Primary hyperparathyroidism and heart disease — a review

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Primary hyperparathyroidism (pHPT), caused by solitary parathyroid adenomas in 85% of cases and diffuse hyperplasia in most of the remaining cases, overproduces parathyroid hormone (PTH), which mobilizes calcium to the blood stream. Renal stones, osteoporosis and diffuse symptoms of hypercalcaemia, such as constipation, fatigue and weakness are well-known complications. However, in Western Europe and North America, patients with pHPT are nowadays usually discovered during an early, asymptomatic phase of the disease. It has been reported that patients suffering from symptomatic pHPT have increased mortality, mainly due to an overrepresentation of cardiovascular death. pHPT is reported to be associated with hypertension, disturbances in the renin—angiotensin—aldosterone system, and structural and functional alterations in the vascular wall. Recently, studies have indicated an association between pHPT and heart disease, and studies in vitro have produced a number of theoretical approaches. An increased prevalence of cardiac structural abnormalities such as left ventricular hypertrophy (LVH) and valvular and myocardial calcification has been observed. Associations have been found between PTH and LVH, and between LVH and serum calcium. LV systolic function does not seem to be affected in patients with pHPT, whereas any influence on LV diastolic performance needs further evaluation. The aim of this review is to clarify the connection between pHPT and cardiac disease.

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Primary hyperparathyroidism and heart disease – a review

Increased mortality

The clinical picture of pHPT in Western Europe and North America has changed over the last decades. From being considered a disease that often manifested itself with renal stones, bone disease and high levels of serum calcium, it is today mainly asymptomatic or associated with diffuse symptoms and lower serum calcium levels. This is a consequence of a change in demographic distribution, increased knowledge about the disease and improved techniques of measuring serum calcium. The typical symptoms of pHPT vary considerably across the globe. In developing countries, radiological evidence of bone disease and renal complications are much more prevalent, which may be explained by long-standing disease in combination with vitamin D deficiency. Consequently, the results from mortality studies in this field are largely dependent on the type of pHPT-patients studied, which might explain much of the contradictory results in the field.

It is today well-confirmed that symptomatic pHPT-patients suffer from increased mortality before and after treatment with parathyroidectomy. Malignant disorders and cardiovascular diseases such as myocardial infarction, stroke and heart failure seem to be excessively prevalent causes of death among pHPT-patients (Table 1). The largest mortality study to date included 4461 patients that underwent surgery between 1987 and 1994, and found that a highly significant increase in all-cause death, as well as in cardiovascular death (risk ratio: men 1.71, 95% CI: 1.34–2.15; women 1.85; 95% CI 1.62–2.11), compared with controls. The patients were evaluated to have mild-moderate disease, but the serum calcium levels were not presented. The observed increase in mortality was independent of age and gender, and was also present several years post-operatively, even though the patients were “cured” by parathyroidectomy and had calcium, PTH and phosphate within the normal range. Others have reported an increased risk of myocardial infarction among pHPT patients more than a year after surgery, despite normalized biochemical parameters. The serum calcium levels were only modestly elevated at baseline (mean 1.65 mmol/l) in this study. Conservative treatment of female pHPT-patients was related to an increased risk of cardiovascular death, which could be abolished by parathyroidectomy. The levels of serum calcium or PTH were not presented in this study. In another study, 19 patients with persistent pHPT following parathyroidectomy were found to have increased cardiovascular morbidity compared to controls.

To date, no particular parameter has been shown to be the best parameter predicting the risk of premature death among patients suffering from pHPT. The pre-operative parathyroid hormone level, serum calcium level and the weight of the parathyroid adenoma have all been reported to correlate with the risk of death. Slightly increased serum calcium levels (mean 2.67 ± 0.07 mmol/l) were independently related to premature cardiovascular death during twenty years of follow-up, and mild hypercalcaemia in pHPT patients increased the risk of myocardial infarction. In one study, even a high calcium level within the normal range, and without a diagnosis of pHPT, was a significant individual risk factor for myocardial infarction during an 18-year follow-up of middle-aged men.

The year of surgery is an important determinant of the risk of death after surgery, which is likely to reflect the pre-operative calcium levels. Indeed, the pre-operative calcium levels per se were shown to be related to the post-operative mortality. For patients operated on in earlier years (around 1970), normalization of the risk of death seemed to occur 10–15 years after surgery. Surgery in later years (around 1980), and consequently milder disease, was associated with an earlier normalization of the death rate, taking place after about 5 years. This is probably due to lower calcium levels in later years and to shorter duration of the disease, secondary to more extensive routine screening.
In one study, the increased post-operative risk of death only seemed to comprise pHPT-patients of about 60 years of age. An increase in mortality restricted to this age group was also reported in untreated hypercalcemic patients. Conservative treatment of this hypercalcemic group gradually increased the mortality compared with controls during follow-up. These findings are, however, not in line with the larger controlled study by Hedba¨ck et al., showing an increased death rate irrespective of age. In a recent study, Vestergaard et al. conclude that, although parathyroidectomy lowered the overall death rate, it was not associated with a decrease in cardiovascular death when compared to conservative treatment. However, the authors emphasise that there may be selection bias, because the patients were not randomised with regard to treatment. The patients’ biochemical profile was not presented.

Others have presented more ambiguous results, with no increased mortality after parathyroidectomy in the patient group as a whole, but a significantly increased cumulative mortality among females 4–12 years post-operatively.

It is still debated whether asymptomatic pHPT-patients are exposed to an increased risk of cardiac disease or mortality. Whereas most mortality studies, mainly including symptomatic European patients, have shown an increased risk of death, Wermers et al. reported that survival in mainly asymptomatic North American patients with pHPT (mean calcium 2.72 ± 0.12) was not adversely affected. However, by age-adjusted multivariate analysis, higher maximal serum calcium level was an independent predictor of mortality. This is the only study to date that has investigated the risk of death among mainly asymptomatic patients. Only 76% of the patients had verified pHPT, whereas 24% of the patients suffered from hypercalcemia without evident cause. The cohort was treated highly heterogeneously and 29% of the patients underwent parathyroidectomy. The rate of death from cardiovascular diseases was significantly lower than expected (Table 1), and this held true even when only taking the histologically or biochemically proven pHPT into account. However, in addition to the fact that a majority of the patients were asymptomatic, it should be noted that the serum calcium levels were lower compared with some, but not all of the studies that report an increased mortality (Table 1). This is especially important since the calcium level was an independent predictor of mortality. Still, it is yet to be proven that asymptomatic pHPT confers increased mortality.

### Interaction with vascular smooth muscle cells and endothelium

Besides the bone and the kidney, PTH affects other organs, and PTH-receptor mRNA has been found in such different locations as the brain, adrenal gland, bladder, ileum, liver, lung, vascular smooth muscle cells, skeletal muscle cells and the heart in rats. In particular, interactions with vascular smooth muscle have been investigated. PTH stimulates the vascular smooth muscle cell by binding to the PTH/PTH related Peptide (PTHrP) receptor and, thus, increases the intracellular cAMP-levels and reduces the influx of calcium. This is believed to explain the vasodilating properties of PTH, found in vitro as well as in vivo. PTH relaxes most vascular beds in the body independent of the endothelium.

Despite the vasodilating properties, PTH-infusion in man has produced contradictory results with regard to blood pressure response. A blood pressure decrease in essential hypertensives and an increased or unaffected blood pressure in normotensive subjects has been reported. These differences are probably due to differences in PTH levels in serum and different study groups.

There is some evidence that the hyperparathyroid condition might influence endothelial cells. The mecha-
nism has still to be elucidated as receptors for PTH have not been found in significant levels on human endothelial cells. However, disturbed functional properties of the vascular wall, which are generally believed to precede atherosclerosis, have been reported to be associated with pHPT. Studies demonstrate a significantly impaired endothelium-dependent vasodilation in pHPT-patients which is reversed by parathyroidectomy.

This has, however, not been confirmed by others. Instead, a decrease in vascular smooth muscle-dependent vasodilation has been observed. However, among both patients and controls there was a high exposure to factors such as smoking and hypertension, all well-known to affect endothelial cell function, which may have influenced the result.

Contradictory results exist as to whether structural alternations in the vascular wall are associated with pHPT or not. One study found an increased intima-media thickness in the carotid artery wall, but others have not confirmed this in the carotid or the brachial arteries. Similarly, increased carotid atherosclerosis or changed dimensions of the arteries have not been proven to be related to pHPT. In contrast to this, autopsy studies of patients suffering from chronic hypercalcemia have reported an increased deposition of calcium in the intima and media of coronary arteries. This finding is probably a result of a more severe and long-standing disease in these patients, compared to patients included in the other studies.

Stiffening of the arteries might cause an augmentation of the pressure in central arteries and thereby an increased afterload on the heart. Indeed, a significantly higher aortic blood pressure was found in patients with mild pHPT, compared to a control group (mean serum calcium among PTH patients was 2.74), despite similar brachial blood pressures. However, Kosch et al. did not find any differences between pHPT-patients and controls with regard to central blood pressure or isobaric distensibility and pulse wave velocity in the carotid and brachial arteries.

Cardiac hypertrophy, chronotropy, inotropy and energy utilization

In the overall population, left ventricular hypertrophy (LVH) is a powerful predictor of cardiovascular mortality. A fairly new research area is the association between pHPT and LVH. There is much to indicate that the LVH among these patients is greater than expected, even when considering blood pressure. In vitro, there are several possible explanations for an increased LV mass. Studies indicate that PTH can influence the cardiomyocyte because it shares receptors with the PTHrP, which was first found as a factor released from malignant tumors. However, during the last two decades, it has been elucidated that PTHrP in vitro, as well as in vivo, acts as a paracrine or autocrine mediator in the heart.

When the PTHrP is released from vascular smooth muscle cells, the endothelium or atrial cardiomyocytes, in response to mechanical stress, hypoxia or vasoactive peptides, it acts both in a chronotropic and an inotropic manner on the isolatedperfused rat heart. An increased systemic level of PTHrP has for instance been found in congestive heart failure. Indeed, functionally it seems to resemble other well-known vasoactive peptides, such as the atrial natriuretic peptide or the brain natriuretic peptide.

PTH acts on adult cardiomyocytes by binding to the PTH/PTHrP receptor, thereby inducing a rise in the intracellular levels of calcium that can be abolished by the calcium channel blocker verapamil. Increased calcium levels activate protein kinase C and mediate hypertrophic as well as metabolic effects on the cardiomyocyte. Activation of the protein kinase C cascade subsequently activates hypertrophic processes inside the cell. Indeed, this has been demonstrated in rat ventricular cardiomyocytes, where PTH-fragments stimulate protein synthesis and induce cytosolic creatinine kinase, a molecule often found in increased concentrations in hypertrophic myocardial cells.

By binding to the PTH/PTHrP receptor, PTH acts chronotropically on pacemaker cells in vitro in supraphysiological concentrations. The chronotropic effect seems to be due to a calcium independent increase in the inward depolarizing sodium current (I\textsubscript{n}), but some report a calcium dependency. In vitro, PTH does not seem to influence the adult cardiomyocyte inotropically. However, it seems that the contractile process can be indirectly affected by attenuation of the inotropic effects of the b-adrenocceptor pathway as a consequence of an increase in coronary blood flow.

PTH also appears to have an effect on the energy utilization in heart cells, and this is supported by several studies in vitro. Administration of PTH is associated with a cessation of the spontaneous contraction of myocardial cells. Furthermore, both in vitro and in vivo, PTH significantly lowers the content of creatinine phosphate, ATP, ADP, AMP and decreases the mitochondrial oxygen consumption in the cardiomyocyte. The effects seem to be mediated by calcium, as indicated by the inhibitory effects of treatment with verapamil. These properties of PTH, that is being able to interfere with energy utilization and increase the protein content of the cardiac myocytes in vitro, and acting through the same receptor as the paracrine/autocrine factor PTHrP, strongly suggests an ability of PTH to interact with the heart in vivo.

In vivo studies

There are several studies in pHPT-patients supporting the in vitro findings (Table 2). In a group of 16 patients suffering from pHPT, as many as 15 had cardiac hypertrophy. Stefaneli et al. reported similar results; 81.6% of pHPT patients had hypertrophy of the interventricular septum. The same group had earlier reported that 68% of the pHPT-patients had LVH at baseline, compared to 28% among sex and age-matched controls, with similar blood pressures. Others have reported a prevalence of LVH.
<table>
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<tr>
<th>Author (ref no.)</th>
<th>N (patients)</th>
<th>N (controls)</th>
<th>Mean age of the patients (years)</th>
<th>BP patients vs controls</th>
<th>Calcium (mmol/l)</th>
<th>PTH (pg/ml)</th>
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<th>LVMI controls</th>
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<td>111 ± 11</td>
<td>NS</td>
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LVMI, left ventricular mass index (g/m²) and NP, not presented.

1 Median (interquartile range).
2 Two groups of patients. Group A parathyroidectomy at baseline and group B parathyroidectomy after 1 year.
3 LV mass presented as interventricular septum diameter.
4 Compared before and 12 months after parathyroidectomy in normotensive patients.
5 LV mass 41.2 months after parathyroidectomy in normotensive patients.
around 50% among these patients. The LVH seems to develop irrespective of the patients’ biochemical profile or symptoms of the disease. This is probably due to patient delay and, thereby, an increased duration of the hyperparathyroid condition in asymptomatic patients, compared with symptomatic ones. Thus, asymptomatic pHPT-patients may have an increased risk of cardiovascular death as well, even though this has yet to be proved in population-based studies.

The increased prevalence of LVH seems to be independent of blood pressure since several studies have shown a significantly greater LV mass index among pHPT-patients than among controls matched for sex, age and blood pressure. This is in line with observations that cardiac hypertrophy is a common finding in normotensive pHPT-patients as well. In one study, only 55% of the recruited pHPT-patients with LVH had a history of hypertension. Hypertensive pHPT-patients also seem to have increased prevalence of LVH compared with hypertensive controls. Dalberg et al. report an increase of the interventricular septum thickness in pHPT patients compared to controls, but the blood pressure was significantly higher among the pHPT patients. In patients with secondary hyperparathyroidism, an increased prevalence of LVH has been reported, which was reversed after parathyroidectomy and a subsequent reduction in PTH levels. This may further strengthen the notion of PTH as a hypertrophic factor. However, the uraemic condition among patients with secondary HPT makes it difficult to extrapolate these findings to patients with pHPT.

Further support for a connection between PTH and LVH is obtained from essential hypertensives without pHPT. In a group of 36 patients, a strong and highly significant correlation was found between PTH-level and LV mass index ($r = 0.759$, $p = 0.00001$), despite PTH-levels within the normal range. This is a correlation even outscoring the influence of renin and aldosterone on LV mass index in the study. Furthermore, in 62 essential hypertensives, a significantly higher PTH level was found among those with LVH compared to those without. However, despite these published results, PTH is not considered to be a major hypertrophic factor among today’s authorities on hypertension, and a recent review on the subject does not include PTH in this context.

Some studies have not detected any cardiac hypertrophy in pHPT-patients, even though Nilsson et al. reported a trend towards increased LV mass ($p = 0.06$). These studies generally included fewer patients with somewhat higher PTH levels, but similar or lower calcium levels, compared with the studies showing an association between pHPT and LVH (Table 2). The observed differences may also be due to different duration of the hyperparathyroid condition, but the study by Nuzzo et al. is the only study presenting data on the duration (11 ± 4 months). The patients included by Nuzzo et al. were younger compared with other studies, and this may indicate a shorter duration of the disease in that study. The lack of an association between pHPT and LVH reported by Barletta et al. may be a consequence of few patients included in this study (14 patients), and lower levels of serum calcium compared to some of the studies showing an association between pHPT and LVH.

No clear results exist as to whether excentric cardiac hypertrophy is related to pHPT or not. Some groups have found the LV end-systolic and end-diastolic dimensions to be normal among pHPT patients and not influenced by surgery. On the other hand, results by Almqvist et al. have indicated that instant parathyroidectomy prevents increase of the LV end-diastolic diameter compared to a year of conservative treatment in patients with mild pHPT. However, only 30 patients were randomized in that study and the LV end-diastolic diameter was not significantly affected by parathyroidectomy per se. The observation by Näppi et al. of left atrium enlargement among pHPT-patients, is confounded by the facts that several patients suffered from cardiovascular disease and the hypertrophy was not reversed by parathyroidectomy. The conflicting outcomes do not seem to be explained by differences in biochemical profile between the study groups.

Regression of cardiac hypertrophy observed post-operatively

If pHPT is associated with cardiac hypertrophy, it seems reasonable that the hypertrophy should decrease post-operatively, even in the absence of changes in blood pressure. Indeed, this has been reported. However, the regression takes years to be completed, which is not surprising given that the regression of LVH in hypertensive patients does not occur until at least 6–9 months after initiating anti-hypertensive therapy. Thus, it is reasonable that the cardiac hypertrophy is not affected significantly 2–3 months or less after parathyroidectomy. One study found a significant reduction in LV mass index after 6 months, whereas no significant regression was detected 6–24 months post-operatively in other studies. Stefenei et al. have, however, in separate studies shown a significant reduction in LV thickness one year, and 41 months post-operatively, without any significant changes in blood pressure. Pre-existing use of antihypertensive therapy and, thereby, likely a history of hypertension, seemed to attenuate the reduction of the ventricular wall thickness. Hence, in the group without antihypertensive therapy, both the interventricular septum and the LV posterior wall thicknesses were reduced, but in the entire study group, only the LV posterior wall was significantly diminished. In at least one of these studies, there was no association between the pre-operative wall thickness and use of antihypertensive therapy. Results by Almqvist et al. indicate that patients randomised to parathyroidectomy at baseline escape further development of LVH, compared to patients treated conservatively for a year before surgery. The latter group developed a significant increase in LV mass index two years after baseline.
Mechanisms behind cardiac hypertrophy

The mechanism behind the proposed effects of pHPT on cardiac hypertrophy remains to be explored. Associations have not been unequivocally found between cardiac hypertrophy and serology markers in patients suffering from pHPT. Piovesan et al. reported a significant correlation between LV mass index and PTH-levels, constituting the most important correlate of LV mass index in the study, even outscoring the effect of blood pressure.24 Others have presented similar results.25 Another study reported a significant correlation between serum calcium and LV mass,26 but cardiac disease was common among these patients. Several groups found neither calcium24,89 nor PTH26,89 to be related to LV mass, and Längle et al. did not report any correlation between structural heart pathology and PTH, phosphate or calcium, irrespective of the patient’s degree of symptoms.89 The phosphate levels, or the calcium-phosphate product, do not seem to be related to the degree of LVH in pHPT-patients,22 and no association has been found between the change in phosphate level and reduction in LVH post-operatively.23 If there is a strong association between serological markers and cardiac hypertrophy in pHPT-patients, it is reasonable to anticipate a relationship between change in these markers after surgery and regression of the cardiac hypertrophy. This possible association has not been investigated.

Based on the findings of in vitro studies, one may speculate that excess PTH leads to accumulation of calcium in the cells, where the ion triggers protein kinase C activity and, hence, induces hypertrophy. This theory is supported by findings of an inhibitory effect of calcium channel blockers on the chronotropic, inotropic and metabolic effects of PTH in cardiac myocytes.18,19,79,84,88 Results indirectly supporting the theory that excess PTH might be an important player in the pathology of LVH come from Vestergaard et al.101 Retrospectively following patients 12 months after parathyroidectomy, the group concluded that a persistent post-operative PTH elevation, without hypercalcaemia, was associated with significantly higher cardiovascular morbidity, compared to the patients with post-operative PTH-levels within the normal range. Similar results were also obtained by Hedbäck et al.39 Persistent PTH elevation after parathyroidectomy was reported in 4% to 40% of cases102,103 and there was also some evidence that normocalcaemic pHPT is more common than earlier believed.104 Stefenneli et al.24 follow the same line of reasoning; patients with persistent post-operative PTH elevation did not show regression of LVH, as seen in the other patients. This subgroup consisted, however, of few patients and a large number of them were treated with anti-hypertensive medication, a factor that in a subgroup analysis seemed to attenuate the post-operative regression of LVH. Symons et al.21 have found elevated serum concentrations of PTH with normal calcium levels in 5 out of 18 examined patients with hypertrophic cardiomyopathy.

A potential cause for increased prevalence of LVH among pHPT-patients might be an augmentation of the blood pressure in the central arteries.67 However, this is yet to be proven and others do not support this notion.63

Left ventricular function

Systolic function

The LV systolic function among patients with pHPT is probably not affected. No significant abnormalities in LV ejection time,22,99 ejection fraction (EF),24,64,96,99 fractional shortening,21,64,96,99 mean circumferential fibre shortening,23 cardiac index26 or LV end-systolic volume64,96 have been found among pHPT-patients. PTH infusion in man does not seem to have any inotropic or chronotropic effects on the heart, as observed in a study with 5 volunteers.64 One group has, however, reported a slightly decreased LVEF in 15 patients with pHPT, but this study did not include a control group matched for blood pressure, and the prevalence of cardiovascular disease among the patients was relatively high.26 Another study has observed an increased cardiac output in 10 pHPT patients compared to controls.105

Diastolic function

One would expect an increased prevalence of diastolic filling impairment in pHPT patients, based on the increased prevalence of LVH, myocardial calcification and hypertension106 associated with pHPT. The energy-depressing effects of PTH found in vitro might also affect the energy-consuming diastolic relaxation. Indeed, some studies report a decrease in the E/A ratio, the Doppler-derived (E) to late (A, caused by the atrial contraction) ratio of transmitral peak flow velocity, which may be a sign of impaired LV diastolic function (Table 3).25,90 In one study, 83% of the patients had an E/A-ratio less than 1.0.25 Dalberg et al. reported a lower E/A ratio among patients compared to controls, but the blood pressure was significantly higher among the pHPT patients.90 In a study including 14 patients and blood pressure matched controls, there was a significantly increased A among the patients with pHPT, with a decreased E/A as a consequence.99 Näppi et al. reported a greater A among pHPT patients compared to controls, but there was no significant difference in the E/A. However, this study did not include a blood pressure matched control group, there was a relative high prevalence of cardiovascular disease among the patients, and post-operative blood pressure data are not presented.26 A prolonged isovolumetric relaxation time, indicating diastolic filling impairment, has been found in two studies of pHPT patients.26,96 On the other hand, one group has found a shorter isovolumetric relaxation time among patients compared to controls.64 Some studies have not reported any differences between patients and controls in the E/A-ratio,24,64 the deceleration time of the early transmitral flow64,96 or the isovolumetric relaxation time.24 Unfortunately, none of the studies have analysed
the pulmonary venous flow or used tissue Doppler. This makes it impossible to exclude that some patients might have had pseudo-normalization of the E/A-ratio, the deceleration time of the early transmitral flow, or of the isovolumetric relaxation time, which could confound the results with regard to an association between pHPT and LV diastolic dysfunction. Therefore, these results must be interpreted cautiously.

Change in cardiac function post-operatively

Despite the fact that systolic parameters do not seem affected in pHPT-patients, some studies have indicated a significant decrease in LVEF and cardiac output post-operatively. However, others have not reported any changes in LVEF, fractional shortening, cardiac output, peak LV ejection rate or LV ejection time. The conflicting results are probably due to relatively small study groups and the pre-operative biochemical profiles do not seem to correlate to the different outcomes.

Among the studies indicating a diastolic filling impairment associated with pHPT, Almqvist et al. report a significant increase in the E/A ratio two years after parathyroidectomy in a group of 25 patients with mild HPT, without any changes in blood pressure. A similar result was found in a study including 14 patients, but the effect was observed one month post-operatively and the patients were not followed further. Furthermore, Almqvist et al. also report a decrease in the peak filling rate of the left ventricle, as measured by equilibrium radionuclide angiography, one year after surgery. In line with this, a significant decrease in the transmitral deceleration time has been found 13 months post-operatively. However, others present unaltered diastolic parameters post-operatively, but one study did not include the post-operative blood pressure data and another observed a reduction in the systolic blood pressure which might have affected the result. The E/A was unaffected by parathyroidectomy in a study by Stefeneili et al. and was not altered in parallel with the reduction of LVH during a 12-month follow-up. The fact that studies have found a correlation between pHPT and diastolic dysfunction gives support to the notion that the diastolic function might be influenced by parathyroidectomy. However, no correlations seem to exist between the outcome and pre-operative levels of PTH and serum calcium.

Calcifications

Several studies have indicated that pHPT-patients have an increased prevalence of valvular calcifications (Table 4). In a prospective study, Stefeneili et al. found that 63% of the included pHPT-patients had calcifications of the aortic valve (50% mild) and 49% of the mitral valve, compared to 12.5% and 15%, respectively, among sex and age-matched controls. In the majority of cases, these alterations were associated with myocardial calcifications. Later on, the same group reported aortic valve calcifications in 46% and mitral valve calcifications in 39% of the cases (mainly mild — moderate). Twenty-five percent had several valves calcified. Längle et al. presented similar results. In the entire patients group,

<table>
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<th>Author (ref no.)</th>
<th>Aortic valve (%)</th>
<th>Mitral valve (%)</th>
<th>Myocardial (%)</th>
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<td>14</td>
<td>14</td>
<td>86</td>
<td>2.83 ± 0.17</td>
</tr>
<tr>
<td>Minimal symptoms</td>
<td>48</td>
<td>33</td>
<td>4</td>
<td>58</td>
<td>3.03 ± 0.36</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>77</td>
<td>14</td>
<td>16</td>
<td>61</td>
<td>3.08 ± 0.47</td>
</tr>
<tr>
<td>Stefeneili²⁰</td>
<td>54</td>
<td>63</td>
<td>49</td>
<td>69</td>
<td>2.99 ± 0.28</td>
</tr>
<tr>
<td>Stefeneili¹⁹</td>
<td>69</td>
<td>54</td>
<td>39</td>
<td>74</td>
<td>2.98 ± 0.41</td>
</tr>
</tbody>
</table>
78% of the patients had one or more cardiac calcific abnormalities, either in the valves or in the myocardium. Seventeen percent presented valvular calcifications. In a controlled study, 69% of the pHPT-patients were found to have mostly mild calcific accumulations in the myocardium compared to 17.5% among controls. The same group reported similar figures in a later, uncontrolled study, where “bright echoes in the myocardium” were found in 74% of the pHPT-patients. Magnetic resonance imaging detected calcifications in only one of these patients, but the authors consider this to be a result of the better resolution of echocardiography to discover calcifications. In another study, myocardial calcification was found to be four times more frequent among pHPT-patients, compared to controls. A significant correlation between LVH and the extent of valvular calcifications has been reported, as well as between LVH and myocardial calcifications. It is tempting to speculate that this is a consequence of long-standing progression of pHPT.

Some studies do not detect increased prevalence of calcifications among pHPT patients. However, the patients included by Nuzzo et al. were younger compared with those in the studies showing increased prevalence of calcifications, which may indicate a shorter duration of the disease. The lack of calcifications could also be due to lower calcium and PTH levels. This is, however, not in line with findings by Langle et al. indicating that cardiac calcifications neither seem to correlate with the degree of symptoms, nor with clinical or biochemical parameters. However, only mild forms of the myocardial and valvular calcifications were characteristic for the asymptomatic patients. Neither a progression nor a regression of the extent of calcific pathology (valvular and/or myocardial) have been found one year or 41 months after parathyroidectomy.

Conclusion

Studies on mainly symptomatic patients with pHPT reveal increased mortality before and after parathyroidectomy, largely due to increased cardiovascular death. A trend has been observed where parathyroidectomy in later years, with a more favourable biochemical profile and a shorter duration of disease, is associated with fewer deaths post-operatively. Proof is lacking that asymptomatic disease is related to increased mortality, although high serum calcium is also related to increased mortality in asymptomatic patients. pHPT is associated with increased prevalence of LVH, independent of blood pressure. The hypertrophy seems to decline after parathyroidectomy, but the regression process takes years to be completed. Valvular and myocardial calcifications are also found in increased proportions in pHPT-patients. Evidence for a regression of the calcifications post-operatively is lacking. The LV systolic function does not seem to be affected by the hyperparathyroid condition, whereas there is an association with diastolic filling impairment. It is controversial whether the diastolic function is influenced by parathyroidectomy or not, and the different findings do not seem to be explained by differences in serum calcium or PTH levels. Studies using adequate echocardiographic methods for the assessment of diastolic filling are needed to further evaluate any association between pHPT and LV diastolic function.

It is an open issue whether the main culprit behind cardiac complications related to pHPT is calcium or PTH. To date, no particular parameter seems to reflect the risk of premature death among pHPT patients. Significant correlations between PTH and LVH, as well as between serum calcium and LVH, have been found in some studies. Post-operative persistent elevations in PTH may cause increased mortality, as well as promote LVH. PTH seems to increase intracellular levels of calcium that subsequently activate protein kinase C, thereby initiating hypertrophic processes such as protein synthesis. Indeed, even in hypertensive patients without pHPT, PTH levels were strongly related to LV mass. PTH also acts chronotropically on pacemaker cells and disturbs energy production in the cell. Irrespective of pHPT, mild hypercalcaemia has been shown to be independently related to premature cardiovascular death and slightly increased or high-normal calcium levels are associated with increased risk of myocardial infarction. LVH and cardiac calcifications are observed regardless of the degree of symptoms or levels of calcium or PTH. On the other hand, asymptomatic disease seems to be related to milder calcific pathology.

It is reasonable to believe that the harmful effects of the hyperparathyroid condition are dependent on both the duration of disease and the levels of calcium and PTH in absolute terms. In the clinical studies, the duration of the disease is an unknown variable, and this may explain the contradictory results regarding pHPT often encountered in clinical studies. Clearly, more research is needed on the potential complications of asymptomatic pHPT, especially in an era when most patients are diagnosed at this stage of the disease.

References

primary hyperparathyroidism and heart disease – a review


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