Psychiatric Symptoms, Bone Density and Non-Specific Symptoms in Patients with Mild Hypercalcemia due to Primary Hyperparathyroidism: A Systematic Overview of the Literature

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Abstract. To determine (1) the relationship between primary hyperparathyroidism with mild hypercalcemia and psychiatric disturbances, bone density, or non-specific symptoms, and (2) the effect of parathyroidectomy on these outcomes, a systematic and critical review of the literature was conducted. Relevant citations were identified using MEDLINE (1966 to August, 1995) and PsycINFO (1967 to August, 1995). Studies were included for the overview if they described patients with mild hypercalcemia (< 12 mg/dl), and if they dealt with at least one of the following outcomes: psychiatric disturbances, bone density, joint pain, constipation, polyuria/nocturia or weight loss. Either a calculated effect size or Z score was used to estimate the effect of the disease or parathyroidectomy on these outcomes. Seven studies met the inclusion criteria for this overview. Two out of three case-control studies on psychiatric symptoms found a significant association between primary hyperparathyroidism with mild hypercalcemia and psychiatric disturbances (effect sizes; 0.17, 1.2 and 1.6). One of the three studies also examined the effect of parathyroidectomy on psychiatric symptoms, and found an effect size of 1.5. All four cross-sectional studies that measured bone mass showed significantly reduced bone density in the forearm and the lumbar spine. The bone loss ranged from 0.9 to 1.4 standard deviation below the age- and sex-adjusted mean value in the forearm, and was 0.5 in the spine. There was no relevant study regarding non-specific symptoms. Among the seven studies, five did not explicitly indicate whether the patients had classical symptoms of either osteitis fibrosa cystica or renal stones. Primary hyperparathyroidism with mild hypercalcemia is associated with psychiatric disturbances and reduced bone density. Nevertheless, further research is needed to determine the symptoms, particularly for a group of patients without either classical bone disease or renal stones. The effects of parathyroidectomy on these outcomes also remain to be determined.

Key words: Primary hyperparathyroidism, Mild hypercalcemia, Psychiatric symptoms, Bone density, Non-specific symptoms

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100,000 at ages 40–59 years, and 188.5/100,000 among those aged 60 years and over. Corresponding figures for men were 4.5, 25.9, and 92.2, respectively [1]. As a result, PHPT has become one of the common endocrinopathies [2], and it is considered the most common cause of hypercalcemia among outpatients [3], particularly among elderly people.

The disease has appeared in a variety of clinical forms, and the dominant type among the forms has taken turns [4]. Either hypermetabolic bone disease (osteitis fibrosa cystica) or urolithiasis is described as a classical consequence of the disease, but the majority of recent patients have neither of these manifestations [1, 4]. Indeed, the only manifestation of the disease may be mild hypercalcemia [5].

Although surgery is the only definite treatment for the disease, the predominance of patients with such a “mild” form of PHPT raises a question among physicians: “Do these patients benefit from surgery?” [6–8].

Several researchers claim that truly asymptomatic PHPT patients are very rare because, even with mild hypercalcemia, patients frequently have various symptoms such as psychiatric, gastrointestinal, and articular symptoms when they are questioned in detail [2, 9, 10]: other investigators, however, do not agree [11–13]. While agreeing that PHPT patients with either osteitis fibrosa cystica or renal stones are considered to require surgery [2, 9, 12, 14, 15], physicians differ regarding whether or not patients with mild hypercalcemia who have neither of these manifestations should undergo parathyroidectomy [2, 9] or be managed conservatively [12, 13, 15]. The decision to recommend surgery for such patients therefore remains controversial. Indeed surgery is not felt to be indicated if patients are elderly, truly asymptomatic and their serum levels of calcium are only mildly elevated [14]. Nevertheless, patients without the classical presentation of PHPT may have unrecognized benefits from parathyroidectomy.

The purpose of this study is to determine if a systematic overview of the literature reveals: (a) the extent to which psychiatric and other non-specific symptoms including constipation, polyuria, joint pain, and weight loss occur in patients with the “mild” form of PHPT, (b) the effect of the “mild” form of PHPT on bone density, and (c) whether or not parathyroidectomy improves either these symptoms or bone density in these patients.

The above symptoms and bone density were chosen as outcomes in this study for the following reasons. First, psychiatric symptoms are important because they affect an essential aspect of humans’ well-being [16]. Second, although non-specific symptoms can also be considered “classical” symptoms of PHPT, they are so common in the general population, particularly among elderly people [17], that any associations between the symptoms and PHPT may be coincidental or unrelated to the disease. Finally, bone density has become a major concern in the management of PHPT because the disease is common in elderly women, a group at high risk for osteoporosis [18, 19].

Materials and Methods

Study identification

MEDLINE (January, 1966–August, 1995) and PsycINFO (January, 1967–August, 1995) were used for the literature search. The key words and textwords used for the search on MEDLINE were as follows: hyperparathyroidism or hypercalcemia, asymptomatic* or mild* or minimally symptomatic*, mental disorders or psychiatric symptoms*, constipation* or bowel habits* or bowel movements*, polyuria* or nocturia*, joint pain* or arthralgia*, weight loss*, and bone density (*: textword). For PsycINFO, the terms “hyperparathyroidism or hypercalcemia” were used for the search.

References in all articles retrieved from the online search, in relevant books and textbooks, were perused for additional citations. All citations were limited to those which had been published and written in English.

More than 700 citations were reviewed to exclude those which were irrelevant to the “mild” form of PHPT. The remaining 254 articles were classified into six categories according to their design: (1) reviews, 55 (22%); (2) reports of one or more PHPT cases which presented psychiatric symptoms, non specific symptoms, or classical bone disease, 48 (19%); (3) studies of natural history with a cohort
of patients with PHPT, 7(3%); (4) cross-sectional studies or case-control studies, 69 (27%); (5) studies examining the symptomatology and/or bone density before and after various interventions, 57 (22%); (6) others (editorials, commentaries, letters, official documents, etc.), 18 (7%).

Study selection

Review articles were assessed for their methodologic quality by using previously described criteria [20, 21]. The remaining 151 citations excluding case reports were evaluated for eligibility for the overview according to the criteria listed in Table 1.

Studies of populations of PHPT patients with mild hypercalcemia but without classical symptoms (either osteitis fibrosa cystica or renal stones) are of particular interest in this overview. Because very few articles which included only that study population have been published, citations which dealt with PHPT patients showing mild hypercalcemia, but which did not explicitly indicate whether the patients had the classical symptoms or not, were also included. Mild hypercalcemia was defined as a serum calcium level < 12 mg/dl (< 3.0 mmol/l). The cut-off value was adopted because most of the recommended levels of serum calcium, as an indication for surgery, range between 11.5 and 12.0 mg/dl [13, 14, 22], and even "conservative" physicians indicate parathyroidectomy when the level exceeds 12 mg/dl [12, 15].

Statistical analysis

Methods and results of statistical analyses were tabulated for each study. When they were not available, appropriate statistical tests were carried out, if possible. Those tests included a z-test, an unpaired t-test, and the Wilcoxon Singed Rank test.

For each study, an effect size was calculated to estimate either the association between the disease and each outcome, or the treatment effect of parathyroidectomy on each outcome [23].

In some studies on bone density, an average value of Z scores was given [24]. A 95% confidence interval (CI) of the mean Z score for a group was constructed [25].

Table 1. Inclusion criteria applied to the literature for the overview

<table>
<thead>
<tr>
<th>Criteria for Inclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Study population</td>
</tr>
<tr>
<td>PHPT patients showing mild hypercalcemia (serum calcium &lt; 12 mg/dl or &lt; 3.0 mmol/l).</td>
</tr>
<tr>
<td>2) Outcomes</td>
</tr>
<tr>
<td>At least one of the following outcomes with statistical analysis or sufficient data which can be analyzed or summarized quantitatively: psychiatric disturbances, constipation, polyuria (or nocturia), joint pain, weight loss, or bone mineral density.</td>
</tr>
<tr>
<td>3) Intervention (for intervention studies)</td>
</tr>
<tr>
<td>Parathyroidectomy</td>
</tr>
</tbody>
</table>

Results

Among the 55 review articles, seven dealt with "asymptomatic" or "minimally symptomatic" PHPT and with at least one of the relevant outcomes [12, 13, 26–30]. None of these, however, described the methods of the literature search, criteria to select articles for review, or the methodological aspects of each included study.

Seven of the 151 original research articles fulfilled the inclusion criteria for the overview. Three studied psychiatric symptoms, and four studied bone density.

Studies on psychiatric symptoms (Table 2)

Three case-control studies described psychiatric symptoms [10, 31, 32], and one of these studies also investigated changes in psychiatric symptoms before and after parathyroidectomy [32]. One study was limited to PHPT with mild hypercalcemia, but did not clearly indicate if classical symptoms were present or absent [10]. The other two studies were not limited to PHPT with mild hypercalcemia; they were included because they provided data from a subgroup of patients with PHPT showing mild hypercalcemia [31, 32].

The three studies used established scales for measuring psychiatric symptoms: the Hopkins Symptom Checklist 56-item version (HSCL-56) [10], the Symptom Checklist-90-Revised (SCL-90-R) [31] and the Comprehensive Psychopathological Rating Scale (CPRS) [32].
Two of the case-control studies measuring psychiatric symptoms used different scales [10, 32]: first, presumed PHPT with mild hypercalcemia versus individually age- and sex-matched normocalcemic controls using the HSCL-56 (Hopkins Symptom Checklist 56-item version) [10], and second, PHPT with mild hypercalcemia versus healthy women using the CPRS (Comprehensive Psychopathological Rating Scale) [32]. The hypercalcemic cases showed only slightly higher total HSCL-56 scores (mean ± SD, 76.6 ± 17.0) than the controls did (73.8 ± 16.0) in the first study, and the effect size was 0.17. In the second study, the total CPRS scores among PHPT patients with mild hypercalcemia (17.3 ± 9.3) were significantly higher than those of the healthy women (4.4 ± 2.0, unpaired t-test, t32=4.31, P=0.0001), and the effect size was 1.6 [32]. The before and after-surgery investigation from the same study showed that there was a significant reduction in the score 1–1.5 years after surgery (from 18.5 ± 9.7 to 4.2 ± 9.9, Wilcoxon Signed Rank test, P<0.0001), and its effect size was 1.5. Solomon et al. reported significantly higher values for the total Symptom Checklist-90-Revised score, in PHPT with mild hypercalcemia (62.1 ± 10.0) than the reference value (50 ± 10) (z-test, z=4.99, P<0.0001) [31]. The effect size was 1.2. A subgroup of patients without renal stones had a smaller but still significant effect size of 1.0. The mean score for the control group in the study, which was also examined before surgery for benign thyroid diseases, was equal to that of the reference value; its effect size was therefore zero [31].

**Studies on bone density (Table 3)**

All four studies on bone density used a cross-sectional design in which bone density in PHPT patients with mild hypercalcemia was measured and compared with a reference value [33–36]. There was no intervention study on bone density. The proportions of patients without either osteitis fibrosa cystica or renal stones were clearly indicated in two studies [33, 34]. Two other studies limited their study populations to PHPT patients with mild hypercalcemia [35, 36], and it was not explicitly mentioned whether some of the patients had the classical manifestations or not. Explicit criteria for

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### Table 2. Studies on psychiatric symptoms in PHPT patients with mild hypercalcemia

**Case-control studies**

<table>
<thead>
<tr>
<th>Investigators [reference No.]</th>
<th>Case (sample size)</th>
<th>% of cases without the classical symptoms*</th>
<th>Control (sample size)</th>
<th>Measurement</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joborn et al. [10]</td>
<td>probable PHPT with mild hypercalcemia (38)</td>
<td>n.d.</td>
<td>age-, sex-matched healthy people (38)</td>
<td>HSCL-56</td>
<td>0.17</td>
</tr>
<tr>
<td>Solomon et al. [31]</td>
<td>a subgroup of PHPT with mild hypercalcemia (17)</td>
<td>n.d.</td>
<td>benign thyroid disease (20)</td>
<td>SCL-90-R</td>
<td>1.2†</td>
</tr>
<tr>
<td>Joborn et al. [32]</td>
<td>a subgroup of PHPT with mild hypercalcemia (24)</td>
<td>n.d.</td>
<td>healthy people (10)</td>
<td>CPRS</td>
<td>1.6†</td>
</tr>
</tbody>
</table>

**Before and after-parathyroidectomy investigation**

<table>
<thead>
<tr>
<th>Investigators [reference No.]</th>
<th>Patients (sample size)</th>
<th>% without the classical symptoms*</th>
<th>Measurement</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joborn et al. [32]</td>
<td>a subgroup of PHPT with mild hypercalcemia assessed before and after surgery (20)</td>
<td>n.d.</td>
<td>CPRS</td>
<td>1.5†</td>
</tr>
</tbody>
</table>

*The classical symptoms: either osteitis fibrosa cystica or renal stones; n.d., not described; HSCL-56, the Hopkins Symptom Checklist 56-item version; SCL-90-R, the Symptom Checklist 90-Revised; CPRS, the Comprehensive Psychopathological Rating Scale; †, statistically significant (P<0.05).
inclusion and exclusion of study subjects were indicated in two studies [33, 34]. Referral patterns of the patients were described in two studies [34, 35]. Bone density was measured by single-photon absorptiometry (SPA) at the forearm [33-36] and quantitative computed tomography (QCT) at the spine [35].

Bone density was significantly reduced in all the studies [33-36] except for one subgroup of "very mild" hypercalcemia (serum calcium ≤ 2.74 mmol/l) [36]. Mitlak et al. also found a significant reduction in a subgroup of patients without either osteitis fibrosa cystica or renal stones [34]. The mean Z score in patients without the classical symptoms ranged from -0.9 to -1.4 [33, 34]. The effect size of PHPT with mild hypercalcemia on the spine was -0.5, and that on the distal forearm was -1.1 [35]. Although all the studies used the same method (single photon absorptiometry) for measuring bone density in the forearm, the exact measured sites were different among the studies. As a result, proportions of the trabecular bone component appeared to be different among those sites. In order to examine the relationship between the proportions and the 95% confidence intervals of the mean Z score, the percentage of trabecular bone at each site was estimated as follows [37-39]: 70% at 1.5 cm from the styloid process [33], 40% at 2.0 cm from the styloid process [33], 40% at 2.0 cm from the styloid process [33], and less than 10% at the distal third of the forearm [33], of the non-dominant radius [34], or at the proximal forearm [35]. The relationships between those estimated proportions and the 95% confidence intervals or effect sizes are shown in Fig. 1. Despite the diversity of trabecular bone content, the reduction in bone density in the forearm was fairly constant.

Discussion

Osteitis fibrosa cystica and renal stones are classical symptoms of PHPT, and the presence of

Table 3. Cross-sectional studies on bone density in PHPT patients with mild hypercalcemia

<table>
<thead>
<tr>
<th>Investigators [reference No.]</th>
<th>Patients (sample size)/[reference data]</th>
<th>% of patients without the classical symptoms*</th>
<th>Measurement bone site (instrument)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rao et al. [33]</td>
<td>PHPT with mild hypercalcemia (80)/[age-, sex-, race-matched]</td>
<td>100%</td>
<td>DF (SPA)</td>
<td>Z score (95% CI) DF: -1.2 (-1.5, -0.9)†</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1/3F (SPA)</td>
<td>1/3F: -0.9 (-1.1, -0.7)†</td>
</tr>
<tr>
<td>Miltak et al. [34]</td>
<td>PHPT with mild hypercalcemia (68)/[age-, sex-, race-matched]</td>
<td>100%</td>
<td>DR (SPA)</td>
<td>Z score (95% CI) DR: -1.3 (-1.5, -1.0)†</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1/3R (SPA)</td>
<td>1/3R: -1.4 (-1.5, -1.2)†</td>
</tr>
<tr>
<td>Wishart et al. [35]</td>
<td>postmenopausal PHPT with mild hypercalcemia (28)/[postmenopausal women]</td>
<td>n.d.</td>
<td>PF (SPA)</td>
<td>Effect size</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>spine (QCT)</td>
<td>DF: -1.1†</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>spine: -0.5†</td>
</tr>
<tr>
<td>Nagant et al. [36]</td>
<td>postmenopausal PHPT with &quot;very mild (≤ 2.74 mmol/l)&quot; (9) or &quot;mild (2.75-3.00 mmol/l)&quot; (12) hypercalcemia/[age-, sex-matched]</td>
<td>n.d.</td>
<td>DR (SPA)</td>
<td>% of the reference data</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1/3R (SPA)</td>
<td>&quot;very mild&quot;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>DR: 99%</td>
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<tr>
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<td></td>
<td></td>
<td>1/3R: 95% &quot;mild&quot;</td>
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<td></td>
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<td></td>
<td></td>
<td>DR: 76%†</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>1/3R: 80%†</td>
</tr>
</tbody>
</table>

*The classical symptoms: either osteitis fibrosa cystica or renal stones; n.d., not described; CI, confidence interval; DF, at distal forearm (1.5 cm from the ulnar styloid process); 1/3F, at distal 1/3 of the forearm; DR, at distal radius (2.0 cm from the ulnar styloid process); 1/3R, at distal 1/3 of the non-dominant radius; PF, at proximal forearm (from at an interosseous space of 8 mm with six scans being performed to proximal at 4-mm intervals); spine, at the center of the L1, L3, L5; SPA, single photon absorptiometry; QCT, quantitative computed tomography; †, statistically significant (P<0.05).
either condition, as well as severe hypercalcemia, is a definite indication for surgery. Physicians may waver in their choice of management (i.e., surgery or no surgery) when a patient shows mild hypercalcemia and does not have the classical symptoms. Despite this interest, the selection criteria for this overview was designed to include studies which did not explicitly exclude patients with either osteitis fibrosa cystica or renal stones because few articles with that study population were available.

One intervention study and two case-control studies on psychiatric symptoms showed large effect sizes (1.2-1.6) [31, 32], and one case-control study indicated a small one (0.17) [10]. To explain this variability, three reasons are possible. First, emotional stress among surgical patients may play a role. Patients in the studies with the larger effect sizes were investigated just before planned surgery [31, 32], but patients in the study with the smaller effect size had been followed-up without parathyroidectomy [10]. The large effect sizes may therefore reflect the patients’ responses to the stress associated with the planned surgery and may not be specifically related with PHPT. Nevertheless, this explanation is weakened by finding that a group of surgical patients with benign thyroid disease showed an effect size of zero [31]. Second, many factors other than hypercalcemia could have influenced the results. For example, hypophosphatemia might be associated with psychiatric symptoms. Among articles included in this overview, however, only one study [10] indicated that serum phosphate levels were significantly lower in patients with mild hypercalcemia than in control subjects. Age, sex, and concomitant diseases may also be important as potential determinants of emotional distress, but these factors were not considered in the reviewed studies. Third, the patients in the studies might have been told by their physicians that PHPT may cause the disturbances, and that parathyroidectomy may improve the symptoms. Such a suggestion may increase the effect size of surgery [40, 41].

A significant reduction in bone density was observed in PHPT patients with mild hypercalcemia [33-36]. The bone loss was significant in trabecular bone dominant site as well as cortical bone dominant site. Though this seems not to agree with a previous finding that trabecular bone may be relatively spared as compared to cortical bone in PHPT [42, 43], the discrepancy can

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### Fig. 1. Relationship between Z scores (solid circle) with their 95% confidence intervals or effect sizes (open square) of bone density and the estimated proportion of trabecular bone component in the measured bone sites in patients with mild hypercalcemia due to primary hyperparathyroidism.

<table>
<thead>
<tr>
<th>Authors [ref. No.] (bone site)</th>
<th>estimated % of trabecular bone component (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wishart et al. [35] (spine)</td>
<td>100</td>
</tr>
<tr>
<td>Rao et al. [33] (distal forearm)</td>
<td>70</td>
</tr>
<tr>
<td>Miltak et al. [34] (distal radius)</td>
<td>40</td>
</tr>
<tr>
<td>Rao et al. [33] (distal 1/3 of the forearm)</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Miltak et al. [34] (distal 1/3 of the radius)</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Wishart et al. [35] (proximal forearm)</td>
<td>&lt;10</td>
</tr>
</tbody>
</table>

\[ Z \text{ score or Effect size of bone density} \]
be explained by two reasons. First, the measurement of bone density in the trabecular bone dominant site of radius may not precisely reflect that of the lumbar spine. The trabecular bone content in the forearm bones is the highest at 1.0 or 1.5 cm from the styloid process, and it decreases rapidly in either the distal or the proximal direction from this point. For example, the contents at 2.0 cm and 3.0 cm from the styloid process are estimated as 40% and 10%, respectively [37]. In fact, the correlation coefficient between the measurements of the radius and the spine has been shown to be only moderate (0.56) [38]. Second, PHPT may not affect the trabecular bone dominant site in the radius to the same degree as in the vertebrae [39].

In summary, it is likely that PHPT with hypercalcemia less than 12 mg/dl is associated with psychiatric symptoms, and with reduced bone density in the forearm. The following facts, however, should be noted. First, only published articles were included in this overview, negative studies which were not accepted or not submitted for publication might, therefore, have been missed (publication bias) [23]. Second, there was no article examining psychiatric symptoms with a study population of patients without the classical symptoms, and there was no eligible study in which the non-specific symptoms (constipation, polyuria, joint pain, and weight loss) were investigated. Third, it remains to be shown whether or not parathyroidectomy improves these disturbances in PHPT patients with mild hypercalcemia but without the classical manifestations. It is, therefore, necessary to conduct further studies to determine the benefit of surgery in these patients.

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References