Subclinical endocrinological disease
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Asymptomatic primary hyperparathyroidism

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Summary
The prevalence of hypercalcaemia in the adult population is probably between 0.6 and 1.1%, sufferers being predominantly women over 50 years of age. Most apparently asymptomatic hypercalcaemic patients are found to have primary hyperparathyroidism, and may in fact show some symptoms of the condition (lowered bone mineral density, cardiovascular disease and/or neuropsychiatric symptoms). The criteria for surgical intervention in these cases are discussed in the light of the high success rate of parathyroidectomy in experienced hands and the lack of effective alternative treatments.

Keywords: primary hyperparathyroidism, osteoporosis, surgery, hypercalcaemia

Prevalence of hypercalcaemia
Several population-based studies have evaluated the prevalence of hypercalcaemia. In a Stockholm City and Country Council personnel health check service with a response rate of 74%, Christensson et al. found persistent hypercalcaemia (Ca > 2.78 mM) in 0.6% of 16 000 healthy people aged between 20 and 63 years, of whom 84% were women, mostly over 50 years old. In 1969 and 1971 all inhabitants of the city of Gävle aged 25 years or more were invited for a health screening. Of these, 16 400 (68%) were examined for a second time and hypercalcaemia (Ca > 2.60 mM) was identified in 1.1%. Again, 80% of the hypercalcaemic individuals were women, and most were over 50 years of age.

Most asymptomatic hypercalcaemic patients are found to have primary hyperparathyroidism while hypercalcaemia of hospitalised patients is most likely to be due to cancer (haematological cancers, bone metastases or humoral hypercalcaemia of malignancy). The association of increased ionised or protein-corrected calcium with increased intact parathyroid hormone is evidence for primary (or tertiary) hyperparathyroidism. Of course a long list of more exceptional types of hypercalcaemia needs to be further explored when the most frequent causes are unlikely.

Follow-up of primary hyperparathyroidism without surgery
In the Mayo Clinics a group of so-called asymptomatic patients (n=142) with primary hyperparathyroidism were selected in 1968-70 for prospective follow-

Table Changing profile of primary hyperparathyroidism (from ref69)

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<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Nephrolithiasis (%)</td>
<td>57</td>
<td>51</td>
<td>37</td>
<td>19.5</td>
</tr>
<tr>
<td>Skeletal disease (%)</td>
<td>23</td>
<td>10</td>
<td>14</td>
<td>2</td>
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<tr>
<td>Hypercalciuria (%)</td>
<td>Nr</td>
<td>36</td>
<td>40</td>
<td>39</td>
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<tr>
<td>Asymptomatic (%)</td>
<td>0.6</td>
<td>18</td>
<td>22</td>
<td>80</td>
</tr>
</tbody>
</table>

Nr=not reported
Box 1

Hyperparathyroidism: follow-up

Long term follow-up of asymptomatic primary hyperparathyroidism requires at least yearly evaluation of:

- serum calcium
- urinary calcium excretion or occurrence of kidney stones
- bone mineral density especially of cortical areas (femur, radius)
- kidney function
- clinical evaluation for the presence of atypically associated diseases (especially neuropsychiatric)

If the criteria for surgical intervention are met during follow-up, only an experienced surgeon should localise and remove the parathyroid tumours. Chronic follow-up seems to be difficult in reality as compliance declines during prolonged follow-up.

Box 2

Hypercalcaemia

Hypercalcaemia always needs further aetiologic exploration as it is nearly always possible to make the correct diagnosis. Successful correction of the primary disease is frequently possible and beneficial.

up for 10 years without surgery. In the first five years, 24 patients and in the second five years another nine patients (together 23%) needed neck exploration. The reasons for these surgical interventions included increase of serum calcium above 2.75 mM (n=8), decrease of renal function (n=6), active kidney stone disease (n=6) and radiologic bone disease (n=4).9,10

After the survey carried out by Ljunghall et al.,17 176 patients (149 women) with mild primary hyperparathyroidism were followed for 15 years without surgical intervention and compared to a normocalcaemic, age- and sex-matched, control group. Survival was significantly lower among the hypercalcaemic than among the normocalcaemic subjects. This difference was restricted to the people below 70 years of age. No deaths were caused by hypercalcaemic crises, nephrolithiasis or renal insufficiency. Parathyroid exploration was subsequently needed or carried out in 39 cases. The 14-year survival of 441 patients with primary hyperparathyroidism treated with surgical intervention was lower than expected, but better than in the non-operated group.15

In a smaller group (n=42) of patients with asymptomatic primary hyperparathyroidism (mean serum calcium: 2.72 mmol/l) who did not meet the surgical criteria established by the 1990 NIH conference, none developed these criteria during a seven-year follow-up period.12 Moreover the biochemical indices of their disease activity did not worsen. Although the cortical bone mass (radius and femur) was decreased (-1.3 and -0.7 Z score, respectively) at the time of diagnosis of primary hyperparathyroidism, it remained unchanged at both cortical and cancellous sites during another six-year follow-up. A group of 24 asymptomatic patients who met the NIH criteria (by virtue of having a slightly higher serum calcium), but who were not operated on, showed a similar stable situation during the same follow-up period.12 Similar conclusions have been drawn from previous studies.13 Long-term follow-up seems to be difficult to achieve in these patients, since even in a research setting, a large number of patients are lost to follow-up.

Policy for asymptomatic primary hyperparathyroidism

The treatment of symptomatic primary hyperparathyroidism is very efficient since most surgeons are capable of localising and removing the causative adenoma(s) or hyperplastic parathyroid glands with a very low failure or recurrence rate. Most surgeons with extensive experience in parathyroid surgery claim not to need pre-operative localisation procedures but in view of the large variation in adenoma localisation (especially in the upper mediastinum) and low success rate of surgical re-interventions, some endocrinologists prefer to use a pre-operative localisation technique, especially to exclude possible retrosternal localisation (e.g., MIBI/pericarinate subtraction scanning). This is a much debated issue and some authors even state that the only localisation procedure should be to localise an experienced surgeon.14 The treatment of asymptomatic primary hyperparathyroidism is also much debated and is, in fact, a classical example of the therapeutic decision-making in a mild chronic disease with potential late complications that can be treated effectively only by surgery.

With regard to the best policy concerning surgery in (supposedly) asymptomatic primary hyperparathyroidism, the following questions have to be answered:

- How frequently does asymptomatic (or uncomplicated) primary hyperparathyroidism progress to a symptomatic (or complicated) stage requiring surgery?
- Can criteria be developed by which patients with the progressive form of the disease can be recognised before significant complications develop?
- What is the risk and success rate of surgical neck exploration for mild hyperparathyroidism?
- Are alternative treatment modalities available, efficient and safe?

<table>
<thead>
<tr>
<th>NIH 1990 Consensus Conference on primary hyperparathyroidism</th>
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<tbody>
<tr>
<td>Criteria for surgical intervention (adapted from 15)</td>
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<tr>
<td><strong>Definite</strong></td>
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<tr>
<td>serum calcium &gt;1 mg/dl or 0.25 mM</td>
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<tr>
<td>above upper normal limit</td>
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<tr>
<td>hypercalciuria (&gt;400 mg/dl or 100 mmol/d)</td>
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<tr>
<td>nephrolithiasis</td>
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<tr>
<td>reduced bone mass (&lt;2 Z scores)</td>
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<tr>
<td>prior acute hypercalcaemia</td>
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<tr>
<td><strong>Relative</strong></td>
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<tr>
<td>age below 50,</td>
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<td>hypertension</td>
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<tr>
<td>peptic ulcer disease</td>
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<tr>
<td>pancreatitis</td>
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<tr>
<td>neuromuscular/neuropsychiatric complications</td>
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</tbody>
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Box 3
Bone mineral density

Bone mineral density is frequently decreased at the time of diagnosis of primary hyperparathyroidism but subsequent further decrease is slow over a 5-7 year period. In contrast, after removal of the parathyroid tumour, bone mineral density usually increases although, rarely, it may normalise.

Box 4

The first question may be answered tentatively on the basis of the cited literature; 20–30% of cases require surgery over a 10 to 15 year follow-up period. In trying to answer the second question one has to ask first whether asymptomatic primary hyperparathyroidism is really asymptomatic. Symptomatic cases are characterised by nephrolithiasis, nephrocalcinosis, osteitis fibrosa cystica, the hypercalcaemic syndrome, peptic ulcer disease and pancreatitis, while seemingly asymptomatic cases may subclinically have an increased rate of bone loss, cardiovascular disease and/or neuropsychiatric disorders.

Osteopenia

Most studies report a decreased bone mineral density, especially of cortical bone (eg, femur and radius) in patients with primary hyperparathyroidism. For example, in 31 patients densitometry showed that in the femoral neck bone mineral density was 89% and in the radius 79% of normal, while the lumbar spine appeared to be normal. In a group of 191 patients with primary hyperparathyroidism an increased percentage with vertebral deformities (more than 25% decrease in vertebral height) was observed, as compared with a control group. During a prospective follow-up of untreated asymptomatic patients no further decrease of bone mineral density was observed during a subsequent seven-year period. Similar conclusions were reached by Parfitt et al. Both studies, however, provide no answer for the discrepancy between the initial low bone mineral density of the primary hyperparathyroid patients and the relatively stable subsequent bone mass. In contrast, the radial bone mineral content, that was more than one standard deviation below the normal average in 76% of 71 patients with primary hyperparathyroidism, increased significantly during the eight to 16 months after surgery but in the majority of cases not to normal.

Cardiovascular disease

A potentially important aspect of symptomatic as well as asymptomatic primary hyperparathyroidism concerns cardiovascular disease. In the abovementioned series of patients of Scholz and Purnell who were not surgically treated, cardiac or cerebrovascular accidents were involved in the death of 14 of 27 patients. In the series of Ljunghall and Palmer, 33 of the 57 persons who died during the 15-year observation period, died from circulatory diseases. Stefenni et al studied 54 patients with primary hyperparathyroidism echocardiographically before and a year after successful parathyroidectomy, compared with a matched control group. They found a three- to five-fold increased prevalence of aortic and mitral valve calcifications and a four-fold increase in the occurrence of myocardial calcifications in patients with primary hyperparathyroidism. These calcifications were unchanged a year after parathyroid surgery, whereas the originally observed signs of left ventricular hypertrophy had regressed markedly. There are also suggestions that chronic hypercalcaemia might be a risk factor for accelerated coronary atherosclerosis. It must on the other hand be stressed that Lind et al in their long-term follow-up study of patients with primary hyperparathyroidism with and without surgical intervention have found late increases of blood pressure in both groups.

Psychiatric disease

Joborn et al found psychiatric symptoms in 102 of 441 patients with primary hyperparathyroidism, of whom 78% had depression or an anxiety state. Prospective investigation of 59 patients with primary hyperparathyroidism (average Ca 2.89 ± 0.30 mM) showed that a large proportion of the patients had psychiatric symptoms. The most pronounced symptoms were abnormal fatigability, failing memory, concentration difficulties and sadness. The severity of the symptoms was not correlated with the degree of hypercalcaemia. All symptoms were largely reversed by parathyroid surgery. In another study, 18 patients with primary hyperparathyroidism were compared with 20 thyroid patients, who also were to be operated upon. The majority of the primary hyperparathyroidism patients showed psychologic symptoms (eg, interpersonal sensitivity, depression, anxiety and hostility), which were found to be greatly improved one month after surgery. It must be added that the classic neuromuscular syndrome is nowadays rarely seen in primary hyperparathyroidism.

The risks of surgical neck exploration by an experienced surgeon are generally low regarding morbidity as well as mortality, even in older (> 65
years) patient groups. The nonsurgical approach to primary hyperparathyroidism is limited to the bone-sparing effects of oestrogen therapy in postmenopausal women with primary hyperparathyroidism whereas other medical treatment regimens were usually not efficient. Ultrasonically guided percutaneous injections of ethanol or similar products in parathyroid adenomas is feasible and several successful interventions in surgical high-risk patients have been reported. Such therapy does not seem to be acceptable for asymptomatic primary hyperparathyroidism because of the risk of introducing lesions outside the parathyroid gland (eg, laryngeal nerves) and should be reserved for symptomatic disease with well localised adenomas but high surgical risk.

Conclusions

The prevalence of hypercalcaemia in the adult population probably amounts to 0.5 – 1.0%. Without surgical intervention the diagnosis of primary hyperparathyroidism may be made with reasonable certainty by the combination of increased ionised/protein-corrected calcium and increased intact parathyroid hormone concentration. During observation periods of 10 – 15 years, 20 – 30% of initially ‘asymptomatic’ patients with primary hyperparathyroidism will come to surgery. A large proportion of ‘asymptomatic’ patients with primary hyperparathyroidism have lowered bone mineral density, cardiovascular disease and/or (neuro)psychiatric symptoms. In case of doubt about the asymptomatic state, surgery appears to be indicated. No criteria have been found by which an early detection of progression of an ‘asymptomatic’ to a ‘symptomatic’ phase of the disease is possible (see also 35).

Surgical neck exploration by an experienced surgeon has a very high (> 95%) success rate with low morbidity and mortality. In view of the high success rate of parathyroidecmy in specialised centres, the low percentage of complications, and the absence of effective alternative treatments, we believe that it is generally advisable to operate on patients with primary hyperparathyroidism if their statistical life expectancy exceeds 10 years, in the absence of additional surgical risks. This conclusion is somewhat more of an interventionist nature than the NIH consensus conference conclusion of 1990.