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Primary Hyperparathyroidism and the Heart: Cardiac Abnormalities Correlated to Clinical and Biochemical Data

Friedrich Längle, M.D.,[1] Claudette Abela, M.D.,[1] Janette Koller-Strametz, M.D.,[2] Martina Mittelböck, M.Sc.,[1] Jutta Bergler-Klein, M.D.,[2] Thomas Stefenelli, M.D.,[2] Wolfgang Woloszczuk, Ph.D.,[3] Bruno Niederle, M.D.[1]

[1]Department of Surgery, Division of General Surgery, University of Vienna Medical School, Währinger Gürtel 18-20, A-1090 Vienna, Austria
[2]Department of Internal Medicine II (Division of Cardiology), Medical School, Währinger Gürtel 18-20, A-1090 Vienna, Austria
[3]Ludwig Boltzmann Institute for Clinical Endocrinology, University of Vienna, Medical School, Währinger Gürtel 18-20, A-1090 Vienna, Austria

Abstract: Comparing patients with primary hyperparathyroidism (PHP) to a normocalcemic control population, those with PHP have a higher incidence of cardiovascular disease and cardiac abnormalities. This study aimed at correlating cardiac findings (valvular and myocardial calcification, myocardial hypertrophy) with clinical data (age, sex, clinical manifestation, nephrolithiasis, nephrocalcinosis, hypertension, skeletal abnormalities, hypercalcemic syndrome) and biochemical data (serum calcium, serum phosphate, serum iPTH level, serum creatinine). A group of 132 consecutive patients with surgically verified PHP (94 women, 38 men; ages 15–86, mean age 57 ± 16 years) were included in this study. Blood chemistry, clinical presentation, radiography, and echocardiography were carried out in all patients for univariate and multivariate analyses of all parameters. There was no statistical correlation between clinical symptoms, biochemical data, and cardiac calcific alterations. Typical skeletal manifestations (osteolysis/subperiostal resorption) and valvular calcifications were significantly correlated to left ventricular hypertrophy ($p = 0.005$). Cardiac abnormalities such as calcific myocardial deposits or mitral and aortic valvular calcifications do not correlate with laboratory findings and clinical presentation at the time of diagnosis. There was no biochemical or clinical variable that could predict the frequency or severity of valvular sclerosis or calcific deposits in the myocardium. However, PHP-related skeletal abnormalities and valvular calcification were predicting factors for left ventricular hypertrophy, a reversible cardiac manifestation of PHP. Myocardial hypertrophy is more often found with classic symptomatic PHP with osseous abnormalities.

It has been documented that up to 61% of patients with primary hyperparathyroidism (PHP) suffer from circulatory diseases. When PHP patients are compared to a control population with normal serum calcium levels, patients with PHP tend to suffer more often from cardiovascular disease [1, 2]. There is an increased risk of premature death in treated and untreated PHP patients, mainly caused by cardiovascular disease [2–8]. There is a correlation between survival and the severity of hypercalcemia [7] that may induce hypertension [9–12], hypercontractility of the heart muscle, left ventricular hypertrophy, increased oxygen demand [13–16], calcification of coronary arteries [17, 18] and valves [13, 18, 19–21], myocardial calcific deposits [21–26], triggered arrhythmias [23, 27], and coronary artery disease [28]. Bondeson et al. reported that up to 44% of a consecutive series of 300 patients with biochemically verified PHP suffer from various manifestations of coronary artery disease [28]. Furthermore, elevated parathyroid hormone (PTH) and serum calcium levels are associated with a high incidence of hypertension [29–31] and changes of the lipid or carbohydrate metabolism [32, 33].

We reported elsewhere a significantly higher incidence of cardiac abnormalities (changes in mechanical performance of the heart muscle, thickness of the left ventricular wall, calcific deposits in the myocardium, and valvular calcifications) in PHP patients compared to sex- and age-matched normocalcemic controls [21, 34]. In the present study we have correlated cardiac abnormalities with clinical and biochemical data from PHP patients.

Patients and Methods

A group of 132 consecutive patients with surgically established PHP (94 women, 38 men; ages 15–86, mean age 57 ± 16 years) were included in this study. All patients were submitted to standardized baseline screening including complete history, physical examination, skeletal and abdominal radiographs, sonography of the abdomen, 12-lead electrocardiogram, and echocardiography. Blood chemistry, including levels of serum calcium, phosphate, calcium phosphate product, creatinine, glucose, and alkaline phosphatase were analyzed on a standard autoanalyzer (Hitachi, Tokyo, Japan).

Immunoreactive intact parathyroid hormone (iPTH, Nichols Institute Diagnostics, San Juan Capistrano, CA, USA) was measured by radioimmunoassay. At least two measurements were averaged.

Echocardiograms were recorded of all patients with an SSH 160 A (Toshiba Medical, Tokyo, Japan) or a SONOS 1000

Correspondence to: B. Niederle, M.D.

(Hewlett Packard, Medical Products, Andover, MA, USA) ultrasonoscope. The studies were performed with a 2.50- or 3.75-MHz transducer in the semilateral recumbent position, including parasternal long- and short-axis views and apical four-chamber views. Aortic valve calcifications were manifested as thickening and bright echos in both M-mode and two-dimensional (2D) recordings [20]. Calcium in the mitral or submitral anulus presented a uniform, dense band of bright echoes posterior to the mitral leaflets and anterior to the left ventricular wall in M-mode and 2D short-axis and long-axis views [19, 20]. The detection of calcific deposits in the myocardium by 2D echocardiography has been previously described in detail: After overall gain reduction, the remaining signal intensity of intramyocardial structures was compared to peripheral echos and, if possible, to additional calcified structures, using at least two different views [21]. Calcifications were assessed to be mild, moderate, or severe, as described previously [34]. All echocardiograms were analyzed in a "blind" mode by two independent investigators (i.e., without knowledge of clinical or biochemical details). Left ventricular hypertrophy was defined as myocardial thickness of 11 mm or more. According to preoperative clinical symptoms, the patients were divided into three groups as defined previously [5]; biochemical and echocardiographic findings of patients with no symptoms (asymptomatic) (group 1) were compared to those with minimal symptoms (group 2) and to patients with classic symptoms of PHP (group 3).

Cardiac abnormalities taken into consideration were: (1) Calcific deposits in the myocardium; (2) Calcification of the mitral valve; and (3) Calcification of the aortic valve. The abnormalities were graded from 0 to 3 according to the degree of calcification (i.e., none, mild, moderate, or severe). A score was calculated by adding up all three values, the minimum value being 0 and the maximum 9. According to the intensity of the cardiac abnormality, three groups were established: (1) No cardiac affinity for calcification; (2) Low cardiac affinity; and (3) High cardiac affinity—with the scores 0, 1 to 5, and 6 to 9, respectively.

Statistical Analysis

Data are expressed as mean values ± standard deviation (SD): Kruskal-Wallis and chi-squared tests were used to compare the data and to investigate whether cardiac abnormalities and their intensity differed among the three groups. Univariate and multivariate analyses were performed to investigate the effects of different parameters (age, sex, clinical manifestation, nephrolithiasis, nephrocalcinosis, skeletal abnormalities, hypertension, hypercalcemic syndrome, serum calcium, serum phosphate, serum iPTH level, serum creatinine) on the cardiac affinity for calcification and left ventricular hypertrophy.

Results

The results of blood chemistry assays and patient characteristics are summarized in Table 1. According to the preoperative clinical symptoms 7 (5%) of 132 patients were asymptomatic (group 1, no clinical symptoms), 48 (36%) suffered from minimal symptoms (group 2, minimal symptomatic patients), and 77 (58%) had the typical renal, osseous, or gastrointestinal manifestations of PHP (group 3, symptomatic patients). There was a significant decrease of the phosphate level ($p = 0.033$) and a significant increase of the iPTH ($p = 0.032$) from the asymptomatic to the symptomatic group. Of 125 patients (asymptomatic cases excluded), 53 (42%) manifested arterial hypertension requiring oral antihypertensive treatment (Table 1). With oral treatment blood pressure was within the normal range. There were 16 (12%) members of groups 2 and 3 who suffered from coronary heart disease.

Table 1. Clinical and biochemical findings of 132 patients with primary hyperparathyroidism.[a]

Parameters	Group 1 ($n = 7$, 5%)	Group 2 ($n = 48$, 39%)	Group 3 ($n = 77$, 54%)	p value
Age (years)	49 ± 20	65 ± 13	58.14	0.003
Sex (men/women)	2/5	9/39	27/50	
Creatinine (mg/dl)	0.73 ± 0.13	0.9 ± 0.3	1.08 ± 0.6	NS[b]
Alkaline phosphatase	175 ± 73	193 ± 125	233 ± 149	NS
Glucose (mmol/L)	106 ± 38	103 ± 28	104 ± 40	NS
Calcium (mmol/L)	2.83 ± 0.17	3.03 ± 0.36	3.08 ± 0.47	NS
Phosphate (mmol/L)	0.96 ± 0.19	0.89 ± 0.35	0.86 ± 66	0.033
Calcium phosphate product	2.71 ± 0.65	2.6 ± 0.99	2.48 ± 1.3	0.05
iPTH (pg/ml)	123 ± 47	174 ± 127	279 ± 263	0.032
Hypertension	—	24 (50%)	29 (38%)	
Coronary heart disease	—	11 (23%)	5 (7%)	
PHP syndrome	—	31 (65%)	35 (45%)	
Osteopenia	—	28 (60%)	40 (52%)	
Subperiosteal resorption, small cyst	—	—	11 (14%)	
Nephrolithiasis	—	—	58 (75%)	
Nephrocalcinosis	—	—	13 (17%)	

Results are given as means ± SD.

Normal range of biochemical data: serum calcium (2.1–2.6 mmol/l), phosphate (0.8–1.55 mmol/L), calcium-phosphate product (1.6–3.9), intact parathyroid hormone (iPTH) (<60 pg/ml).

[a]The patients were classified into three clinical groups (group 1 = asymptomatic patients; group 2 = minimally symptomatic patients; group 3 = symptomatic patients).

[b]NS: not significant in Kruskal-Wallis test.

There were 64 (48%) cases of left ventricular hypertrophy; 2 (28%) in group 1, 22 (47%) in group 2, and 40 (52%) in group 3 showed hypertrophy of the left ventricular wall. Analyzing the above parameters, 21 (78%) of 27 patients with skeletal manifestations, such as subperiostal resorption or small cysts, had left ventricular hypertrophy ($p = 0.031$).

Additional echocardiographic findings (myocardial calcific deposits and valvular calcification) are shown in Tables 2 and 3. Of the 132 patients, 103 (78%) had one or more cardiac abnormalities; 22 (17%) of this group had calcific myocardial deposits, mainly in the interventricular septum; 22 (17%) showed only valve calcifications; and 59 (44%) had both of the above calcific cardiac changes (Table 2). Among the 132 patients, 6 (86%) in group 1, 38 of 48 (80%) in group 2, and 59 of 77 (77%) in group 3 had one or more cardiac abnormalities (Table 2). Table 3 shows the number of patients in each clinical group with valvular calcifications, the valve affected, and the number of patients with myocardial calcific deposits. In the

Table 2. Echocardiographic findings correlated to the clinical presentation of PHP at the time of diagnosis.

Cardiac abnormality	Group 1 (n = 7)	Group 2 (n = 48)	Group 3 (n = 77)	Total (n = 132)
Group I: no abnormalities	1 (14%)	10 (21%)	18 (23%)	29 (22%)
Group II: only myocardial calcific deposits	2 (24.5%)	4 (8%)	16 (21%)	22 (17%)
Group III: only valve calcification	0	10 (21%)	12 (16%)	22 (17%)
Group IV: combination II + III abnormalities	4 (57%)	24 (50%)	31 (40%)	59 (45%)

Group 1 = asymptomatic patients; group 2 = minimal symptomatic patients; group 3 = symptomatic patients.
The chi-square p value was not significant in any case.

Table 3. Valves with calcifications and patients with myocardial deposits and left ventricular hypertrophy,[a] by PHP clinical group.

Pathology	Group 1 (n = 7)	Group 2 (n = 48)	Group 3 (n = 77)
Aortic valve calcification	1 (14%)	16 (33%)	11 (14%)
Mitral valve calcification	1 (14%)	2 (4%)	12 (16%)
Aortic/mitral valve calcification	2 (28.5%)	16 (33%)	20 (26%)
Calcific myocardial deposits	6 (86%)	28 (58%)	47 (61%)
Left ventricular hypertrophy	2 (28.5%)	22 (46%)	40 (52%)

Group 1 = asymptomatic patients; group 2 = minimal symptomatic patients; group 3 = symptomatic patients.
The chi-square p value was not significant in any case.
[a]Muscular thickness ≥ 11 mm.

asymptomatic group there were 4 (57%) cases with valvular calcification and 6 (85%) with calcific deposits in the interventricular septum. Only mild forms of calcific myocardial deposits and mitral and aortic valvular calcifications were characteristic of group 1. There was a lack of statistical significance in comparison to the degree of valve and muscle changes in groups 2 and group 3 (Table 4).

Summarizing the affinity scores of heart calcifications, 29 (21%) patients had no cardiac abnormalities; 95 (71%) belonged to the low cardiac affinity group and 8 (8%) to the high cardiac affinity group (Table 5). The occurrence of cardiac calcifications is directly correlated with left ventricular hypertrophy (p = 0.005); in 34% (10 of 29) of the patients with no cardiac calcifications, in 48% (46 of 95) of the low affinity group and in 100% (8 of 8) of the high affinity group, hypertrophy of the cardiac muscle was demonstrated.

There was no statistical significance in multivariate analyses when comparing biochemical and clinical parameters as to distribution and extent of calcific cardiac abnormalities. Regarding the comparison of clinical parameters with left ventricular hypertrophy, there was a significant correlation with skeletal changes (subperiostal resorption or small cysts) (p = 0.013) and valvular calcifications (p = 0.0008).

Discussion

Left ventricular hypertrophy, calcific deposits in the myocardium, and aortic and mitral valvular calcifications are frequent findings in patients with PHP. Prospective echocardiographic studies documented cardiac abnormalities at a significantly

Table 4. Calcific cardiac abnormalities (classification and affinity score) and myocardial hypertrophy compared to PHP clinical manifestations.

Cardiac abnormality and affinity score (classification)[a]	Group 1 (n = 7)	Group 2 (n = 48)	Group 3 (n = 77)	Chi-square p value
Calcific myocardial deposits				
None	1	20	30	NS
Mild	4	17	26	
Moderate	2	10	13	
Severe	0	1	8	
Mitral valve calcification				
None	4	30	45	NS
Mild	3	11	23	
Moderate	0	4	7	
Severe	0	3	2	
Aortic valve calcification				
None	4	16	46	0.036
Mild	3	22	15	
Moderate	0	6	12	
Severe	0	4	4	
Left ventricular hypertrophy				
No	5	25	36	NS
Yes	2	22	40	

Group 1 = asymptomatic patients; group 2 = minimal symptomatic patients; group 3 = symptomatic patients.
NS: not significant.
[a]None = 0; mild = 1; moderate = 2; severe = 3.

Table 5. Cardiac calcific affinity score compared to the clinical manifestations by PHP group.

Cardiac affinity	Affinity score	Group 1	Group 2	Group 3
None (n = 29, 21%)	0	1 (14%)	10 (20%)	18 (21%)
Low (n = 95, 72%)	1–5	6 (85%)	35 (72%)	54 (69%)
High (n = 8, 8%)	6–9	0	3 (6%)	5 (8%)

Group 1 = asymptomatic patients; group 2 = minimally symptomatic patients; group 3 = symptomatic patients.
The chi-square p value was not significant in any case.

higher rate of PHP patients than in normocalcemic controls [21, 34]. The present study was designed to evaluate whether these changes can be correlated to biochemical parameters or clinical manifestations of PHP.

Our data show that patients with asymptomatic, minimally symptomatic, and classic symptomatic PHP demonstrated left ventricular hypertrophy in 28%, 47%, and 52%, respectively. Calcifications in the myocardium as well as valvular sclerosis were observed in 86%, 80%, and 77%, respectively. Cardiac abnormalities were studied by modified echocardiographic studies, including recordings with maximal gain reduction [21, 34]. Using this technique [21, 34], areas of bright echos (indicating calcifications) persisted in regions classified "normal" during routine echocardiography with normal gain [35]. There was, however, no statistical difference between the three clinical groups and the above-mentioned cardiac abnormalities. Although most asymptomatic patients, i.e., 86% (6 of 7), exhibited the full pattern of cardiac abnormalities, intensity grades were only mild and moderate. These findings raise the question whether so-called asymptomatic PHP really exists and

if an early operation can influence the course of these cardiac manifestations. In a recently published evaluation of patients suffering from PHP, left ventricular hypertrophy (an independent cardiovascular risk factor) showed significant regression after successful parathyroidectomy, whereas calcifications persisted without evidence of progression [34]. In another study, Hedbäck et al. showed that early surgery decreases the risk of premature death, even with mild cases of PHP [36]. Thus there is evidence that a more liberal indication for surgery may have positive effects on prognosis.

Cardiac calcifications with fatal outcome have been described in patients with acute PHP [15]. Fatal cardiac disorders in uremic patients with renal (secondary or tertiary) hyperparathyroidism seem to be a consequence of myocardial calcification [37] and calcific aortic or mitral valve diseases, well documented in end-stage renal disease [19, 20]. Elevated parathyroid hormone [13, 18], magnesium, alkalosis during hemodialysis, hypercalcemia [38], or an increased calcium-phosphate product (commonly accepted as the most important factor) [19, 20] are possible predisposing parameters for the development of the above-mentioned cardiac findings. All patients of our series showed the typical biochemical findings of PHP; however, their calcium-phosphate product was within the normal range or lower. Thus our findings are in contrast to those of Katz et al. [25], who are of the opinion that soft tissue calcification occurs only in patients with an elevated calcium-phosphate product. On the other hand Palmieri et al. [39] concluded that PTH accentuates the dystrophic process by enhancing the already increased calcium flux into the heart muscle. They also postulated that normal secretion of PTH may have a deleterious effect in congenital or acquired conditions associated with altered plasma membranes [39]. Cardiac abnormalities such as valvular sclerosis and calcific myocardial deposits seem to be a variety of soft tissue calcification in PHP that may be observed even at an early stage of the disease.

In the present study no correlation was found between biochemical or clinical parameters and localization or severity of the cardiac abnormalities. We documented a statistically significant correlation between the incidence of typical skeletal manifestations of PHP (subperiostal resorption or small cysts) and the occurrence of valvular calcifications with left ventricular hypertrophy. Both manifestations—osseous abnormalities and hypertrophy of the myocardium—may be detected more often in patients with a longer history of PHP (classic symptomatic patients) and not necessarily in acute PHP subjects with extremely elevated serum calcium levels. The correlation between valve calcification and left ventricular hypertrophy may also be the result of a long-standing history of PHP. In many patients it was impossible to define exactly the onset of the disease. However, we cannot be sure whether these cardiac abnormalities are due to elevated PTH levels or to hypercalcemia per se. In mammalian models Nickols demonstrated a direct effect of PHP on the myocardium [40]; he found a dose-dependent reduction in blood pressure as a result of a direct interaction of PHP with the vascular smooth muscle of arteries and resistance vascular beds and a direct (nonreflex) positive inotropic and chronotropic effect on cardiac tissue. The latter effect may result in cardiac muscle hypertrophy. On the other hand, Stefenelli showed a direct relation between increasing intracellular calcium levels of the myocyte and hypercontractility of the myocardium, which may be an additional mechanism of left ventricular hypertrophy [41]. After successful parathyroidectomy and normalization of parathyroid hormone and serum calcium levels, the hypertrophy of the myocardium is reversible [34].

In conclusion, cardiac abnormalities such as left ventricular hypertrophy and calcific myocardial deposits and calcifications of the mitral or aortic valve are frequently found in PHP, irrespective of the clinical presentation at the time of diagnosis. There was no biochemical or clinical variable that could predict the frequency or intensity of the calcific cardiac manifestation in PHP patients. However, PHP-related skeletal changes coincided with left ventricular hypertrophy. Thus echocardiographic studies should be performed in all patients with PHP to exclude distinct cardiac abnormalities and in a subgroup of patients with severe valve calcifications.

Résumé

Les patients ayant une hyperparathyroïdie primitive (HPP) ont plus de maladies cardiovasculaires que la population normocalcémique. Le but de cette étude a été de corréler les données cardiaques (calcifications myocardiques et valvulaires, hypertrophie myocardiques) avec des données cliniques (âge, sexe, manifestations cliniques, lithiase urinaire, néphrocalcinose, hypertension, anomalies squelettiques, hypercalcémie) et biochimiques (calcémie, phosphorémie, taux d'iPTH, créatinine). 132 patients consécutifs traités pour HPP (94 femmes et 38 hommes, âgés de 15 à 86 (moyenne = 57 ± 16) ans) ont eu ce bilan et tous ces facteurs ont été étudiés en analyse mono et multi-factorielle. Il n'a pas été retrouvé de corrélation entre les symptômes cliniques, biochimiques et les calcifications cardiaques. Les manifestations squelettiques typiques (ostéolyse/résorption souspériostée) et les calcifications valvulaires étaient significativement corrélées avec l'hypertrophie ventriculaire gauche ($p = 0.005$). Les anomalies cardiaques telles que les calcifications myocardiques, valvulaires mitrales et/ou aortiques ne sont pas corrélées avec les données de laboratoire ou la présentation clinique au moment du diagnostic. Il n'y avait aucun variable clinique ou biochimique qui prédise la fréquence ou la sévérité de la sclérose valvulaire ou les calcifications myocardiques. Les anomalies squelettiques et calcifications valvulaires, cependant, étaient prédictives d'hypertrophie ventriculaire gauche, une complication réversible de l'HPP. L'hypertrophie myocardique est retrouvée plus souvent dans la forme classique d'HPP symptomatique avec des anomalies osseuses.

Resumen

Al comparar pacientes con hiperatiroidismo primario (HPP) con personas pertenecientes a una población normal control, aparece que en el HPP hay una mayor incidencia de enfermedad cardiovascular y de anormalidades cardíacas. El presente estudio está orientado a correlacionar los hallazgos cardíacos (calcificación valvular y miocárdica, hipertrofia miocárdica) con las características clínicas (edad, sexo, manifestación clínica, nefrolitiasis, nefrocalcinosis, hipertensión, anormalidades del esqueleto, síndrome hipercalcémico) y los datos bioquímicos (calcio sérico, fosfato sérico, nivel sérico de iHPT, creatinina sérica).

Ciento treinta y dos pacientes con HPP verificado quirúrgicamente (94 mujeres y 38 hombres con edades entre 15 y 86 (media 57 ± 16) años fueron incorporados en el estudio, con la inclusión, para análisis uni y multivariable, de la química sanguínea, síntomas de presentación clínica, radiografía y ecocardiografía.

No apareció correlación estadística entre los síntomas clínicos, los datos bioquímicos y las alteraciones de calcificación cardíaca. Las manifestaciones esqueléticas (osteolisis/resorción subperióstica) y las calcificaciones valvulares aparecieron significativamente correlacionadas con la hipertrofia ventricular izquierda ($p = 0.005$).

En conclusión, las anormalidades cardíacas tales como depósitos calcíficos en el miocardio, calcificaciones valvulares mitrales y/o aórticas no se correlacionan ni con los valores de laboratorio ni con los síntomas de presentación clínica en el momento del diagnóstico. No se encontró variable alguna, bioquímica o química, que pudiera predecir la frecuencia o la severidad de la esclerosis valvular o de los depósitos calcíficos en el miocardio. Sin embargo, tanto las anormalidades esqueléticas como la calcificación valvular aparecieron como factores de predicción de la hipertrofia ventricular izquierda, la cual es una manifestación reversible del HPP. La hipertrofia miocárdica se presenta con mayor frecuencia en un HPP clásico con anormalidades óseas.

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