Parathyroid adenomas and cardiovascular risk

N Garcia de la Torre, J A H Wass and H E Turner

Department of Endocrinology, The Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital, Old Road, Headington OX3 7Li, UK

(Requests for offprints should be addressed to H Turner; Email: helen.turner@orh.nhs.uk)

Abstract

In recent decades, primary hyperparathyroidism (pHPT) has changed its clinical presentation from a disease with bone and renal involvement to a frequently asymptomatic disorder detected on routine biochemistry. Nevertheless, it remains unclear whether patients with untreated mild asymptomatic hyperparathyroidism are at risk for other complications such as increased morbidity and mortality from cardiovascular diseases. There are limited data on the incidence of cardiovascular abnormalities in mild pHPT. However, pHPT has been associated with increased risk of death from cardiovascular disease, hypertension, left ventricular hypertrophy (LVH), valvular and myocardial calcifications, impaired vascular reactivity, alterations in cardiac conduction, impaired glucose metabolism, dyslipidaemia, and alterations in body composition. The nature of some of these associations is in question, because cure of pHPT does not lead to improvement of the cardiovascular disorder e.g. hypertension. In contrast, currently available data suggest that LVH, impaired glucose metabolism and dyslipidaemia may improve after surgery and that successful parathyroidectomy could decrease the excess mortality in patients with pHPT due to cardiovascular disease.

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Introduction

Primary hyperparathyroidism (pHPT) has changed its clinical presentation from a classical disease characterized by significant hypercalcaemia with important bone and renal involvement to a disorder with mild hypercalcaemia and lack of apparent symptoms and complications. In recent decades, long-term follow-up studies of untreated patients with pHPT rarely show serious complications, such as progressive hypercalcaemia or renal impairment. Based on these observations, guidelines for diagnosis and conservative management of mild hyperparathyroidism were published by the National Institutes of Health (NIH) in 1991 (Proceedings of the NIH 1991). The major conclusion of this group was that, while surgery should always be considered an appropriate option, many patients with asymptomatic pHPT can be safely followed without surgery. Such patients were defined as those lacking ‘significant bone, renal, gastrointestinal or neuromuscular symptoms typical of pHPT’. The Consensus Development Conference recommended surgery in the patients with one or more of the criteria listed in Table 1. Very recently, new indications for surgery in patients with pHPT have been published (Bilezikian et al. 2002). The differences with the 1990 guidelines are shown in Table 2.

Nevertheless, it remains unclear whether patients with untreated mild asymptomatic hyperparathyroidism are at risk for other complications such as increased morbidity or mortality from cardiovascular disease (angina, myocardial infarction, cerebrovascular accident, transient ischaemic attack, heart failure, arrhythmia, atherosclerosis, and thromboembolic disease).

In this article we review the current evidence for a link between pHPT and increased cardiovascular risk and the potential mechanisms for this relationship.

Primary hyperparathyroidism and risk of premature death

The first suggestion of a link between pHPT and increased cardiovascular risk appeared in 1985 (Ronni-Sivula 1985). Several studies carried out in patients diagnosed between the 1950s and 1980s showed evidence that pHPT with hypercalcaemia is associated with increased morbidity and mortality, mainly due to cardiovascular diseases (Ronni-Sivula 1985, Palmér et al. 1987, Hedbäck et al. 1990, Ljunghall et al. 1991). Nevertheless, some authors claim that the increased risk of death would not concern the patients of today, who usually have very mild disease, and they suggest that patient series demonstrating increased mortality from pHPT are historical (Silverberg & Bilezikian 1997). For example, in the
I. Overt manifestation of pHPT:
   A. Radiographic nephrolithiasis or otherwise documented kidney stone or stones
   B. Reduced creatinine clearance (not otherwise explained)
   C. Radiographically evident hyperparathyroid bone disease
   D. Classic hyperparathyroid neuromuscular disease
   E. Symptoms attributable to hypercalcaemia per se
   F. Preceding episode of life-threatening hypercalcaemia

II. Serum calcium concentration greater than 3 mmol/l (12 mg/dl)

III. Urinary calcium excretion greater than 10 mmol/24 h (400 mg/24 h)

IV. Bone mineral density less than 2 S.D. below age-, sex-matched control

V. Age less than 50 years

VI. Uncertain prospect for successful medical monitoring:
   A. Patient requests surgery
   B. Consistent follow-up seems unlikely
   C. Coexistent illness that may contribute to, or confound detection of disease progression

The variables, specific for HPT, that have been found to influence the risk of death in patients with pHPT are preoperative serum calcium (Leifsson & Ahrén 1996, Lind et al. 1997, Lundgren et al. 2001), preoperative parathyroid hormone (PTH) level (Söreide et al. 1997), and parathyroid adenoma weight (Hedbäck & Öden 1998b).

Serum calcium levels have been demonstrated to be an independent predictor of mortality even within the normal range. Leifsson and Ahrén (1996) explored the distribution of calcium in a large population-based health survey including 33 346 individuals, and correlated the values to mortality during a follow-up of 10.8 years as mean. The mortality rate during the follow-up period in men less than 50 years of age was 20% higher in those with a serum calcium greater than 2.45 mmol/l than in those with serum calcium less than 2.45 mmol/l. Furthermore, those with serum calcium above 2.60 mmol/l had a doubled (odds ratio = 2.0) mortality rate compared with that of subjects with serum calcium below 2.60 mmol/l. This increase was principally due to cardiovascular disease. In another study (Lind et al. 1997), a cohort of 2183 males aged 50 years were investigated for serum calcium and followed-up over the next 18 years. The serum calcium levels were significantly elevated at baseline in the subjects who developed myocardial infarction when compared with the rest of the cohort (2.37 vs 2.35, P < 0.03) and Cox’s proportional hazard analysis showed that serum calcium was an independent risk factor for myocardial infarction. In a more recent study of a cohort of untreated hypercalcaemic patients (serum calcium > 2.60 mmol/l) with pHPT according to biochemical criteria, the median survival time was 20 years versus 25 years in the normocalcaemic age- and sex-matched controls (Lundgren et al. 2001). The excess mortality was significant for cardiovascular disease only, and this accounted for 43% of the deaths among the patients (31% of controls). Cox’s proportional hazard analysis

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Indications for surgery in primary hyperparathyroidism according to the Consensus Development Conference (1990)</th>
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</thead>
<tbody>
<tr>
<td>I. Overt manifestation of pHPT:</td>
<td></td>
</tr>
<tr>
<td>A. Radiographic nephrolithiasis or otherwise documented kidney stone or stones</td>
<td></td>
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<tr>
<td>B. Reduced creatinine clearance (not otherwise explained)</td>
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<td>II. Serum calcium concentration greater than 3 mmol/l (12 mg/dl)</td>
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<tr>
<td>III. Urinary calcium excretion greater than 10 mmol/24 h (400 mg/24 h)</td>
<td></td>
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<tr>
<td>IV. Bone mineral density less than 2 S.D. below age-, sex-matched control</td>
<td></td>
</tr>
<tr>
<td>V. Age less than 50 years</td>
<td></td>
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<tr>
<td>VI. Uncertain prospect for successful medical monitoring:</td>
<td></td>
</tr>
<tr>
<td>A. Patient requests surgery</td>
<td></td>
</tr>
<tr>
<td>B. Consistent follow-up seems unlikely</td>
<td></td>
</tr>
<tr>
<td>C. Coexistent illness that may contribute to, or confound detection of disease progression</td>
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</tbody>
</table>

Table 2 Guidelines for surgical treatment in patients with pHPT in 1990 and 2002.

<table>
<thead>
<tr>
<th></th>
<th>1990</th>
<th>2002</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium above limit</td>
<td>1.6 mg/dl (0.40 mmol/l)</td>
<td>1 mg/dl (0.25 mmol/l)</td>
</tr>
<tr>
<td>Urinary calcium</td>
<td>&gt; 400 mg/24 h (10 mmol/24 h)</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>Reduced by 30%</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>No indication for surgery</td>
<td>If persistently abnormal</td>
</tr>
<tr>
<td>Bone mineral density</td>
<td>Z score &lt; −2 S.D. at distal radius</td>
<td>T score &lt; −2.5 S.D. at the lumbar spine, hip, or distal radius</td>
</tr>
<tr>
<td>Age</td>
<td>Patients under 50 years of age</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Medical surveillance</td>
<td>Not possible</td>
<td>Unchanged</td>
</tr>
</tbody>
</table>
Table 3 Proposed causes of increased cardiovascular risk associated with primary hyperparathyroidism

1. Hypertension
2. Left ventricular hypertrophy
3. Valvular and myocardial calcification
4. Dysfunction in vascular reactivity:
   - Endothelial vasodilatory response altered
   - Vascular smooth muscle reactivity altered
5. Vascular structural changes
6. Arrhythmias
7. Insulin resistance and diabetes mellitus
8. Hyperlipidaemia
9. Increased body mass index and body fat mass
10. Increased serum levels of urate

revealed that serum calcium was independently related to the overall mortality and to the cardiovascular mortality in the patients. After adjustment for other risk factors (glucose, diastolic blood pressure, heart volume, age and sex), the hazard ratio for hypercalcaemia with regard to cardiovascular death was 1.72 (95% CI, 1.24–2.37) and for the overall mortality it was 1.38 (95% CI, 1.07–1.79).

The weight of diseased parathyroid tissue (Hedbäck et al. 1995, Hedbäck & Odén 1998b) and the concentration of parathyroid hormone (Sörense et al. 1997) have also been found to influence independently the risk of death. In the analysis of 713 cases with a single parathyroid adenoma, the glandular weight was significantly related to the risk of death ($P < 0.001$). The relationship between adenoma weight and risk of death as evaluated with the hazard function for death was estimated with a Poisson model (Hedbäck et al. 1995).

Elevated PTH levels were found by multivariate analysis to significantly increase the risk of death ($\text{PTH} > 100 \mu\text{Eq/ml}$ had a risk ratio $=1.483, P = 0.01$) in a cohort of 1052 patients with pHPT (Sörense et al. 1997).

The cardiovascular and metabolic functions that have been described to be affected in pHPT are summarized in Table 3 and discussed below.

Effect of primary hyperparathyroidism on blood pressure

Blood pressure (BP) has been found to be elevated in pHPT, but the cause and question of reversibility by parathyroid surgery are controversial. Potential mechanisms producing hypertension (BP $>140/90 \text{ mmHg}$) include (i) increased blood calcium levels, (ii) elevated intracellular calcium, (iii) increased PTH, (iv) raised plasma renin activity, and (v) hypomagnesaemia.

Calcium infusion has been shown to increase systolic and diastolic BP in subjects with normal or moderately elevated BP (Hvarfner et al. 1989). In a recent study, acute hypercalcaemia induced by calcium infusion in healthy subjects resulted in a dose-related impairment in endothelial vasodilatatory function and an increase in systolic BP (Nilsson et al. 2001).

The concentration of intracellular calcium in platelets has been found to be elevated in both essential hypertension and normotensive patients with pHPT (Fardella & Rodriguez-Portales 1995). In the patients with pHPT, intracellular calcium was strongly correlated with the levels of PTH ($r = 0.87$) and successful removal of a parathyroid adenoma decreased intracellular calcium and this was also strongly correlated with the decrease in PTH ($r = 0.84$). The close correlation between PTH and intracellular calcium suggests that PTH may act as an ionphore for calcium entry into cells and perhaps reflect a pre-hypertensive condition in normotensive patients with pHPT. Increased cytosolic free calcium in platelets has been shown to be elevated also in untreated hypertensive patients with pHPT (Schiff et al. 1997). Moreover, parathyroidectomy of these patients resulted in the reduction of cytosolic free calcium and led to normotension. Nevertheless, a previous study showed that despite significantly elevated BP and extracellular hypercalcaemia, platelet cytosolic free calcium concentrations were lower in patients with pHPT than in controls and values tended to increase after parathyroidectomy (Dominiczak et al. 1990). Thus, the role of intracellular calcium in platelets as a generator of hypertension in pHPT is not clear.

PTH infusion results in persistent hypercalcaemia and hypertension in normal subjects (Hulter et al. 1986) and although the authors could not observe significant changes in plasma renin activity, further studies suggest a direct effect of PTH on renin secretion. Gennari et al. (1995) studied 34 patients with pHPT due to a parathyroid adenoma. Ten patients were hypertensive. Before parathyroidectomy, no significant difference was observed between normotensive and hypertensive patients in circulating levels of calcium, intact immunoreactive PTH and daily total urinary catecholamine excretion. In contrast, plasma renin activity and plasma aldosterone levels were higher in hypertensive patients. After surgery, serum calcium and intact PTH levels were reduced to normal in all patients, while BP, plasma renin activity and plasma aldosterone levels became normal in eight of ten hypertensive patients. These results are consistent with the hypothesis of a direct effect of PTH on renin secretion, which could contribute to the pathogenesis of hypertension. Another study links hypomagnesaemia and hypertension in pHPT (Sangal et al. 1989). The retrospective analysis of 89 patients with surgically proven pHPT showed a mean serum magnesium significantly lower in hypertensive patients ($n = 43$) than in normotensive patients ($n = 46$), with no effect on age, sex, serum calcium and phosphate levels, and creatinine clearance. It has been suggested that serum magnesium levels may play a critical role in regulating vascular tone, since hypomagnesaemia can potentiate the contractile activity of a variety of neurohumoral substances and induce vasospasm (Altura et al. 1981).
The nature of the association between hypertension and pHPT is not consistent with the effect of parathyroidectomy on BP. However, although some reports suggested that parathyroidectomy improved systolic BP in many patients (from 150/90 to 140/85,  $P = 0.01$ for systolic BP) (Dalberg et al. 1996), this could not be confirmed by the majority of the studies (Salahudeen et al. 1989, Sancho et al. 1992, Rodriguez-Portales & Fardella 1994). The reason for this discrepancy could be that in the former study (Dalberg et al. 1996) patients were re-evaluated one year after surgery, while in the negative studies patients were reassessed 2 to 6 months after parathyroidectomy (Salahudeen et al. 1989, Rodriguez-Portales & Fardella 1994). It therefore seems reasonable to speculate that changes in BP need to be observed for a longer period of time. However, no improvement in BP has been shown following parathyroidectomy in patients followed for 60 months (Sancho et al. 1992). In this study, renal impairment was excluded, and the patients were younger than in the Dalberg cohort (45 vs 61 years); therefore renal dysfunction or vessel stiffness in older patients do not seem to be the cause for the different results in these two studies. Thus, it seems that the association of hypertension and pHPT is not consistent with the effect of parathyroidectomy on BP.

**Relation between primary hyperparathyroidism and left ventricular hypertrophy**

A high prevalence (above 60%) of left ventricular hypertrophy (LVH) has been reported by some authors in both hypertensive and normotensive patients affected by pHPT (Dominiczak et al. 1990, Stefenelli et al. 1993, 1997, Dalberg et al. 1996, Piovesan et al. 1999). Direct evidence for a hypertrophic effect of PTH on cardiomyocytes has been shown in vitro using ventricular cardiomyocytes isolated from adult rats. On isolated ventricular cardiomyocytes a hypertrophic response is characterized by increased protein synthesis, increased protein mass, and re-expression of fetal-type proteins. The PTH peptides PTH(1–34) and PTH(28–48) stimulated $^{14}$C-phenylalanine incorporation and induced cytosolic creatine kinase (CK), used to determine protein synthesis, whereas PTH(39–69) did not (Schlüter & Piper 1992). This was accompanied by an increase in total cellular protein mass. PTH(1–34) and PTH(28–48), but not PTH(39–69), were similarly potent in induction of cytosolic CK. PTH variants increased CK activity of cardiomyocytes dose-dependently. Full-length PTH exerted its maximal effect at a ten-fold lower concentration than PTH(1–34); the maximal effects were identical. Induction of cytosolic CK was mainly due to a re-expression of the fetal type creatine kinase isoform CK-B (Schlüter et al. 1996). An increase in CK-BB activity by PTH could be mimicked by addition of phorbol myristate acetate, a protein kinase C activator, and decreased by staurosporine, a protein kinase C inhibitor. These data, therefore, demonstrate that PTH exerts a direct hypertrophic effect on cardiomyocytes via activation of protein kinase C and that a functional domain covering the amino acids 28–34 is responsible for this effect.

It could be argued that the high incidence of hypertension in patients with pHPT is the major cause of LVH. However, in one study, only 55% of patients with pHPT and LVH had a history of hypertension (Stefenelli et al. 1997). Multiple regression analysis in a model including biochemical parameters and BP values, showed that serum PTH levels were associated with LVH as the strongest predicting variable (Piovesan et al. 1999). As expected, systolic and diastolic BP were also predictors of LVH, but with a lower degree of correlation. Moreover, several studies reported a decrease in LVH after successful parathyroidectomy, associated with the normalization of PTH levels (Dominiczak et al. 1990, Stefenelli et al. 1993, 1997), and without changes in mean BP values and number of hypertensive patients (Piovesan et al. 1999). Other data suggest a causative role for PTH in promoting and maintaining LVH. Stefenelli et al. (1997) reported the absence of any variation in LVH in a subgroup of patients with pHPT in whom PTH levels did not decrease after surgery. In contrast, LVH was reduced in the patients where PTH levels did return to the normal range after surgery. In addition, the high prevalence of LVH in hyperparathyroidism secondary to chronic renal failure and its regression after parathyroidectomy and reduction of PTH levels (Sato et al. 1995) supports the hypothesis of a hypertrophic effect of PTH in this condition.

Smith et al. (2000) suggest augmentation of central arterial pressure as a possible cause for LVH in pHPT. They showed that subjects with mild pHPT (mean serum calcium 2.74 mmol/l) have increased arterial stiffness, as evidenced by higher augmentation of central aortic pressures measured by arterial pulse wave analysis. As arteries stiffen, profound changes occur in the arterial pressure waveform. Pulse wave velocity increases adding to the central systolic pressure wave, producing an augmented central systolic pressure (O’Rourke & Kelly 1993). Central pressure is the major determinant of left ventricular afterload and the subsequent development of LVH (O’Rourke & Kelly 1993, Saba et al. 1993). It is therefore becoming apparent that increased large artery stiffness is an important contributor to the development of cardiovascular disease and has been shown to be an independent marker of cardiovascular risk (Arnett et al. 1994, Glasser et al. 1997). The observation of increased arterial stiffness in pHPT may explain the prevalence of echocardiographic LVH among hypertensive and normotensive patients with pHPT (Stefenelli et al. 1997, Piovesan et al. 1999). Furthermore, higher central arterial pressures would be expected to adversely affect overall cardiovascular function and may also explain the increased risk of cerebrovascular disease reported in pHPT compared with controls (Lind &
Ljunghall 1995), although in this study the difference did not reach conventional statistical significance ($P = 0.06$). However, the study performed by Smith et al. (2000) has an important limitation: five out of the 21 patients with pHPT included in the study had impaired fasting glucose. Fasting serum insulin concentrations were also significantly elevated in the pHPT group compared with those in the controls. All indices of arterial stiffness have been shown to be higher with increasing concentrations of fasting glucose, even in non diabetic patients (Salomaa et al. 1995). Thus, more studies with matched fasting glucose levels between patients and controls are required to avoid confounding results regarding vascular compliance in pHPT.

Echocardiographically measured left ventricular mass is considered the strongest independent predictor of cardiovascular morbidity either in hypertensive patients or in the general population (Levy et al. 1990, Koren et al. 1991, Ghali et al. 1992). Therefore, LVH could play some role in cardiovascular morbidity and mortality in pHPT. On the basis of these data (high prevalence of LVH in pHPT, possible role of PTH in its pathogenesis, reversibility after surgery and prognostic value for cardiovascular morbidity and mortality) an echocardiographic study may be advisable in the evaluation of patients with primary hyperparathyroidism. However, caution should be taken in clinical decision making, since there is a difference between the conclusions from group data and the predictive value required in individual clinical management.

Valvular and myocardial calcification in primary hyperparathyroidism

A high prevalence (from 62% to 74%) of premature valvular and myocardial calcification detected by echocardiography, has been reported in patients with pHPT in several studies (Niederle et al. 1990, Stefenelli et al. 1993, 1997), but the valvular sclerosis was only severe enough to produce stenosis in a small number of these patients. However, other studies did not demonstrate a higher ratio of cardiac calcification in patients with pHPT compared with controls (Dalberg et al. 1996). The population with increased cardiac calcification described by Stefenelli et al. (1997), was more severely affected (mean serum calcium 3.03 mmol/l) than the patients described by Dalberg et al. (1996), with more modest increases in serum calcium (mean serum calcium 2.78 mmol/ l), and this may explain the discrepancy. Table 4 summarizes the results obtained in these studies.

The echocardiographic follow-up of the patients with pHPT revealed no significant progression of valvular calcification as well as no significant changes in Doppler measurements and calculated valvular area 41 months after successful parathyroidectomy (Stefenelli et al. 1997). During this long-term follow-up, none of the patients had syncope, severe dyspnoea, or new onset of angina pectoris. This may have clinical implications since the presence and potential progression of aortic stenosis have prognostic clinical value (Pellikka et al. 1990). However, this prospective study (Stefenelli et al. 1997) had no control group, and the progression of valvular sclerosis in patients with pHPT under medical management compared with those who undergo surgery is unknown.

Impaired vascular reactivity

Functional or structural alteration of vascular endothelial and muscle cells can lead to impaired vasoreactivity prior to clinical symptoms of coronary artery disease. An early event in the pathogenesis of arterial vessel wall alteration is impairment of endothelial function. Endothelial dysfunction is a crucial factor in atherogenesis, an important cardiovascular risk factor, and is related to disturbed vessel wall properties (Celermajer et al. 1992, Joannides et al. 1995). In the last decade there has been increasing evidence from animal studies that the endothelium is a target organ of PTH, since PTH regulates the production of a non-cyclo-oxgenase endothelium-dependent relaxing factor (Schleiffer et al. 1993, 1995). Recently, Jiang et al. (1998) demonstrated the expression of the PTH receptor in vascular endothelial cells in the rat by reverse transcription-polymerase chain reaction, also suggesting that the endothelium may be a target tissue of PTH. In addition, in patients who underwent renal transplantation, increasing endothelial dysfunction measured by Doppler analysis of the vessel wall movements is correlated with high PTH levels independently of calcium levels. This suggests that PTH concentrations have a deleterious effect on elastic properties of the arterial wall (Barenbrock et al. 1998). In clinical studies disturbed endothelial function with significantly impaired flow-mediated vasodilation in otherwise healthy patients with pHPT has been demonstrated (Kosch et al. 2000a). Impaired endothelial vasodilatory function in pHPT and no significant difference in the intima-media thickness of the carotid and brachial arteries between patients and controls, have been reported by Nilsson et al. (1999) and Kosch et al. (2000b), who also showed that successful parathyroidectomy can reverse the endothelial vasodilatory dysfunction. These data suggest that endothelial dysfunction in pHPT may occur due to reversible biochemical alterations rather than structural changes. The mechanism for this effect of hyperparathyroidism is not clear. However, the observed normalization of endothelial dysfunction, assessed by brachial flow-mediated vasodilation measured by a multigate pulsed Doppler system, after parathyroidectomy in otherwise healthy patients with primary hyperparathyroidism (Kosch et al. 2000b) suggest, that hyperparathyroidism per se affects the endothelium rather than potentiating the effects of renal insufficiency or hypertension. In the studies performed by Kosch et al. (2000a,b) conditions known to affect endothelial function such as smoking, renal failure,
hypercholesterolaemia, presence of atherosclerotic plaques and hypertension were excluded to highlight the effect of PTH excess. Nevertheless, the design of these studies does not allow discrimination of direct, receptor-mediated effects of PTH from effects of chronic hypercalcaemia, hypophosphataemia and other metabolic changes that are associated with hyperparathyroidism.

In contrast to this, Neunteufl et al. (1998) suggested that altered arterial reactivity in the course of pHPT may predominantly involve the arterial media and not the endothelium. Flow-mediated dilatation following reactive hyperaemia (endothelium-dependent) and nitroglycerin-induced dilatation (endothelium-independent) were assessed in the brachial artery using high resolution ultrasound. Endothelium-independent vasodilatation was impaired in pHPT patients without clinical evidence of coronary artery disease compared with controls, while endothelium-dependent dilatation was similar in both study groups. However, there was a high incidence of cardiovascular risk factors such as smoking, hypertension and diabetes in both patients and controls, all known to affect endothelial function negatively. This may have masked possible differences between the groups. The same patient cohort was analysed 3 years after successful parathyroidectomy (Neunteufl et al. 2000) and no improvement of flow-mediated dilatation or nitroglycerin-induced dilatation was found. No changes were observed with respect to the risk factor profile either. Although parathyroidectomy did not result in an improvement in vascular reactivity, the authors suggest that further progression of vascular disease may have been prevented, since endothelium-dependent as well as endothelium-independent dilatation remained unaltered during the follow-up period.

In addition to functional effects, PTH has been shown to stimulate structural alterations such as proliferation of smooth muscle cells in rats (Amann et al. 1995). In contrast, no proliferative response to PTH could be detected on cultured human vascular smooth muscle cells (VSMCs); however, owing to limited availability of arterial VSMCs at the time of the study, only a single experiment was performed (Chadwick et al. 2000). Thus, further studies using arterial VSMCs would be necessary to investigate this issue fully, but a major effect of PTH seems unlikely. Other structural alterations have been suggested by Neunteufl et al. (2000) who reported an irreversible loss of smooth muscle cell function in patients with pHPT, which may be due to initial vascular calcification. Indeed, necropsy analyses of patients with chronic hypercalcaemia revealed accelerated deposition of calcium not only in myocardial fibres but also in the media and intima of coronary arteries (Roberts & Waller 1981). In the studies performed by Kosch et al. (2002b) and Nilsson et al. (1999), the authors did not demonstrate structural changes as an increase in intima-media thickness in carotid and brachial arteries (Nilsson et al. 1999, Kosch et al. 2000b). This may, in part, be due to the fact that they only included patients with probable early pHPT, who were devoid of standard cardiovascular risk factors.

Cardiac conduction in primary hyperparathyroidism

In experiments in rabbits, hypercalcaemia has been reported to be associated with a slowing of conduction in the sinus and atrioventricular nodes, and with an increased excitability and decreased refractoriness, thereby theoretically facilitating re-entry and the development of complex ventricular arrhythmias (Watanabe 1981). However, it is not clear from the literature whether moderate hypercalcaemia causes cardiac arrhythmias and whether such rhythm problems can be corrected by normalization of the calcium level. Rosenqvist et al. (1992) evaluated the prevalence of cardiac arrhythmias and conduction disturbances by 12-lead ECGs and 24-h long-term ECGs during presurgical hypercalcaemia and 3 months after postsurgical normalization of serum calcium levels in 20 patients with pHPT. They showed that moderate hypercalcaemia (mean serum calcium 2.85 mmol/l), in spite of causing a shortening of the repolarization phase (QT-interval), has no clinically significant effect on cardiac conduction, with no significant change regarding heart rate variations or cardiac arrhythmias. Further studies have shown that the preoperative ECGs from 139 patients with pHPT, compared with 97 normocalcaemic controls, had a shorter duration of the ST-segment (representing the systolic interval), an increased amplitude of the QRS complex (representing ventricular muscle mass), and a longer duration of the T wave (Lind & Ljunghall 1994). In addition, the patients with pHPT had an increased number of ectopic ventricular complexes during bicycle ergometry assessed with a 12-lead ECG continuously recorded during the exercise, compared with controls (Nilsson et al. 2000). Nevertheless, the clinical relevance of these findings has not been evaluated further.

Table 4 Prevalence of myocardial and valvular calcification in patients with primary hyperparathyroidism versus controls.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients with pHPT/controls</th>
<th>Myocardial calcification</th>
<th>Aortic calcification</th>
<th>Mitral calcification</th>
<th>Total cardiac calcification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nierderle et al. (1990)</td>
<td>21/21</td>
<td>62% vs 5%</td>
<td>57% vs 5%</td>
<td>33% vs 14%</td>
<td></td>
</tr>
<tr>
<td>Stefenelli et al. (1993)</td>
<td>54/54</td>
<td>69% vs 17%</td>
<td>63% vs 12%</td>
<td>49% vs 15%</td>
<td></td>
</tr>
<tr>
<td>Dalberg et al. (1996)</td>
<td>44/23</td>
<td>Data not shown</td>
<td>Data not shown</td>
<td>Data not shown</td>
<td></td>
</tr>
<tr>
<td>Stefenelli et al. (1997)</td>
<td>123/0</td>
<td>74%</td>
<td>46%</td>
<td>36%</td>
<td>43% vs 61%</td>
</tr>
</tbody>
</table>
Glucose tolerance and insulin sensitivity in primary hyperparathyroidism

Insulin resistance is associated with a defect in nitric oxide synthesis and sympathetic overactivity leading to endothelial dysfunction and potentiation of the overall cardiovascular risk (Scherrer & Sartori 2000). Abnormal glucose metabolism and high prevalence of diabetes mellitus (DM) have been reported in patients with pHPT. An investigation of a consecutive series of 205 patients with proven pHPT, revealed an observed prevalence of DM of 7.8% (Taylor 1991). Comparisons were made, after corrections for age and sex, with the prevalence of DM in non-hyperparathyroid patients attending the same metabolic clinic, and in general populations of Oxford, Poole, Southall and Coventry, UK. The body mass indices (BMI) of the male and female patients with pHPT did not differ from those of the non-hyperparathyroid group. The prevalence of 7.8% was statistically significantly higher than that of DM in all these populations except, for unknown reasons, in Coventry. The increases ranged from 2.3- to 3.6-fold. In a retrospective analysis of 441 patients undergoing surgery for pHPT the prevalence of DM was 8.2%, which was three times higher than in the unselected age-matched population (Ljunghall et al. 1983). To determine whether this is related to the metabolic abnormalities in pHPT or to the presence of other risk factors for glucose intolerance in these patients, Kumar et al. (1994) studied the glucose metabolism in pHPT without other risk factors for DM, compared with age- and BMI-matched healthy subjects. Insulin sensitivity and beta-cell function were derived by mathematical modelling from the glucose and insulin data during a continuous infusion of glucose. pHPT patients attained significantly higher plasma glucose levels at the end of the glucose infusion and insulin sensitivity was significantly lower in pHPT than in controls. However, no significant correlations were found between insulin sensitivity or beta-cell function and PTH, ionized calcium or inorganic phosphate levels. The insulin resistance present in pHPT, in the absence of obesity and hypertension, may possibly lead to glucose intolerance and diabetes. Very recently new data reassuring the association between pHPT and DM type 2 have been published. Procopio et al. (2002) evaluated the frequency of impaired glucose tolerance (IGT) and undiagnosed DM by oral glucose tolerance test, together with the indices of insulin resistance (homeostasis model assessment and insulin sensitivity index composite) in 59 consecutive pHPT patients without known DM and 60 controls matched by sex, age, BMI and other risk factors for diabetes. They showed a significantly higher prevalence of IGT in pHPT (40.7%, 95% CI, 27.8–53.6) than in controls (25.0%, 95% CI, 13.7–36.3) and significantly higher prevalence of undiagnosed DM in pHPT group compared with controls (15.3%, 95% CI, 5.8–24.7 vs 5.0%, 95% CI, 0–10.7 respectively). In addition, the indices showed that insulin resistance was significantly higher in pHPT than in controls: homeostasis model assessment (median, 95% CI, 2.6, 2.5–3.9 vs 1.7, 1.6–2.5 respectively) and insulin sensitivity index composite (3.5, 3.4–4.6 vs 5.1, 4.9–7.2 respectively).

The converse, the prevalence of pHPT in patients with DM, has also been investigated (Taylor & Khaleeli 1997). Seven patients were found within 704 proven type 1 and type 2 diabetic outpatients, giving an observed prevalence of 0.99%, which is significantly higher than that of pHPT in four general populations, ranging from 0.10% and 0.12% (South Africa) to 0.35% (USA) and 0.36% (Stockholm). When adjusted to the age and sex distribution of the general population from which the diabetic patients were derived, the prevalence of 0.82% remained significantly greater. This converse prevalence, at three- to four-fold, is therefore of the same order of magnitude as that of DM in pHPT.

There is experimental evidence linking hypophosphataemia to the association between DM and pHPT. Hypophosphataemia per se has been found to be associated with impaired glucose metabolism (DeFronzo & Lang 1980). Six non-diabetic subjects with chronic hypophosphataemia (two idiopathic hypercalciuria, two idiopathic phosphate mia, one inherited X-linked phosphataemia, and one adult-onset vitamin D-resistant osteomalacia) and six controls were infused with glucose to maintain a constant hyperglycaemic level (6.9 mmol/l). In a further experiment exogenous insulin was infused at a constant rate to maintain a level of 718 pmol/l together with glucose at a rate sufficient to maintain basal levels. In both experiments the rate of glucose infusion to maintain glycaemia was lower in the hypophosphataemic group than in the controls. Plasma phosphate concentrations ranged from 0.5 to 0.9 mm/l, and therefore were comparable to the levels observed in pHPT. The authors conclude that hypophosphataemia is associated with impaired glucose metabolism in both the hyperglycaemic and euglycaemic states, and that this association primarily reflects decreased tissue sensitivity to insulin.

Amylin, a protein that is processed and released from pancreatic beta-cells in parallel with insulin, has been suggested to play a role in the impaired glucose tolerance in pHPT (Valdemarsson et al. 1996). Amylin is currently being studied with regard to a role for insulin resistance in non-insulin dependent diabetes. Plasma amylin in seven patients with pHPT and six healthy controls was analysed during an oral glucose tolerance test. pHPT was associated with an increased plasma level of amylin and correlated with serum insulin levels (Valdemarsson et al. 1996), suggesting a possible effect of increased amylin level in impaired glucose tolerance in pHPT. This also suggests a role for PTH and/or increased serum calcium in amylin release.

The possibility that removal of overactive parathyroid tissue may diminish the severity of coincident DM has been a controversial subject. As long ago as 1978, Akgun and Ertel reported that in two diabetic patients with pHPT, removal of
the parathyroid adenoma caused a marked improvement in glucose tolerance; in one of the patients with type 1 diabetes the daily dose of isophane insulin fell from 40 to 20 IU (Akgun & Ertel 1978). Further studies have given conflicting results, but most of them conclude that alteration in glucose metabolism in pHPT is reversible, at least partially, after surgical intervention. The results from these studies are summarized in Table 5. According to these data, there can be little doubt that in some but not all patients with both disorders, diabetic status improves, or does not progress, after successful parathyroid resection. More data are required, but the possibility that parathyroidectomy may stop, or even reverse, the progression of diabetes and impaired glucose tolerance may become an additional factor in evaluating whether to treat hyperparathyroid patients medically or surgically.

**Dyslipidaemia in primary hyperparathyroidism**

A high prevalence of lipid profile abnormalities has been reported in pHPT. An analysis of 102 patients with pHPT and matched controls recruited from 5202 females attending population-based mammography screening at age 55 to 75, revealed higher cholesterol and triglycerides values in the patients compared with controls (Lundgren et al. 1998). There was no significant difference between the patients and controls regarding blood pressure, presence of DM, smoking habits, daily exercise and variables of body composition. Triglycerides (total and very-low-density lipoprotein (VLDL) and VLDL-cholesterol were higher, whereas high-density lipoprotein (HDL)-cholesterol was lower in the patients than in the controls. The number of individuals taking oral contraceptives during fertile ages was similar but fewer patients than controls had used post-menopausal oestrogen replacement therapy, which could have some effect on the results. Nevertheless, a further study by the same group demonstrated the link between pHPT and dyslipidaemia, since the second one showed lipid abnormalities to be normalized after parathyroidectomy (Hagström et al. 2002). The same population-based screening programme was used to recruit post-menopausal women with mild, asymptomatic pHPT (mean serum calcium 2.57 mmol/l) and matched controls. They analysed 87 case-control pairs, 69 of whom completed a 5-year follow-up period. pHPT at baseline was characterized by decreased serum HDL-cholesterol, increased total triglycerides, VLDL-triglycerides and VLDL-cholesterol levels and

<table>
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<tr>
<td>Prager et al. (1983)</td>
<td>9 pHPT/no DM</td>
<td>Oral and i.v. glucose tolerance test</td>
<td>No changes</td>
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<td></td>
<td></td>
<td>Tolbutamide test</td>
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<td>Arginine infusion test</td>
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<td>i.v. insulin tolerance test</td>
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<td>i.v. glucose tolerance test</td>
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<td>Ljunghall et al. (1983)</td>
<td>26 pHPT/no DM</td>
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<td>Cheung et al. (1986)</td>
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<td>Bannon et al. (1988)</td>
<td>36 pHPT/DM (35 type 2 &amp; 1 type 1)</td>
<td>i.v. glucose tolerance test Insulin secretion</td>
<td>Significantly lowered insulin secretion</td>
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<td>Prager et al. (1990)</td>
<td>8 pHPT/no DM</td>
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<td>Kautzky-Willer et al. (1992)</td>
<td>16 pHPT/no DM</td>
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<td>Quin &amp; Gumpert (1997)</td>
<td>1 pHPT/DM type 2</td>
<td>Oral glucose tolerance test HbA1c (glycated haemoglobin)</td>
<td>Slight tendency to reduction (not significant) in insulin secretion and in the hepatic insulin extraction Normalized From 9.4% to 4.6% without treatment</td>
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<tr>
<td>Richards &amp; Thompson (1999)</td>
<td>61 pHPT/DM (58 type 2 &amp; 3 type 1)</td>
<td>Dietary regimen and dosage of antidiabetic drugs or insulin</td>
<td>Improvement in 38% of the patients, with reduction in dosage of the previous treatment</td>
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an elevated atherogenic index (total cholesterol – HDL-cholesterol/low-density lipoprotein (LDL)-cholesterol) compared with controls. These alterations were inversely correlated to the serum parathyroid hormone level. Parathyroidectomy, with or without additive hormone replacement therapy (oral oestradiol and norethisterone), normalized the dyslipidaemia in pHPT patients, and they lacked differences from the controls. Five-year surveillance of pHPT without treatment was associated with maintained increase in total triglycerides (2.15 mmol/l vs 2.37 mmol/l at five years). Improvement in HDL-cholesterol (1.29 mmol/l vs 1.51 mmol/l at five years) and LDL-cholesterol levels (5.46 mmol/l vs 4.43 mmol/l at five years) as well as the atherogenic index (5.0 vs 3.7 at five years) were observed in the untreated group. However, in this untreated group the triglycerides and atherogenic index values remained significantly higher and the HDL levels significantly lower than in the matched controls. Therefore, the authors suggest reappraisal of the treatment strategy in postmenopausal women with mild asymptomatic pHPT.

It has been shown that pHPT patients have an impairment of glucose metabolism (see above). The metabolic disturbances accompanying insulin resistance could also contribute to moderately increased triglycerides and decreased HDL-cholesterol concentrations in pHPT, in accordance with what is otherwise seen in subjects with insulin resistance (Bonora et al. 1998). In a study where the group of patients with pHPT and impaired glucose tolerance decreased their fasting glucose values after parathyroidectomy from 5.94 to 5.10 mmol/l (P < 0.05), the total triglyceride concentration was also significantly lower after surgery in this group, but was not changed in the overall group of patients with pHPT who underwent parathyroidectomy (Valdemarsson et al. 1998). Whether lipid abnormalities may be secondary to insulin resistance in patients with pHPT needs further investigation.

Another potential mechanism for dyslipidaemias would be the presence of renal impairment secondary to pHPT. Dyslipidaemias have been associated with kidney disease progression, and increased concentrations of VLDL and intermediate-density lipoproteins (IDL) in chronic renal failure are thought to result from a defect in degradation of plasma triglyceride-rich lipoproteins (Lee et al. 2002).

Elevated serum triglycerides correlate with the incidence of cardiovascular disease (NIH Consensus Conference 1993, Stampfer et al. 1996, Austin & Hokanson 1998). Triglycerides have been found to increase coagulation factor activity and to decrease fibrinolysis. In addition, lipoprotein particles rich in triglycerides such as VLDL, and small dense LDL, might increase the production of macrophage-related foam cells in the arterial wall and thereby accelerate atherosclerosis and media hypertrophy (NIH Consensus Conference 1993, Krauss 1998). Low HDL-cholesterol is highly correlated with increased triglyceride levels and a decreased LDL particle diameter, and correlates independently with cardiovascular disease (Stampfer et al. 1996, Krauss 1998). Therefore, the results above indicate that serum lipids and lipoprotein fractions should be evaluated before conservative follow-up is considered in patients with mild pHPT.

Other causes for increased cardiovascular risk in primary hyperparathyroidism

A cross-sectional study with 41 postmenopausal women with mild pHPT and 43 eucalcaemic, age-matched postmenopausal controls revealed differences regarding body composition between patients and controls (Grey et al. 1994). Women with pHPT were heavier (75.5 kg vs 66.3 kg, P = 0.002), had higher fat mass (33.3 kg vs 26.1 kg, P = 0.001) and had a more android pattern of fat distribution (android-to-gynoid fat ratio 1.05 vs 0.84, P = 0.0004) than the controls. These factors, which could possibly be explained, in part, by the presence of lassitude and fatigue in patients with mild pHPT and, therefore, less physical activity, may be relevant to the increased incidence of cardiovascular disease in this condition. Another possible explanation is that the insulin resistance that possibly occurs in patients with pHPT might promote increased fat mass. However, the authors did not analyse the lipid profile and insulin sensitivity to assess whether these abnormalities of fat distribution were a component of the ‘syndrome X’ in patients with pHPT. Alternatively, because adipocytes and osteoblasts share a common progenitor cell-type (Hicok et al. 1998), PTH which directly activates osteoblasts may also influence adipocyte differentiation and function. There are currently no available data on PTH receptor expression in adipocytes.

The possible relationship between urate and clinical atherosclerotic disease in pHPT has also been analysed. Several previous studies have suggested that increased urate is associated with cardiovascular disease (Fessel 1980, Irribarren et al. 1996, Torun et al. 1998). However, its role as an independent risk factor has remained uncertain (Wannamethee et al. 1997, Johnson et al. 1999). An increased concentration of urate has been described in pHPT (Lundgren et al. 1998, Valdemarsson et al. 1998, Westerdahl et al. 2001), but the mechanism for a metabolic process leading to increased urate levels in pHPT is as yet unclear. Hypoperfusion of the renal capillary network in pHPT has been suggested to be of importance for a reduction in tubular urate secretion and thereby to hyperuricaemia (Hisatome et al. 1992) and serum urate has been found to be inversely correlated to renal function in pHPT before surgery (Valdemarsson et al. 1998). Nevertheless, it is unclear whether renal dysfunction is the sole explanation for elevated serum levels of urate or whether it is also an expression of specific metabolic disturbances in
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Figure 1 Possible mechanisms implicated in the increased vascular risk associated with primary hyperparathyroidism.

pHPT. Westerdahl et al. (2001) showed by multiple logistic regression analysis that urate was an independent risk factor for arteriosclerotic disease in pHPT, and the only three variables positively associated with urate were male gender, fasting blood glucose and serum levels of triglycerides. Therefore, these results suggest that increased urate levels in pHPT patients might be an indicator for a metabolic disorder accompanying pHPT and this is not explained by renal dysfunction per se. It has been shown that patients with pHPT have increased levels of triglycerides and impairment of glucose metabolism (see above). The clearance of uric acid has been reported to decrease in proportion to increases in insulin resistance in healthy subjects, leading to an increase in serum urate concentration (Facchini et al. 1991). Thus, increased urate levels might then, in addition to impaired glucose disposal and increased triglyceride levels, be another expression of a metabolic disorder (Lee et al. 1995, Clausen et al. 1998, Rathmann et al. 1998).

The interrelation between different cardiovascular risk factors in pHPT is shown in Fig. 1.

Conclusions

It remains to be clearly documented that the raised risk of death due to the increased cardiovascular risk is prevented by early parathyroid surgery. The study that demonstrated increased survival with time after surgery (Hedbäck et al. 1991) was based on a minimum follow-up period of 4 years and a mean follow-up period of 12.9 years; it showed a trend towards normalization of the risk of death over several years. Recently, a much larger study has been published. Nilsson et al. (2002) analysed mortality in 10 995 Swedish patients who had parathyroidectomy of a single adenoma between 1958 and 1997. Swedish population standardized for age, sex, and calendar year was used as control. In total, the study included 102 515 person-years in the patients (first postoperative year was excluded from the analysis). Results showed an increased risk of death after operation for pHPT (mortality ratio 1.2, 95% CI, 1.19–1.27). The increased risk persisted far beyond 15 years postoperatively and occurred in both sexes and in all age groups. The principal causes of excess mortality were cardiovascular diseases, DM, and urogenital diseases. Nevertheless, in patients operated on between 1985 and 1997 (n = 6386), overall mortality did not differ from that of the normal population. This improvement may be a late consequence of liberalized calcium screening that was introduced about 30 years ago and indicates that operation at the early stages of the disease may offer a survival advantage. Although the long-term outcome of cardiovascular function in asymptomatic pHPT patients after surgery needs to be evaluated by prospective studies, also taking into account genetic and other associated risk factors for cardiovascular disease, it seems likely that successful parathyroidectomy could decrease the excess mortality in these patients due to cardiovascular disease. Thus, it would seem advisable to change current management strategies for
patients with mild pHPT. Based on current evidence, we would suggest that LVH, impaired glucose metabolism and dyslipidemia are additional parameters to consider when evaluating the management of patients with asymptomatic pHPT, since these factors may improve after surgery. More studies are required to fully establish the indications for parathyroidectomy, but rather than this it might be advisable to perform surgery in all cases of pHPT, and set up the exceptions in which medical treatment should be considered an appropriate option.

References


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Koren MJ, Devereaux RB, Casale PN, Savage DD & Laragh JH 1991 Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. Annals of Internal Medicine 114 345–352.


NIH Consensus Development Conference Statement 1993 Triglyceride, high density lipoprotein, and coronary heart disease. NIH Consensus Development Panel on Triglyceride, 13B-17B.


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