hypocalcaemic groups differed significantly from the normocalcaemic group in terms of age, calcium status and lithium therapy duration (Table 3). Twenty-four patients in the hypercalcaemic group had elevated but stable creatinine values, thus explaining the apparent difference in kidney function detected in the analysis (Table 3). No obvious reason
(diuretics, chronic kidney failure, neck surgery, severe disease) could explain why those in the hypocalcaemic group had intermittent hypocalcaemic episodes, and remained largely in the lower reference range for TCa.

There were considerable variations in serum calcium levels during the observation period, in particular in the hypercalcaemic group. Further biochemistry was retrieved in 66 patients with either surgically confirmed or with strongly suspected LHPT. Of those, 7 had already undergone PTX, 8 were planned for PTX in the near future (one reoperation), and 56 with biochemistry supporting suspected LHPT. These patients had a median TCa of 2.55mmol/l (range 2.32-3.1) together with increased PTH value of 9.8pmol/l (range 3.3-39). All other parameters (phosphate, creatinine, vitamin-D) were largely normal, though it is worth noting that urinary calcium excretion was generally low, with 9 patients (31%) having values below 1.2 mmol/24hrs.

Surgical results of 16 PTX (one reoperation) were also presented. Sestamibi scan had been performed in ten of the cases with reliable, predictive information correlated to surgical findings in only two (both cases histopathology shown adenomas). A total of 36.5 parathyroid glands were extirpated 26.5 were identified as hyperplastic (Table 4). Ten patients are hitherto normocalcaemic but the follow-up times are relatively short. Two hemithyroidectomies were performed revealing follicular thyroid cancer.

Table 4. Surgical results for fifteen lithium-treated patients having undergone sixteen parathyroidectomies, including one re-operation, for hyperparathyroidism.

<table>
<thead>
<tr>
<th>Surgical method*</th>
<th>Histopathological diagnosis</th>
<th>Calcium at follow-up (ref.2.10-2.50mmol/l), median (range)</th>
<th>Follow-up (months), median (range)</th>
<th>Cure?</th>
</tr>
</thead>
<tbody>
<tr>
<td>UNE= 4* BNE= 12</td>
<td>Adenoma= 5 Hyperplasia= 26½ Normal=3</td>
<td>2.36 (2.19-2.89)</td>
<td>27 (12-144)</td>
<td>Cure= 10 Recurrent= 2 Persistent= 4</td>
</tr>
</tbody>
</table>

*Unilateral Neck Exploration (UNE) indicates that only one side of the neck is exposed during an operation for hyperparathyroidism, whereas in Bilateral Neck Exploration (BNE) both sides are exposed.

#One re-operation: right lower gland extirpated in 2006 revealing hyperplasia and the patient had persistent disease. At re-operation in 2016, UNE of left side revealed two macroscopically enlarged glands, though one was later judged to be an adenoma, the other revealed normal parathyroid histology.
Paper IV: Long-term surgical results

Seventy-one lithium-treated patients had undergone a total of 78 PTX, five women underwent two operations and one woman underwent three. The median age at the primary operation was 61 (39-81) years, with a median lithium therapy duration of 19 (0.5-40) years. A summary of results is presented in Table 5. Median follow-up was 6.3 (IQR 4-11) years. BNE was used in all but two of the primary 71 operations. Thirty-two patients (45%) were judged to have adenomas, 2 (3%) with double adenomas, and 37 (52%) with hyperplasia. A median of 3 (2-4) parathyroid glands were identified in those with adenomas and 1.5 (1-1.5) were extirpated. Whereas, in the hyperplasia group, a median of 4 (3-4) glands were identified and 2.5 (2.5-3) were extirpated. Duration of lithium therapy was significantly longer in the hyperplasia group, 20 (IQR 15-25) years compared to 10 (IQR 3.5-27) years in the adenoma group.

Table 5. A summary of results of primary parathyroidectomy surgery at six-months and latest follow-up in 71 lithium-treated patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Result</th>
<th>Extent of surgery: no. of extirpated glands</th>
<th>Normocalcaemia at 6 months (%)</th>
<th>Normocalcaemia at median 6.3 yrs (IQR 4-11) follow-up (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women (no.)</td>
<td>55</td>
<td>65</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>Men (no.)</td>
<td>16</td>
<td>94</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td>Total calcium median (IQR), mmol/l (ref.2.15-2.50)</td>
<td>2.76 (2.68-2.88)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ionised calcium median (IQR), mmol/l (ref.1.15-1.34)</td>
<td>1.48 (1.36-1.55)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTH (% of upper reference value)</td>
<td>173 (112-158)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine at last follow-up, median (range), µmol/l (ref.45-90)</td>
<td>98 (82-115)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis - Adenoma</td>
<td>34</td>
<td>1.5 (1-2)</td>
<td>76</td>
<td>59</td>
</tr>
<tr>
<td>Hyperplasia</td>
<td>37</td>
<td>2 (0-4)</td>
<td>70</td>
<td>57</td>
</tr>
</tbody>
</table>

*Due to different methods used to measure PTH, data is expressed as percentage of the upper reference value

The overall cure-rate was 58%, and similar results were seen in both histopathological groups at 6 months and latest follow-up. A tendency to incrementally increasing calcium values was surmised in the 14 normocalcaemic patients at latest follow-up. Gland weight was lower in those found to be cured. Although no statistically verifiable difference was detected between the number of extirpated glands in relation to “cure” in separate each group (in the adenoma group 1.5 vs 1, and in the hyperplasia group 3 vs 2),
results indicated that more radical surgery was conducive to attaining normocalcaemia (Figure 5). It should be noted that 9 patients at follow-up were hypocalcaemic and required substitution with calcium and vitamin D. Six patients, thought to have persistent disease at 6 months follow-up, were subsequently normocalcaemic at latest follow-up. Of those 6 women who underwent re-operations, two became normocalcaemic, and one developed hypoparathyroidism.

Figure 5. Cure in relation to the number of parathyroid glands extirpated in lithium-treated patients with adenomas or hyperplasia.
Discussion

Paper I

As far as I know, Paper I represents the largest prevalence study of LHPT in psychiatric out-patients. It revealed that 18% were suspected of LHPT, while a further 20% had intermittent episodes of hypercalcaemia. The estimated prevalence of LHPT, and indeed hypercalcaemia in lithium-treated patients, has varied widely in earlier studies, from 2.7-80% (98-101). This depends on three main factors: firstly, how the LHPT was confirmed (e.g. in Bendz et al.(98) it was surgically confirmed, thus giving only 2.7%, compared to biochemically, as in Lally et al. (32), estimated 5.3% LHPT in 333 patients); secondly, the size of the cohort studied (e.g. Nordenström et al. (80) described 6 LHPT patients, Twigt et al. (102) had a cross-section analysis of 314) (Appendix 1); thirdly, since LHPT develops with time, the duration of lithium treatment is of great importance (McHenry et al. (40) reported an median treatment duration of 8 years, while Lally et al. (32) reported a mean of 15 years) but after two decades approximately a quarter of patients have LHPT or clear disturbances in calcium metabolism. McKnight et al. in a meta-analysis of lithium toxicity estimates the absolute risk of LHPT to be 10% (37).

Making assessments about parathyroid function is always difficult without a complete laboratory work-up, which should include calcium (preferably iCa), PTH and vitamin D (47). One of the major challenges with the study has been the variable inconsistency of calcium monitoring. Recently adjusted international recommendations for the treatment of BD with lithium may go some way in improving this issue, though it will likely take time for relatively new knowledge about lithium’s impact on calcium metabolism to be converted into local guidelines (30, 34, 36). It is still controversial to consider LHPT as a separate endocrinopathy rather than an “expression” of pHPT. Clinically, this patient group has been somewhat overlooked in terms of evaluating the possible benefits of surgical intervention, in that most patients have only normal to moderately elevated calcium levels, similar in some respects to asymptomatic HPT. However, patients with this latter condition have shown clear benefits of surgery in terms of improved QoL (95, 103). In addition, Lundgren et al. has reported an underdiagnosis of HPT in a particular risk group, i.e. women over 55 years old (104). We constructed a working-definition based on the considerable experience of
the senior researchers involved in the project and careful attention to the literature (33, 37, 57, 59, 61, 105).

One main reason for such a definition is to allow for early detection of patients who potentially could develop hypercalcaemia or LHPT. As yet, there exists no consensus document for the management of hypercalcaemia or HPT in lithium-treated patients (102), though the European Society of Endocrine Surgeons consensus report on sporadic multiple parathyroid gland disease concisely describes the current surgical approach to LHPT (62). It is suggested, and our own studies confirm this suggestion, that LHPT differs substantially from pHPT and, thereby, needs to be managed differently (59, 106). One intriguing difference, discussed extensively by Mak et al., is the inappropriate elevation of PTH in relation to serum calcium levels (107). Albert et al. also confirm the tendency to higher levels of PTH in lithium-exposed patients, even soon after starting with lithium (108). Careful monitoring is needed, which is why an algorithm was developed to help clinicians in the management of calcium metabolism in lithium-treated patients.

We identified that age, gender (i.e. females), and lithium duration were all important factors in the development of hypercalcaemia, but it might be that age and lithium duration are closely related cofactors. Several authors have shown that age and gender are significant factors in the development of LHPT (33, 57, 105, 109), and in this sense similar to pHPT, but Twigt et al. (102) could only show that lithium duration was significant. Although lithium theoretically should exert its systematic effects on all parathyroid glands equally, it is only approximately 40% that develop calcium disturbances. The reasons for this remain unclear, but it may involve individual or a combination of morbidity factors (e.g. polypharmacy, kidney function) and/or genetic factors. More studies are needed to clarify this.

Only five patients had undergone PTX. Our interpretation of this is that mildly elevated serum calcium and/or PTH – which generally characterise LHPT – are accepted by most psychiatrists as tolerable or “just above the reference value”, and therefore not requiring further clinical investigation. However, these findings in themselves create a new series of questions: what implications do moderately elevated calcium levels have for the individual receiving lithium therapy? How is their skeletal status? Should more receive surgery? What causes the variability in LHPT patients’ calcium homeostasis, where many pendulate between normo- and hypercalcaemia? And, not least, since so many have BD, are calcium disturbances associated with their
fundamental illness and not the treatment? This latter question became the starting-block for the next study!

**Paper II**

Bipolar disorder (BD) is strongly associated with endocrine conditions such as diabetes type II and cortisol disturbances (110). In a recent study, it has even been demonstrated that of four genetic loci associated with five major psychiatric diagnoses, including BD, two are specifically involved in the expression of calcium channels (111). We, therefore, had to rule out that LHPT was not the consequence of the BD disease in itself. Our comparisons of the calcium homeostasis in BD patients with and without lithium therapy, as well as an additional control population, showed lithium to be overwhelmingly associated with the development of hypercalcaemia, even in adjusted models of analysis. Thus, LHPT is not primarily associated with BD. With such a strong association, it is imperative that careful monitoring be implemented. One possible way of increasing awareness of this condition in Sweden would be to incorporate reporting-items concerning parathyroid function in the national Bipolar Register (112).

The study, once again, confirmed that age and gender were key factors associated with hypercalcaemia, and additionally even thyroid dysfunction. While the association of lithium and development of hypercalcaemia is compelling especially in some risk groups, there are currently no predictors which indicate who is most likely to develop hypercalcaemia or LHPT (102). Indeed, any causal relationship is still unconfirmed (113). Mak et al. noticed that PTH increased when lithium was introduced in 53 adults without an increase in calcium and propose some form of “counterregulating factor offsetting the hypercalcemic effect of PTH”, which is unknown (107). On the other hand, Christiansen et al. report that both PTH, calcium and magnesium increased in 13 individuals who had been “lithium naive” earlier, increases which took place in the first two years (114). It is, therefore, prudent that more careful monitoring be applied to those who match these criteria. The aforementioned risk factors might also be influential in deciding the extent of surgery, should it be necessary.

GAF is often used by psychiatrists to assess the patient’s level of symptoms and general functioning. This instrument is dependent on the assessor. Validated instruments are needed to evaluate the implications of hypercalcaemia and HPT for the individual patient treated with lithium. In our randomised study, explained later in this introductory essay, we use a range of
instruments (MADR-S, AS-18, SF-36, VAS - see Table 7) in order to decipher and detect what may often be very discrete symptoms. In general, there is a poor correlation between psychosymptomatology and the development of hypercalcaemia, though acutely elevated calcium can lead to psychosis and coma (115). It may be the case that the symptomatic consequences of even mildly elevated serum calcium levels are underestimated (116, 117). A problem illustrated by several authors is that of doctor’s delay, i.e. in clinical practice it often takes a considerable amount of time to differentiate the patient’s possible symptoms related to hypercalcaemia/LHPT (e.g. muscle weakness, fatigue, “loss of incentive”) from their affective disorder for which they are receiving lithium treatment (68, 102, 118). Today there exist no specific, validated tools to help in differentiating between the conditions which is why regular monitoring and the judicious use of symptom scoring, from a range of instruments, is to be advised.

In the seven surgical cases reported, the pre-operative median TCa was 2.73mmol/l and PTH=106 ng/l. A median of 3 parathyroid glands were identified but only a median of 2 were removed. Six patients had recurrent disease, one with persistent disease and was re-operated 10 years after the initial operation. MGD is to be regarded as the major histopathological diagnosis, meaning that an optimal first operation is vital. The surgical results in this study go some way in confirming that normocalcaemic HPT or mildly elevated hypercalcaemia is often seen in the presence of MGD (119). Further, it would suggest that subtotal PTX could be a suitable surgical strategy for this specific patient group.

**Paper III**

This comprehensive study of lithium-treated patients demonstrates, yet again, that hypercalcaemia is an unambiguous side-effect of lithium therapy, affecting approximately a third of all patients. Furthermore, through the sheer multitude of tests retrieved, a considerable inter- and intraindividual variation could be seen. This possibly clarifies the reason why some individuals thought to have LHPT at one point in time can later present with normocalcaemia (or even tendencies to hypocalcaemia) through robust fluctuations in calcium homeostasis. This surely is one major difference between LHPT and pHPT. It is also the reason, we think, that the mean calcium for the entire group at the start and at the end are not dramatically different, though the ranges are. Furthermore, we noticed that there was, at times, great inter-individual variation between TCa and iCa and has been influential in studies in determining the prevalence of hypercalcaemia:
Bendz et al. used TCa and estimated hypercalcaemia prevalence to be 3.6%, while Toffaletti et al. used iCa and found the prevalence of hypercalcaemia to be 7.4% (82). In addition, to the best of our knowledge, this is the first study to illustrate the rather bewildering existence of hypocalcaemia in a small group of lithium-treated patients. No apparent reason could be ascertained and we interpret this phenomenon as a reflection of a wider dysfunction, possibly as a result of chronic lithium therapy. Unfortunately, no co-incident PTH determination nor vitamin D were taken at the episodes of hypocalcaemia, but kidney failure- as assessed by creatinine- could be ruled out. Lithium duration showed a reasonable correlation in the development of hypercalcaemia ($R^2=0.45$), and even hypocalcaemia ($R^2=0.52$). Thus, all patients having medicated with lithium ten years or more should undergo more attentive monitoring.

Mallette & Eichhorn described that serum calcium and PTH increased within the first four weeks of lithium treatment, but within upper normal ranges (120). The results achieved in this study go still farther than describing solely calcium disturbances, but additionally illustrate what characterises LHPT, namely, normal to mildly elevated TCa, PTH ranging from normal to high (and often inappropriately high in relation to serum calcium), phosphate ranging from normal to moderately elevated serum phosphate, and urinary secretion of calcium which is low or very low, as in many cases in this study (59, 61, 105, 107). Interestingly, low urinary calcium excretion ay be explained by lithium’s direct effect on renal tubule, probably through the inhibition of cyclic AMP (105, 109). These characteristics also signify a clear difference with pHPT. In fact, parallels may be drawn to familial hypocalciuric hypercalcaemia (FHH). Both LHPT and FHH in many senses are thought of as “asymptomatic”, and biochemical similarities in terms of (mild) hypercalcaemia, normo- or hypophosphatemia, and hypocalciuria are fairly apparent (121). Furthermore, both conditions are characterised parathyroid hyperplasia and poor surgical results (121). Surgery has little place in terms of treatment of FHH due to its genetical aetiology; little is known about the genetic aetiology of LHPT, but defects in Wnt/β-catenin signalling leading to increased nonphosphorylated β-catenin seems to have significance in the development of tumours in HPT (44, 122).

Corroborating with multiple previous studies, the surgical results presented in this paper confirmed MGD as the predominant histopathological diagnosis (57, 75, 78, 79, 123). Most operations performed utilised BNE, though four UNE were also performed. Sestamibi scanning gave little predictive information in these cases, and it has been argued that scanning may
be redundant if the surgical strategy for suspected LHPT should be BNE (59, 124). An average of two parathyroid glands were removed, and although the cure rate was 62.5%, recurrent/persistent disease is already found in five patients, and most of those determined as cured were operated on in the time period 2016-2017. More time is necessary for observation of these relatively newly operated patients. Lengthy periods of observation are otherwise strongly recommended, in general, for all lithium-treated patients who undergo PTX. It does raise the question whether surgery is the best strategy to manage suspected LHPT. A few reports have published good results from case-studies on the use of calcimimetics (125). Though more studies are needed, including health-economic evaluations (126).

**Paper IV**

This is hitherto the largest published surgical study providing long-term results of PTX on lithium-treated patients who develop HPT and also reports the longest follow-up. This was the first study to provide robust, though rather disheartening, long-term results that demonstrated markedly different results from the management of pHPT. The rate of persistence or recurrence was estimated to 42% after the primary operation.

<table>
<thead>
<tr>
<th>Author</th>
<th>Participants (n=)</th>
<th>Histopathology</th>
<th>Follow-up (maximum no. months)</th>
<th>Cure-rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stancer &amp; Forbath, 1989, (123)</td>
<td>3</td>
<td>2 H 1 A</td>
<td>36</td>
<td>100</td>
</tr>
<tr>
<td>McHenry et al., 1990, (40)</td>
<td>7</td>
<td>3 H 4 A</td>
<td>3</td>
<td>100</td>
</tr>
<tr>
<td>Nordenström et al., 1992, (80)</td>
<td>6</td>
<td>5 H 1 A</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Abdullah et al., 1999, (90)</td>
<td>11</td>
<td>5 H 3 A, 3 DA</td>
<td>36</td>
<td>78</td>
</tr>
<tr>
<td>Awad et al., 2003, (72)</td>
<td>15</td>
<td>1 H 11 A, 3 DA</td>
<td>24</td>
<td>93</td>
</tr>
<tr>
<td>Hundley et al., 2005, (74)</td>
<td>12</td>
<td>6 H 3 A, 3 DA</td>
<td>10</td>
<td>25 #</td>
</tr>
<tr>
<td>Carchman et al., 2008, (68)</td>
<td>16</td>
<td>4 H 10 A, 2 DA</td>
<td>50</td>
<td>100 *</td>
</tr>
</tbody>
</table>

H= hyperplasia, A= adenoma, DA= double adenoma; # 6 patients could not be determined because of lack of data, but a further 2 had recurrence; * 2 patients had normocalcaemic hyperparathormonemia.
A number of reasons might have contributed to that result. Firstly, no cohesive surgical strategy regarding how to operate these patients was accepted at that time. Even though BNE was employed in most cases, only three glands on average were identified and only an average of two were removed. Secondly, hyperplasia was present in 52% of cases and hyperplasia most often effects all parathyroid glands. These observations underpin the necessity of attempting to identify all parathyroid glands and the importance of considering a subtotal parathyroidectomy as reasonable surgical alternative (62). However, it should be noted that other studies have advocated focused PTX and have demonstrated good results, though their patient groups were younger and follow-up was limited (57, 68, 90) (Table 6). Norlén et al. quite rightly also points out the undesirable possible consequences of more radical surgery and emphasises the need for caution in order to avoid causing hypoparathyroidism (79). Nine patients in this study did indeed suffer from hypoparathyroidism at the latest follow-up. In addition, the coexistence of two independent phenomenon, i.e. lithium treatment and pHPT, should not be overlooked (80, 127). Single glandular disease was, in this series, reported in 45% of cases, with two having double adenomas. Theoretically, these patients could be candidates for focused PTX, though, as the surgical results from the smaller series of cases in Papers II & III also reveal, the risk for recurrence many years later in the presence of continual lithium therapy is compelling. As yet, pre-operative imaging does not provide a high enough level of certainty that could enable focused PTX in this patient group.

There is an increased frequency in comparison to pHPT of double adenomas (Table 6) in patients with LHPT, with two cases reported in this study. It may be the case that patients with lithium therapy have a “true” single adenoma, though we believe those are in the minority. In Paper III, the patient who was re-operated had first one gland removed judged to be hyperplastic, and at the reoperation 2 glands were removed where one was determined to be an adenoma. As referred to earlier, the pathological diagnosis of adenoma versus hyperplasia is often challenging, and if persistent or recurrent disease does occur, the original diagnosis must be questioned and re-evaluated.

**General Conclusions**

Frederick N. Johnson skilfully contextualises the significance of Cade’s contribution by declaring that the discovery of lithium’s efficacy “is considered by many of those working in the field of psychiatric research to have been
one of the most significant in the history of pharmacotherapy” (128). Lithium is an excellent stabilising drug, but as with all drugs, side-effects are ever present. As clinicians, it is our duty to detect, monitor and treat all eventual side-effects to the best of our knowledge and ability. One such side-effect of lithium therapy is hypercalcaemia. Based on the studies presented in this thesis, we can make the following conclusions:

1. The prevalence of LHPT is high, estimated to be 18%. Furthermore, another 20% of patients experience intermittent episodes of hypercalcaemia.
2. Lithium usage is strongly associated with the development of hypercalcaemia in patients with bipolar disorder. Hypercalcaemia develops over many years and is more common in women. Hypercalcaemia is not caused by the bipolar disease in itself but to long-term use of lithium.
3. Calcium homeostasis is unstable in almost half of the patients on chronic lithium treatment, showing episodes of both hypo-, normo- and hypercalcaemia.
4. The results of traditional parathyroid surgery for suspected LHPT are poor with long-term cure rates of 50 per cent, or lower. The most important reason for this is the fact that LHPT in most cases is due to multiglandular parathyroid disease.
5. LHPT seems different from primary HPT in both histopathology and biochemistry.
6. Current monitoring of calcium homeostasis in psychiatric praxis does not facilitate an optimal evaluation of the patients’ parathyroid function. Few patients are assessed by an endocrinologist or endocrine surgeon regarding suspected HPT.
7. The effects on body and soul of normalizing serum calcium levels in patients with LHPT is virtually unknown and randomized studies analysing surgical intervention are highly warranted.
Forthcoming studies

Randomized study – surgery vs watchful waiting

So many questions still exist concerning the appropriate treatment of LHPT and, as yet, no international consensus document exists describing how these patients should be medically managed. The long-term medical implications of chronic lithium-treatment with simultaneous parathyroid dysfunction- with regards for example the cardiovascular system, calcium turnover in the skeleton, general quality of life – have yet to be fully described and understood. With this in mind, we have begun a prospective randomised study. The overriding aim is, firstly, to evaluate the results of parathyroid surgery (with the aim of identifying all parathyroid glands and extirpation of 3 or 3½ glands) versus “watchful waiting”, i.e. controlled monitoring over time and, secondly, to describe pathophysiology and pathosymptomatology in lithium-treated patients with suspected hyperparathyroidism.

Ethics

The study is ongoing and is conducted according to the Declaration of Helsinki. The Ethics Committee at Uppsala University has reviewed and approved the study protocol (Dnr 2014/435). The study is approved by the biobank coordinators at each respective institution. All included patients gave written informed consent.

Materials and methods

The study was initiated in spring 2016 and is a collaborative project between the surgical departments at the University Hospital in Örebro and the County Hospital Ryhov, Jönköping. Patients with suspected LHPT or who had already undergone parathyroid surgery and showed signs of persistent or recurrent disease were identified through an inspection of medical records for the purpose of the prevalence study (Paper I and III)(129). These identified patients were referred from the respective psychiatric departments to the surgical departments for out-patient assessment. Renewed blood tests were performed and if the patient met the criteria for the study, s/he was then asked regarding participation. The inclusion criteria for this study are:

- Suspected LHPT as defined by elevated ionised/total/corrected calcium and simultaneous elevated PTH.
- Age group ≥20 years old to ≤75 years old.
• The patient has a good understanding of Swedish.
• Lives in own residence.
• Has on-going lithium treatment.
• Exclusion criteria include:
  • Highly elevated calcium levels (TCa >3.00mmol/l or iCa >1.50mmol/l).
  • Age group <20 years old or >75 years old.
  • Difficulties in comprehending Swedish.
  • Resides at a care facility.
  • Complicated co-morbidity such as severe cardiovascular or pulmonary disease, or severe kidney insufficiency.
• The patient is participating in another study.

If the patient met the inclusion criteria and was willing to participate in the study, the patient was then randomised either to surgery or “watchful waiting”. The patients will be followed over two years and are planned for a minimum of five out-patient assessments (Figure 6). At the time of writing, twelve patients have been successfully randomised (Figure 7). Randomisation blocks comprised of six patients each. Patients and investigators are aware of the assigned treatment.

Apart from a complete review of medical history and a physical examination, the following indices are taken at baseline and at the end of the study (24 months): lithium concentration, TSH, creatinine, serum phosphate, iCa, TCa, PTH, 25-hydroxyvitamin D (25-OHD), liver function tests-AST/ALT/ALP/albumin, magnesium, albumin/creatinine ratio, urine dipstick test, urine osmolality, 24-hour specimen of urine calcium, weight and length in order to calculate BMI.
Furthermore, bone densitometry (DEXA) was performed and FRAX calculated, muscle function tested with 30-second chair stand test (130), heart function assessed with echocardiography, psychiatric well-being rated with MADR-S (131) and AS-18 (132). Additionally, the authors (AM, JJ, GW) have developed a questionnaire based on a visual analogue scale (VAS) concerning possible symptoms related to LHPT (Table 7). The questionnaire is currently not validated. Quality of life was evaluated by the 36-item short form health survey (SF-36, version 1)(133, 134). SF-36 is translated into
Swedish and is a survey of eight dimensions related to the concept of health, comprising physical function, physical role function, mental health, bodily pain, general health, vitality, emotional role function, and social function. Normative values are available for a Swedish population (135).

**Figure 7.** Flow diagram illustrating the current status of recruitment and randomisation in LHPT study.

Blood tests, 30-second chair stand test and symptom questionnaire are carried out every 6 months, a total of five times over 24 months. Also, MADRS, AS-18 and SF-36 are evaluated at start, 12 months and 24 months. All surgery is performed by experienced endocrine surgeons and the primary surgical strategy is BNE. All patients randomised to surgery are referred for Sestamibi scan preoperatively. Exirpated tissue is sent for histopathological assessment. It is also planned that prepared material will be sent to Uppsala University for further analysis including immunohistochemistry to detect...
any potential differences in tumour tissue in LHPT compared to pHPT, in what is thought might be a unique material (personal correspondence with Prof. Gunnar Westin).

**Endpoints of this study**

The primary endpoint of the study is to evaluate the role that radical parathyroid surgery plays in the normalisation of hyperparathyroidism in lithium-treated patients and in their psychiatric well-being and quality of life. Further secondary endpoints include a description of any possible changes in skeletal integrity, heart function, muscle function, symptom fluctuation, surgical results and complications.

**Case description** A 58-year-old man was referred to the outpatient surgical ward in Örebro in 2017. The patient had medicated with lithium for 23 years and debuted with the first episode of hypercalcaemia 20 years previously. Furthermore, the patient medicated for hypertension and hypolipidemia. TCa had varied between 2.56-2.85 mmol/l, at most iCa=1.53 mmol/l and PTH=27.2 pmol/l (Figure 8). The patient reported no instance of nephrolithiasis. DEXA scan was normal. tU-Ca=5 mmol/24hrs, i.e. normal, S-PO₄=1.67 mmol/l. The Sestamibi scan showed uptake dorsomedial of the right thyroid lobe, but even possibly dorsolateral to the left thyroid lobe. The patient reported no distinct symptom commonly associated with HPT. LHPT was highly suspected and surgery recommended.

![Figure 8](image.png)

*Figure 8. An illustration of the dynamics of iCa (green line, with normal reference span illustrated with thick green horizontal line) and PTH (red line, with normal reference span illustrated with thick pink horizontal line) over two years. Maximum iCa=1.53 mmol/l and PTH=27.2 pmol/l. An arrow indicates time-point of operation.*
The patient underwent subtotal parathyroidectomy with autotransplantation in the left arm’s brachioradialis muscle. The right thyroid lobe was deemed to be nodulous and therefore removed. Histopathology revealed hyperplasia in all three extirpated parathyroid glands, and as can be seen from Figure 9, depicting one of the glands, all glands were markedly enlarged. No signs of malignancy could be detected. Transient hypocalcaemia was experienced by the patient which could be counteracted with the intake of dairy products. Supplementary calcium and vitamin-D was prescribed, and at latest follow-up the patient was normocalcaemic, euperathyroid and on all accounts feeling well. The patient declined participation in the current study in that he wanted to be operated on, but agreed to participate in the follow-up study.

Results

At this stage of the study, only descriptive statistics are given. Eleven women and one man (median age=61 yrs, range=51-73yrs) have currently been enrolled, six patients in each arm of the study (Figure 7). Median treatment length was 21 years (range 11-30 yrs). Hitherto, five patients have been operated. Ten patients had an essentially normal DEXA scan, though two patients – one in each arm of the study – showed signs of osteopenia. All electrocardiograms at the start of the study were normal. All but one patient in the surgery group (Grp 1) and all patients in the watchful waiting group (Grp 2) were hypercalcaemic (Table 8). The patient in Grp 1 with TCa=2.46 also had PTH=16.1 simultaneously. Interestingly, four patients (33%) had urinary calcium excretion rates below 1.3 mmol/24hr, but only one had elevated excretion rate. One patient had hypermagnesemia (1.07mmol/l), though most patients had magnesium deter-
minations above 0.85mmol/l. Once again, apart from one patient with hypophosphatemia, all participants had either normal or elevated serum phosphate determinations. During the initial clinical assessment, Grp 1 participants performed a median of 12 (0-20) sit-to-stand cycles (30-s chair stand test) and in Grp 2 the result was 11 (0-12). At study start, Grp 2 participants scored higher in MADR-S and AS-18, thereby indicating the presence of more distinct affective symptoms, though the symptom scale questionnaire was similar to Grp 1 (Table 9). Somewhat in contrast, Grp 2 reported higher values in vitality (VT), emotional role function (RE) and mental health (MH) than Grp 1.

Of those five patients who underwent surgery, none had previously undergone neck surgery. A total of 13 parathyroid glands were extirpated, two glands each in two cases (and in one of these cases only two glands could be identified), and three glands each in three cases. Histopathological examination revealed 11 hyperplastic glands (six with nodular hyperplasia), one adenoma and one judged to be normal. Interestingly, two patients underwent hemithyroidectomy because of an apparent resistance identified perioperatively and which was later found to be follicular cancer. Sestamibi scanning gave incorrect predictive information in two cases and indicated no uptake in three cases. No complications to surgery, other than temporal hypocalcaemia, could be detected. Two separate episodes in two individuals of acute, though temporary, kidney dysfunction were detected during the study period. Creatinine in both these individuals has normalised. No patients thus far have shown signs of chronic kidney failure.

At six months follow-up the 30-s chair stand test improved markedly in three participants in Grp 1, though remained unchanged in two. A slight improvement could also be seen in Grp 2. At latest follow-up, all operated patients were normocalcaemic and, based on clinical examination and health/symptom instruments, all were feeling well and improved health could be surmised. However, the patient where only two parathyroid glands were identified at the original operation had an elevated PTH at both follow-up assessments, possibly indicating persistent disease. Of interest, one patient in Grp 2 became normocalcaemic at both occasions during follow-up, though at the same time having a disproportionately high PTH (>15 pmol/l). Regarding psychiatric well-being and quality of life, at 12 months follow-up Grp 1 participants scored lower on MADR-S and the symptom scale – though slightly higher in AS-18 – and increased values in all the domains of SF-36 that could be improved, with scores on a par with the reference population. In comparison, Grp 2 participants scored higher in
both MADR-S and AS-18, though lower in the symptom scale, with varying results in SF-36, reporting a slight improvement in general health (GH) but diminished mental health (MH).

**Discussion**

The current study is, as far as we know, the first prospective randomised surgical study to evaluate the benefits of parathyroidectomy in lithium-treated patients with suspected LHPT. The study is ongoing, both in terms of evaluation and recruitment, so all results are highly preliminary. That said, a few points of interest seem to be emerging.

The biochemical characterisation of LHPT tends to display normal to moderately elevated calcium and often with a disproportionately elevated PTH, normal or increased S-PO$_4$ and Mg, normal or low (or indeed, very low) urinary calcium excretion rates (61, 105). This latter characteristic may explain the absence of nephrolithiasis in LHPT patients (59, 61, 136). In addition, as was illustrated in Paper III and in this study by the patient in Grp 2 who became normocalcaemic, biochemical fluctuations do occur which, in turn, may confuse or impede the diagnosis or adequate management of the patient. This profile is in clear contrast to the fairly constant and, sometimes, continual progression of hypercalcaemia in patients with pHPT(63).

The indication in Paper IV (75) that more radical surgery increased the possibility of cure, in terms of normocalcaemia, was the motivating factor in aiming to do BNE with subtotal or total parathyroidectomy with autotransplantation, as demonstrated in the case presentation. This approach is controversial, but since lithium-treatment is mostly life-long and LHPT is predominantly a MGD, there is a compelling need for this surgical strategy to be properly evaluated (77). In practice, more radical surgery is not always possible. One of the two patients in Grp 1 at latest follow-up could be classed as being normocalcaemic but also hyperparathyroid, with normal 25-OH-D status. An optimal first operation is, of course, paramount. Preoperative Sestamibi scanning was, thus far, not shown to give instrumental guidance and one can question the benefit of routine imaging in this patient group if the surgical strategy is to be BNE(59). On the other hand, Carchman et al. (68) did report better results with preoperative imaging.

Eleven (85%) of extirpated glands revealed the histopathological diagnosis hyperplasia. This confirms a series of antecedent studies characterising LHPT as MGD where the primary diagnosis is hyperplasia, most likely due
to lithium’s universal effects (58, 67, 109, 136). In this regard, it is somewhat bewildering why not all patients develop hypercalcaemia, some indeed remain euparathyroid throughout the entire treatment period with lithium. It must, therefore, be remembered that the patient may develop “true” pHPT, with the more prevalent histopathological diagnosis adenoma and fewer biochemical fluctuations, as in the other patient in Grp 1 at 12 months follow-up (80). This, of course, is speculative.

Hypercalcaemia and HPT in lithium-treated patients is commonly detected as a result of screening and seldom due to control and management of symptoms. There is often significant doctor’s delay due to the indeterminate nature of symptoms and the interconnectivity with the individual patient’s affective disorder (68, 90, 102). Symptoms concerning tiredness and muscle fatigue frequently scored higher points in the symptom scale questionnaire in this study (Table 7). Tentative indications are given at follow-up that the operated patients in this study may in general be feeling better (Table 9), also shown in studies of seemingly asymptomatic pHPT patients (137, 138), but these may also be transient effects of extra monitoring (85). It will be of great value and interest to evaluate well-being both at the end of the study period but also, for example, in five years’ time.

Lastly, the final patient material will most likely be limited in terms of its dimensions. However, I am hopeful that the results will give new insights into the nature of LHPT and appropriate long-term management. Naturally, any eventual insights would further be strengthened by multicentre, preferably international, studies.
Table 7. Patient questionnaire in Swedish for the evaluation of possible symptoms pertaining to LHPT.

Tänk tillbaka på de senaste veckorna och besvara dessa frågor utifrån den grad du har upplevt symtomen, alltifrån inte alls till extremt mycket, från 0 till 10. Markera med ett kryss över svaret som stämmer bäst överens:

<table>
<thead>
<tr>
<th>Jag känner mig orkeslös.</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inte alls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mycket litet</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Delvis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4</td>
<td>5</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ganska mycket</td>
<td></td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extremt mycket</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Jag känner att jag har ”tappat livsgnistan”.</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inte alls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mycket litet</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delvis</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ganska mycket</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extremt mycket</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Jag har varit trött i musklerna, t.ex. svårare att resa mig ur fotölen eller ur bilen.</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inte alls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mycket litet</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delvis</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ganska mycket</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extremt mycket</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Jag har känt mig mer törstig än vanligt.</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inte alls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mycket litet</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delvis</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ganska mycket</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extremt mycket</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Jag har haft problem med förstoppning.</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inte alls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mycket litet</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delvis</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ganska mycket</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extremt mycket</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Jag har kissat mer än vanligt.</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inte alls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mycket litet</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delvis</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ganska mycket</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extremt mycket</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Jag har känt av värk i lederna.

<table>
<thead>
<tr>
<th>Inte alls</th>
<th>Mycket litet</th>
<th>Delvis</th>
<th>Ganska mycket</th>
<th>Extremt mycket</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td></td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

Jag har upplevt att jag är mer glömsk.

<table>
<thead>
<tr>
<th>Inte alls</th>
<th>Mycket litet</th>
<th>Delvis</th>
<th>Ganska mycket</th>
<th>Extremt mycket</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td></td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

Jag känner mig helt frisk.

<table>
<thead>
<tr>
<th>Inte alls</th>
<th>Mycket litet</th>
<th>Delvis</th>
<th>Ganska mycket</th>
<th>Extremt mycket</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td></td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>
Table 8. Clinical data for the twelve patients (11 women and one man; median age 61 yrs) enrolled in the study up till now. Group 1 are patients randomized to surgery (op) where “Study start” values are pre-operative values and values at 6 months follow-up are postoperative. Group 2 are patients randomized to watchful waiting (w.w.). All values are given in median (ranges).

<table>
<thead>
<tr>
<th>Value, (ref.)</th>
<th>Study start*</th>
<th>6 mths follow-up*</th>
<th>12 mths follow-up*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1 (op)</td>
<td>Group 2 (w.w.)</td>
<td>Group 1 (op)</td>
</tr>
<tr>
<td>[Li], (0.5-0.9 mmol/l)</td>
<td>0.6 (0.5-0.6)</td>
<td>0.6 (0.4-0.8)</td>
<td>0.6 (0.2-0.9)</td>
</tr>
<tr>
<td>Creatinine, (45-90 µmol/l)</td>
<td>66 (62-133)</td>
<td>74 (56-94)</td>
<td>71 (64-160)</td>
</tr>
<tr>
<td>tCa, (1.15-1.33 mmol/l)</td>
<td>1.37 (1.31-1.49)</td>
<td>1.4 (1.33-1.43)</td>
<td>1.21 (1.17-1.22)</td>
</tr>
<tr>
<td>tCa, (2.15-2.50 mmol/l)</td>
<td>2.56 (2.46-2.89)</td>
<td>2.64 (2.56-2.7)</td>
<td>2.28 (2.22-2.39)</td>
</tr>
<tr>
<td>PTH, (1.6-6.0 pmol/l)</td>
<td>11.2 (6.1-16.9)</td>
<td>11.8 (7.6-19.1)</td>
<td>6.7 (4.7-10.6)</td>
</tr>
<tr>
<td>tU-Ca, (1.3-6.5 mmol/24hr)</td>
<td>5.7 (0.8-7.5)</td>
<td>1.5 (1.1-6)</td>
<td>–</td>
</tr>
<tr>
<td>TSH, (0.3-4.2 mlU/l)</td>
<td>2.45 (0.27-3.1)</td>
<td>1.7 (0.95-2.7)</td>
<td>3.4 (0.17-5.3)</td>
</tr>
<tr>
<td>S-P(O4), (0.8-1.5 mmol/l)</td>
<td>0.94 (0.64-1.65)</td>
<td>1.00 (0.85-1.18)</td>
<td>1.12 (0.93-1.18)</td>
</tr>
<tr>
<td>25-OH-D, nmol/l*</td>
<td>61 (47-100)</td>
<td>63 (34-90)</td>
<td>81 (56-89)</td>
</tr>
<tr>
<td>Mg, (0.70-0.95 mmol/l)</td>
<td>0.88 (0.84-0.93)</td>
<td>0.84 (0.72-1.07)</td>
<td>0.89 (0.83-0.9)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>37.2 (28.9-46.1)</td>
<td>31.0 (27.1-37.8)</td>
<td>33.3</td>
</tr>
</tbody>
</table>

* Presentation of tests from 12 patients.
§ Presentation of tests from 5 patients in group 1 and 6 patients in group 2.
Y Presentation of tests from 2 patients in group 1 and 5 patients in group 2.
Φ Reference values for women are 45-90 µmol/l and for men 60-105 µmol/l.
Χ Values over 50 nmol/l are most often considered as acceptable.
Table 9. Results from symptom instruments (MADR-S, AS-18, symptom questionnaire (see Table 7)) and SF-36 QoL for the twelve patients (11 women and one man; median age 61 yrs) enrolled in the study up till now. Group 1 are patients randomized to surgery (op) where “Study start” values are pre-operative values and values at 12 months follow-up are postoperative. Group 2 are patients randomized to watchful waiting (w.w.). Normative values for a reference Swedish population are given for SF-36.

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Study start*</th>
<th>12 mths follow-up†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ref. population</td>
<td>Group 1 (op)</td>
</tr>
<tr>
<td></td>
<td>median (range)</td>
<td>median (range)</td>
</tr>
<tr>
<td>MADR-S</td>
<td>7 (1-25)</td>
<td>12.5 (2-24)</td>
</tr>
<tr>
<td>AS-18</td>
<td>13 (8-39)</td>
<td>25.5 (6-38)</td>
</tr>
<tr>
<td>Symptom scale‡</td>
<td>47 (13-59)</td>
<td>46 (28-50)</td>
</tr>
<tr>
<td>SF-36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PF</td>
<td>87.9 (0-100)</td>
<td>80 (25-95)</td>
</tr>
<tr>
<td>RP</td>
<td>83.2 (0-100)</td>
<td>100 (0-100)</td>
</tr>
<tr>
<td>BP</td>
<td>74.8 (0-100)</td>
<td>45 (37.5-100)</td>
</tr>
<tr>
<td>GH</td>
<td>75.8 (0-100)</td>
<td>50 (25-85)</td>
</tr>
<tr>
<td>VT</td>
<td>68.8 (0-100)</td>
<td>20 (10-80)</td>
</tr>
<tr>
<td>SF</td>
<td>88.6 (0-100)</td>
<td>50 (25-100)</td>
</tr>
<tr>
<td>RE</td>
<td>85.7 (0-100)</td>
<td>33.3 (0-33.3)</td>
</tr>
<tr>
<td>MH</td>
<td>80.9 (0-100)</td>
<td>56 (24-84)</td>
</tr>
</tbody>
</table>

* Presentation of tests from 12 patients.

¥ Presentation of tests from 2 patients in group 1 and 5 patients in group 2.


Χ Symptom scale refers to the scale as presented in Table 7.

SF-36 domains: PF=physical function, RP=role of function, BP=bodily pain, GH=general health, VT=vitality, SF=social function, RE=emotional role function, MH=mental health.
SUMMARY IN SWEDISH (sammanfattning på svenska)


Syftet med denna avhandling är att beräkna förekomsten av LHPT, beskriva vad som kännetecknar sjukdomen utifrån laboratoriedata och patologiska fynd, samt att utifrån hittillsvarande resultat av kirurgisk behandling, kunna ge förslag på förbättrat handläggning.

I den första studien ingick 423 litiumbehandlade patienter från Örebro län och Jönköpings kommun. För att rätt kunna uppskatta förekomsten av LHPT granskade vi patienternas journaler med särskilt fokus på blodprover, aktuella läkemedel och genomgångna operationer av bisköldkörtlarna. Vi fann att 77 patienter (18%) uppfyllde kriterierna för att misstänka LHPT, medan ytterligare 21% visade tecken på återkommande förhöjt kalkvärde i blodet. Endast fem patienter hade blivit opererade med borttagning av bisköldkörtlar (s.k. paratyreoidektomi).

Eftersom vissa tidigare studier givit misstanke om att det kanske är den bipolära sjukdomen i sig som orsakar störningarna i kalkomsättningen, analyserade vi därför i Studie II blodkalkprover från 313 litiumbehandlade bipolära patienter (BP) och jämförde dem med värdena hos 148 BP utan litium samt 102 individer utan känd psykiatrisk diagnos. Det visade sig att 26% av BP med litium hade förhöjd kalknivå i blodet medan det inte fanns någon skillnad mellan BP utan litium samt 102 individer utan känd psykiatrisk diagnos. Det visade sig att 26% av BP med litium hade förhöjd kalknivå i blodet medan det inte fanns någon skillnad mellan BP utan litium (1,5%) och kontrollgruppen (3%). Dessutom presenterade vi resultat från 7 patienter som hade genomgått paratyreoidektomi. Analys av de borttagna bisköldkörtlar visade hyperplasi (vävnadsökning) till skillnad från adenom (benign tumör) som är vanligare vid pHPT. Alla 7 patienter uppvisade fortsatta tendenser till förhöjt kalkvärde även efter operation.

Under våra studier har vi ofta noterat att många litiumbehandlade patienter har ganska kraftiga svängningar i sina blodkalkvärden. I Studie III
avsåg vi därför att i detalj beskriva svängningarna i blodkalkvärdena hos litiumbehandlade patienter över hela behandlingstiden. Samtliga 297 litiumbehandlade patienter, som hade ätit litium i minst 1,5 år, i Jönköpings kommun inkluderades. Totalt 8504 kalkvärden kunde hittas genom journalgranskning, inklusive 234 före litiumstart. 40% av patienterna hade störningar i sina kalkvärden: 102 patienter med upprepade förhöjda blodkalkvärden eller starkt misstänkt LHPT, dessutom 17 patienter med upprepade tendenser till för lågt kalk. Vi presenterade resultat från totalt 16 paratyreoideaoperationer och de flesta borttagna körtlar visade tecken till hyperplasi.

Studie IV utgör en långtidsuppföljning av 71 litiumpatienter som genomgått sammanlagt 78 paratyreoideaoperationer på sex olika svenska sjukhus i försök att bota deras LHPT. Endast 52% av dem blev långsiktigt botade, vilket står i skarpt kontrast till den kirurgiska behandlingen av pHPT där 95–98% blir av med sin sjukdom. Också i denne studie visade det sig att en majoritet av de sjuka bisköldkörtlarna var hyperplastiskt omvandlade. Vi kunde slutligen konstatera att man får ett bättre resultat av kirurgi om 3–3½ bisköldkörtlar tas bort vid den första operationen.

Vi planerar för ett fortsatt forskningsarbete med denna patientgrupp och har startat en randomiserad pilotstudie där patienter med LHPT erbjudes att deltaga. Patienterna randomiseras till operativ behandling eller uppföljning. Både grupperna följes standardiserat under två år varefter fysisk och psykisk funktion liksom livskvalité evalueras. Skulle patienter i gruppen aktiv uppföljning försämras i sin labvärden kommer de att erbjudas operation innan studietiden löpt ut och likaså erbjudes de operation efter två år.
Acknowledgements

To all the participants in the studies, both completed and on-going, and staff members who have helped and continue to help every step of the way – I wish to extend my sincere gratitude.

To Professor Göran Wallin, my main supervisor: from day one you have been supportive, encouraging, interested, always loyal. It has been a fantastic journey – one that will continue – and better company would be hard to find!

To emeritus Professor Johannes Järhult, co-supervisor: you have spent a lifetime looking at the insides of people! But you have shown and taught me about the other, deeper dimensions of what it means to be a human being. I wish to thank warmly all the other co-authors of the papers presented in this thesis. Your contributions are greatly appreciated!

A special thanks to Ms. Ruzan Udumyan, co-author of Paper II, for your indispensable assistance with statistical analyses in Papers I & II.

For all my wonderful colleagues at the Department of Geriatrics at the University Hospital in Örebro. I am so lucky to be a part of your working lives. Your dedication and warmth inspires me every day.

A special thanks to Futurum Research Unit in Jönköping for considerable personal and economic support.

Many thanks to the Research Committee at Region Örebro County Council for your economic support throughout the duration of these projects.

To Lizber – my great aunt Elisabeth Campbell – who sent me on my journey of learning, and to whom this thesis is dedicated.

To my mother, and father (now deceased, and who gave me my stethoscope which I use daily in clinical work), and to my big brothers John, Michael and Kevin (deceased), and big sister Sharon – for all your love throughout the years.

To Fr. Jim High – for the single truth that I wouldn’t be here today were it not for you. Thank you.

To Fr. Jim McCruden – a constant in my life – for all that you have given me and mean to me. Thank you.

To Moira Henderson – fiercely loyal, always a source of good advice and comfort, faithful friend. Thank you.

To Pia, my mother-in-law – what an exception to the rule! For all the laughs and happy moments, and all the other times! Thank you.

Tae ma bairns: Molly, Jack, Martin and Catriona – whit did yi dae tae get a faither like me 😊? I love you desperately.

And to the lassie that didn’t want to be mentioned – Anna, my wife. You made this possible more than anyone. You were right when named me COB (II). But I say as Byron, “Ah, Anna, what home could be mine but with you!”
REFERENCES


58 ADRIAN MEEHAN  Lithium-associated hyperparathyroidism


Ljungberg O. Riktlinjer för omhändertagande och rapportering av parathyreoideapreparat utformade av KVAST (Kvalitets- och standardiseringsgruppen inom Svensk Förening för Patologi. 2006;9.


ADRIAN MEEHAN  Lithium-associated hyperparathyroidism


122. Martin PM, Stanley RE, Ross AP, Freitas AE, Moyer CE, Brumback AC, et al. DIXDC1 contributes to psychiatric susceptibility by regulating dendritic spine and glutamatergic synapse density via GSK3 and Wnt/beta-catenin signaling. Mol Psychiatry. 2018;23(2):467-75.


Appendix 1.

An overview of the majority of studies and case presentations describing hypercalcaemia and/or hyperparathyroidism in patients with concomitant lithium therapy.

F=female, M=male, mths=months, SGD=single glandular disease, MGD=multiglandular disease, DA=double adenoma, Li=lithium, HPT=hyperparathyroidism, MIP=minimal invasive parathyroidectomy.

<table>
<thead>
<tr>
<th>Researcher, Country, Year</th>
<th>Participants (n=)</th>
<th>Study Design</th>
<th>Study Details</th>
<th>Prevalence (%)</th>
<th>comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prevalence Studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meehan et al., Sweden, 2018 (submitted)</td>
<td>297</td>
<td>Retrospective analysis</td>
<td>16 parathyroidectomies revealing hyperplasia in 63% of extirpated glands; 6% with intermittent hypocalcaemia</td>
<td>34% hypercalcaemia or LHPT</td>
<td></td>
</tr>
<tr>
<td>Meehan et al., Sweden, 2017</td>
<td>313/148/102</td>
<td>Retrospective analysis</td>
<td>7 patients operated; MGD in 4 cases, persistent or recurrent disease in all</td>
<td>26% hypercalcaemia</td>
<td></td>
</tr>
<tr>
<td>Meehan et al., Sweden, 2015</td>
<td>423</td>
<td>Cross-sectional</td>
<td>Retrospective inspection; affective out-patient wards in two cities.</td>
<td>18% LHPT; hypercalcaemia 21%</td>
<td></td>
</tr>
<tr>
<td>Lally et al., Ireland, 2013</td>
<td>333</td>
<td>Cross-sectional</td>
<td>Retrospective inspection; West Galway primary care catchment area.</td>
<td>5.3%</td>
<td></td>
</tr>
<tr>
<td><strong>Surgical Studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norlén et al., Australia, 2014(79)</td>
<td>45</td>
<td>Retrospective analysis</td>
<td>33F:15M. Median follow-up 5.9 yrs. SGD=44%, MGD=56%. Cure rate=84%</td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td>Wade et al., USA, 2013(73)</td>
<td>19</td>
<td>Retrospective analysis</td>
<td>11 F, 8 M. Median 19 mths follow-up. MGD=32%, SGD=68%.</td>
<td>4.38%</td>
<td>10% hypercalcaemia</td>
</tr>
<tr>
<td>Marni et al., USA, 2012(78)</td>
<td>27</td>
<td>Retrospective analysis</td>
<td>22 F, 5 M. Median 7 mths follow-up. MGD=62%, SGD=38%.</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Mandalrajah et al., UK/France, 2011(77)</td>
<td>15</td>
<td>Retrospective analysis</td>
<td>11 F, 4M. SGD=4 (27%), MGD=11 (7.3%)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Kandil et al., USA, 2011(69)</td>
<td>7</td>
<td>Retrospective analysis</td>
<td>4 SGD, 1 DA, 2 MGD (1 re-operated)</td>
<td>10% hypercalcaemia</td>
<td></td>
</tr>
<tr>
<td>Jarhult et al., Sweden, 2010(75)</td>
<td>71</td>
<td>Retrospective analysis</td>
<td>55 F, 16 M. SGD=45%, MGD=52%, DA=3%. Recurrence=42%</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Carchman et al., USA, 2008(68)</td>
<td>16</td>
<td>Retrospective analysis</td>
<td>13 F, 3M. SGD=75%, MGD=12%, DA=12%. 2 reoperations.</td>
<td>1.3% (incidence)</td>
<td></td>
</tr>
<tr>
<td>Hundley et al., USA, 2005(74)</td>
<td>12</td>
<td>Retrospective analysis</td>
<td>10 F, 2M. MGD=50%. Recurrence in 2/10. 6 re-operations.</td>
<td>2.7%</td>
<td></td>
</tr>
<tr>
<td>Alawi et al., USA, 2003(72)</td>
<td>15</td>
<td>Retrospective analysis</td>
<td>11 F, 4 M. 14 cases with adenomas, 2 with double adenomas; 1 with MGD.</td>
<td>4.3% (incidence)</td>
<td></td>
</tr>
<tr>
<td>Abdullah et al., Australia, 1999(90)</td>
<td>11</td>
<td>Retrospective analysis</td>
<td>9 F, 2 M. SGD=6, MGD=5. Recurrence in 2.</td>
<td>Hypercalcaemia in 20%</td>
<td></td>
</tr>
<tr>
<td>Nordenström et al., Sweden, 1992(80)</td>
<td>6</td>
<td>Retrospective analysis</td>
<td>5 patients had MGD; 1 with SGD. Li duration may be important.</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>McHenry et al., Canada, 1990(40)</td>
<td>7</td>
<td>Retrospective analysis</td>
<td>4 F, 3 M. 100% cured at 3mths follow-up. MGD=43%, SGD=57%</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td><strong>Case studies/others</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albert et al., Italy, 2015(113)</td>
<td>31</td>
<td>Naturalistic study</td>
<td>No patient showed signs of hypercalcaemia.</td>
<td>Normocalcaemic HPT=12.9%</td>
<td></td>
</tr>
<tr>
<td>Ibrahim et al., USA, 2015(119)</td>
<td>210</td>
<td>Pooled analysis</td>
<td>12 studies included; SGD in 103 patients=99%; MIP recommended</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>Study Type</td>
<td>Findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>-----------------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Twigt et al., Holland, 2013(102)</td>
<td>314/15 Cross-sectional analysis</td>
<td>Point prevalence hypercalcaemia 15.6% (Ca &gt;2.60mmol/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albert et al., Italy, 2013(108)</td>
<td>58/54 Case control/cross-sectional</td>
<td>HPT= 8.6%, hypercalcaemia= 24.1%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nair et al., India, 2013(140)</td>
<td>1 Surgical case description</td>
<td>Parathyroid carcinoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ballemannina et al, USA, 2011(76)</td>
<td>1 Case report &amp; literature review</td>
<td>Support for MGD and subtotal parathyroidectomy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Broome &amp; Solorzano, USA, 2013(199)</td>
<td></td>
<td>MGD common.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Szalat et al., Israel, 2013(157)</td>
<td>4 Surgical case description</td>
<td>2F, 2M. SGD=25%, MGD=25%, DA=25%.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perera et al., Australia, 2009(70)</td>
<td>2 Surgical case description</td>
<td>2 F. SGD, misleading sestamibi. Recurrence in both cases.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saunders et al., USA, 2009(59)</td>
<td></td>
<td>Support for screening.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nair et al., India, 2013(140)</td>
<td>1 Surgical case description</td>
<td>Adenoma; re-operated.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rizwan &amp; Perrier, USA, 2009(118)</td>
<td></td>
<td>Hypercalcaemia in 10-15%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gama et al., UK, 1999(142)</td>
<td>1 Case presentation</td>
<td>Lithium cessation; normocalcaemic at 1 yr follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>De Celis et al., Spain, 1998(143)</td>
<td>1 Surgical case description</td>
<td>Adenoma, but “parathyroid glands seemed enlarged”.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mak et al., China, 1998(107)</td>
<td>33 2yr prospective longitudinal study</td>
<td>Li treatment lead to PTH elevation, even at 6 mths follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wolf et al., USA, 1997(100)</td>
<td>1 Surgical case description</td>
<td>MGD – hyperplasia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kalinner &amp; Peterson, Sweden, 1993(144)</td>
<td>207 Cross-sectional</td>
<td>Parathyroid hormone elevated in 23%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Komatsu et al., Japan, 1993(145)</td>
<td>13/19 Case control study</td>
<td>No significant HPT or hypercalcaemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bendt et al., Sweden, 1996(98)</td>
<td>8 Cross-sectional/lithium withdrawal study</td>
<td>Prevalence of hypercalcaemia=4.5%, persistent hypercalcaemia=3.6%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nordenstrom et al, Sweden, 1994(146)</td>
<td>26 Cross-sectional/case-control</td>
<td>54% hypercalcaemic (ionized Ca), x PTH. No bone re-duction.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taylor &amp; Bell, USA, 1993(147)</td>
<td>1 Case presentation</td>
<td>Normalization of lab values takes several weeks after cessation of Li.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feldman &amp; Pachman, USA, 1990(20)</td>
<td>1 Surgical case description</td>
<td>Subtotal parathyroidectomy: MGD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stancer &amp; Forbath, Canada, 1989(123)</td>
<td>3/19 Surgical case description</td>
<td>8(42%) with HPT; 3 underwent HPT operation-2 with MGD, 1 SGD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cairns et al., UK, 1985(148)</td>
<td>1 Surgical case description</td>
<td>Persistent nephrogenic DM, HPT hypothyroidism; MGD at surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ananth &amp; Dubin, USA, 1982(149)</td>
<td>3 Case presentations; of which 2 surgical</td>
<td>2/3 underwent surgery; adenoma found in each case.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shen &amp; Sherman, USA, 1982(130)</td>
<td>1 Case description</td>
<td>Hypercalcaemia recurs intermittently; “set-point” alteration proposed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grazee KK, USA, 1981(151)</td>
<td>1 Surgical case description</td>
<td>Hypercalcaemia after 1 yr Li treatment, SGD.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MacGregor G.A., UK, 1977(81)</td>
<td>1 Case description</td>
<td>Hypercalcaemia with Li introduction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>N</td>
<td>Study Type</td>
<td>Description</td>
<td>Notes</td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
<td>---</td>
<td>---------------------</td>
<td>---------------------------------------</td>
<td>-------</td>
<td></td>
</tr>
<tr>
<td>Christensson T.A.T., Sweden, 1976 (71)</td>
<td>6</td>
<td>Retrospective case analysis</td>
<td>Hypercalcaemia after a mean of 1 yr Li treatment, SGD in 4 cases.</td>
<td>__</td>
<td></td>
</tr>
<tr>
<td>Garfinkel et al., Canada, 1973 (39)</td>
<td>1</td>
<td>Case description</td>
<td>1 female with hypercalcaemia</td>
<td>__</td>
<td></td>
</tr>
</tbody>
</table>
Publications in the series
Örebro Studies in Medicine


35. Söderqvist, Fredrik (2009). Health symptoms and potential effects on the blood-brain and blood-cerebrospinal fluid barriers associated with use of wireless telephones.


41. Gustafsson, Sanna Aila (2010). The importance of being thin – Perceived expectations from self and others and the effect on self-evaluation in girls with disordered eating.

42. Johansson, Bengt (2010). Long-term outcome research on PDR brachytherapy with focus on breast, base of tongue and lip cancer.

43. Tina, Elisabet (2010). Biological markers in breast cancer and acute leukaemia with focus on drug resistance.


46. de Leon, Alex (2010). *Effects of Anesthesia on Esophageal Sphincters in Obese Patients.*


52. Loiske, Karin (2011). *Echocardiographic measurements of the heart. With focus on the right ventricle.*


64. Nordin Olsson, Inger (2012). Rational drug treatment in the elderly: "To treat or not to treat".


67. Thuresson, Marie (2012). The Initial Phase of an Acute Coronary Syndrome. Symptoms, patients’ response to symptoms and opportunity to reduce time to seek care and to increase ambulance use.


75. Gustavsson, Anders (2012): Therapy in Inflammatory Bowel Disease.


83. Lönn, Johanna (2013): The role of periodontitis and hepatocyte growth factor in systemic inflammation.


96. Sundh, Josefin (2013): *Quality of life, mortality and exacerbations in COPD.*


98. Palmetun Ekbäck, Maria (2013): *Hirsutism and Quality of Life with Aspects on Social Support, Anxiety and Depression.*


102. Söderström, Ulf (2014): *Type 1 diabetes in children with non-Swedish background – epidemiology and clinical outcome*

103. Wilhelmsson Göstas, Mona (2014): *Psychotherapy patients in mental health care: Attachment styles, interpersonal problems and therapy experiences*


105. Demirel, Isak (2014): *Uropathogenic Escherichia coli, multidrug-resistance and induction of host defense mechanisms*


109. Törös, Bianca (2014): Genome-based characterization of Neisseria meningitidis with focus on the emergent serogroup Y disease


120. Pelto-Piri, Veikko (2015): Ethical considerations in psychiatric inpatient care. The ethical landscape in everyday practice as described by staff.


139. Elwin Marie (2016): *Description and measurement of sensory symptoms in autism spectrum.*

140. Östlund Lagerström, Lina (2016): "The gut matters" - *an interdisciplinary approach to health and gut function in older adults.*


157. Olsson, Emma (2017): *Promoting Health in Premature Infants – with special focus on skin-to-skin contact and development of valid pain assessment.*


