Long-Term Effects of Parathyroidectomy on Hypertension Prevalence and Circadian Blood Pressure Profile in Primary Hyperparathyroidism

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ABSTRACT

Our aims were to evaluate the prevalence and outcome of hypertension in patients with primary hyperparathyroidism (PHPT), previously and after follow-up of parathyroidectomy. A group of 46 consecutive patients with sporadic PHPT due to adenoma undergoing surgery were followed an average of 3.5 years (range 36 to 53 months). In 16 nonselected, consecutive parathyroidectomized patients, with normalized biochemical measurements, circadian rhythm of blood pressure was evaluated with ambulatory blood pressure monitoring (ABPM). Prevalence of hypertension in PHPT was 54.35%, and there was no significant association of PTH, total and ionic calcium levels with SBP and DBP. During follow-up, none of the patients with presurgical hypertension became normotensive and five of the normotensive patients developed clinical hypertension. In ABPM, 6/11 hypertensive and 3/5 normotensive subjects showed nondipper behavior. Serum total calcium was significantly related to night-time systolic blood pressure (SBP) (r = 0.620, P < 0.02), and night-time diastolic blood pressure (DBP) (r = 0.758, P < 0.002). In dippers, creatinine clearance was significantly higher (91.3 ± 18.5 vs. 64.3 ± 11.5 ml/min, P < 0.01), while serum total calcium was lower (2.42 ± 0.13 vs. 2.23 ± 0.17 mmol/L, P < 0.04) than in nondippers. In conclusion, our results suggest that parathyroidectomy has little effect on hypertension prevalence. Renal impairment, a condition that did not improve after parathyroidectomy, may be a causal factor of hypertension in PHPT. Also, the high prevalence of nondipper behavior in hypertensive and normotensive subjects after parathyroidectomy, suggests that target organ risk persists. We hypothesized that slight elevations of serum total calcium even in the normal range could be involved in the alteration of the circadian rhythm of blood pressure.

KEYWORDS: parathyroidectomy; blood pressure profile; primary hyperparathyroidism

INTRODUCTION

Primary hyperparathyroidism (PHPT) is associated with a higher prevalence of hypertension than general population (1–3). Even though it has been described as a relationship between high levels of serum parathyroid hormone (PTH) with high blood pressure there is no evidence of a casual link (4,5). Some other pathogenic factors have been suggested as hypercalcemia (3,6), a parathyroid hypertensive factor (7), an increase in renin-angiotensin system (8–10), endothelin and adrenomedullin systems (11), and renal function impairment (3,12–15). In PHPT patients (16) and in normotensive subjects that underwent curative parathyroidectomy, an abnormal sensitivity to pressor agents has been reported (17). While some studies showed a decrease in blood pressure levels after parathyroidectomy (6,7,18–22), other studies did not show any change in the prevalence of hypertension (12,23–25).

There are few studies about the circadian behavior of blood pressure and their relationship with PTH and calcium concentrations in patients with PHPT (25, 26). Only one study reported 24-h ambulatory blood pressure (BP) profile changes after successful parathyroidectomy (24).

The objectives of the present study were to evaluate (i) the prevalence of hypertension in patients with
PHPT and its relation with serum PTH levels, serum calcium, and renal function; (ii) the control degree of hypertension achieved before and after long-term follow-up of successful parathyroidectomy; and (iii) the circadian profile of BP after the cure of the endocrinopathy.

**PATIENTS AND METHODS**

Forty-nine patients (41 women and 8 men) with a diagnosis and surgical treatment for the sporadic type of PHPT at the Hospital de Clínicas San Martin Buenos Aires School of Medicine from January 1998 to December 2004 were included. Their mean age was 58.9 ±17.3 years. Patients with multiple endocrine neoplasias (MEN), and secondary and tertiary hyperparathyroidism were excluded from the study. The diagnosis of PHPT was based on one or more of the following criteria: persistent elevation of total and ionized serum calcium, increased serum immunoreactive intact PTH, characteristic radiographic features of PTHP, histological evidence after parathyroidectomy of parathyroid adenoma (n = 46), hyperplasia (n = 2), or carcinoma (n = 1).

We included only patients with a diagnosis of parathyroid adenoma, in whom we evaluated demographic data, prevalence of arterial hypertension, antihypertensive treatment, and therapeutic response. The diagnostic criteria for hypertension were office-seated SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg on three or more measurements during at least two clinical visits, as well as a history of hypertension. None of the hypertensive patients were previously treated to surgery with thiazides. Serum and urinary concentrations of creatinine and serum concentrations of calcium, phosphate, and albumin were determined in an automatic analyzer (Hitachi 705, Boehringer Mannheim, Mannheim, Germany). Ionized calcium was measured with the Ciba-Corning 288 (Ciba–Croning, Norfork, UK). Total serum calcium values were adjusted for albumin concentrations.

Serum intact PTH was measured by radioimmunoassay (PTH, Nichols Institute Diagnostics, San Juan Capistrano, CA). Creatinine clearance was calculated using the Cockroft-Gault formula (27). Anthropometric measurements included weight and height, determined with subjects wearing light clothes and without shoes. Body mass index (BMI) was calculated according to the formula body weight (kg)/height (m)^2.

All parathyroidectomized patients were re-examined after an average of 3.5 years (range 36 to 53 months), with normalized levels of serum PTH and serum calcium. In 16 nonselected, consecutive patients with this condition, 24 h-ABPM was always performed on a working day using the oscillometric technique with a portable Takeda 2430 blood pressure device (A&D Co., Ltd. Higashi Ikeburo, Tokyo, Japan) provided with an appropriate size cuff according to the arm circumference of the patient. All subjects were instructed to rest or sleep between 2300 and 0700 h. The device was adapted to the patient’s left arm and was programmed to record BP at 15 min intervals during the 0700–2300 h daytime period and at 30-min intervals during the 2300–0700 h nighttime period. All subjects gave informed consent to participate in the study, which was approved by the institution’s ethics committee. In all of the patients we obtained all clinical and biochemistry measurements referred to in the retrospective study. The patients who exhibited falls >10% in SBP and DBP during the time period 2300–0700 h with respect to the values for 0700–2300 h were classified as dippers; all those not exhibiting these characteristics were considered nondippers. According to the ABPM data, patients were classified as those with nocturnal normotension (nocturnal BP < 125/80 mm Hg) or nocturnal hypertension (nocturnal blood pressure > 125/80 mm Hg) (28).

**Statistical Analysis**

In each group, data were expressed as means ± SD. As women were considerably older than men, analysis of covariance (a two-way ANCOVA) age was a co-vari-able; gender and BMI (BMI < 25 vs. BMI ≥ 25) as main sources of variability were arranged. Mean values were adjusted for age differences. The Levene test was applied to verify the equality of variances. Relations between variables were assessed using Spearman’s correlation test in both genders. All statistical procedures were performed using the SPSS 10.0 software package (version 9.0.1, SPSS Inc., Chicago, IL). Values of P < 0.05 were considered to be statistically significant.

**RESULTS**

**Preoperative Data**

The clinical, biochemical, and histological characteristics of surgical pieces in the 46 patients with PHPT caused by adenoma are shown at Table 1. There was no difference between the hypertensive and normotensive patients in age, gender, body weight, serum PTH, serum total and ionic calcium, pathology and weight of the specimen removed. In PHPT patients, there was no significant association of serum PTH levels, serum total, and ionic calcium levels with SBP and DBP. Twenty-six percent were in stage 2, and 39% in stage 3 of renal impairment. Creatinine clearance was...
lower in hypertensive patients than in normotensive patients with PHPT. A significant inverse correlation was found between ionic calcium and PTH (r = −0.399, P < 0.03), age, and creatinine clearance (r = −0.661, P < 0.01), and SBP and creatinine clearance (r = −0.479, P < 0.01).

**Postoperative Follow-Up**

During follow-up, none of the patients with presurgical hypertension became normotensive and 5 (28.6%) of the patients who were normotensive before parathyroidectomy developed clinical hypertension. In the group as a whole, creatinine clearance was significantly lower than in the preoperative assessment (75.3 ± 25.0 vs. 91.5 ± 32.4 mL/min, P < 0.05).

In 24-h-ABPM, 6/11 hypertensive and 3/5 normotensive subjects showed nondipper behavior and nocturnal hypertension. There was an inverse correlation between PTH and diurnal SBP (r = −0.664, P < 0.02), and 24-h DBP (r = −0.669, P < 0.02). Serum total calcium showed a significant association with nighttime SBP (r = 0.620, P < 0.02) and nighttime DBP (r = 0.758, P < 0.002). In dippers, the creatinine clearance was significantly higher than in nondippers (91.3 ± 18.5 vs. 64.3 ± 11.5 mL/min, P < 0.01), while serum total calcium was lower (8.93 ± 0.69 vs. 9.69 ± 0.53 mg/dL (P < 0.04) (Figure 1). There was a significant inverse relationship between creatinine clearance and nighttime SBP (r = −0.572, P < 0.05).

**DISCUSSION**

Our study showed a higher prevalence of hypertension in patients with PHPT than that reported in the general population of Latin American countries (29, 30). Curative parathyroidectomy was not followed by a reduction in the prevalence of hypertension. Moreover,
after the parathyroidectomy, there was a significant percentage of patients who were normotensive preoperatively that developed hypertension. A longitudinal study that reported a reduction in BP after parathyroidectomy was performed in the immediate postoperative period (31). Hence, it may reflect the effect of general anesthesia and bedrest on blood pressure. Other studies had a follow-up of less than 3 years (21,22). We observed that an increase in the prevalence of hypertension after a long period of successful parathyroidectomy suggest that other factors in addition to PTH levels may play a pathogenic role in hypertension. Our results of the absence of a relationship between serum PTH levels with casual BP in patients with PHPT were similar to those published by Lumachi et al. (32).

Serum calcium increase has been implicated in the pathogenesis hypertension in PHPT (6). It has been suggested that PTH has a permissive role increasing calcium influx to the cell and, consequently, its vasoconstriction effects (6). Letizia et al. (33) reported a correlation between serum ionic calcium and both diurnal and 24 h-DDBP in patients with PHPT, suggesting that the increase of serum ionic calcium may be an independent factor of peripheral resistance elevation. On the other hand, Nilsson et al. (24) found a similar prevalence of hypertension in PHPT and in matched normocalcemic control subjects (in both groups, 3/21 patients).

In the present study there was a surprisingly high proportion of patients with nondipper behavior, not only in hypertensive but also in normotensive patients after long-term parathyroidectomy. In this regard, it has been reported that alterations in blood pressure circadian rhythm have more prevalence in secondary hypertension than in essential hypertension (34–36). Our findings are at odds with the Nilsson et al. report (24) who in their three hypertensive patients did not find a blunted decline in nighttime BP after 1 year of parathyroidectomy. This discrepancy may be attributed at least in part to the characteristics of the sample studied and methodology differences.

To our knowledge the present study is the first that evaluated the relationship between PTH and serum calcium levels with circadian rhythm of BP after a long period of curative parathyroidectomy. We found significant correlations between serum total calcium and both ambulatory SBP and DBP. Moreover, serum total calcium levels were higher, yet in a normal range in nondipper than in dipper patients, and in those with nocturnal hypertension than in nocturnal normotension. With regard to these data, it is tempting to speculate that even slight elevations of total serum calcium could not only have an important pathogenic role in BP increase in PHPT but could also be involved in the altered circadian rhythm of BP that we found after long-term parathyroidectomy.

Functional and structural renal damages have been considered to be a causal factor in the hypertension of PHPT (12,23,25). Aging would not be the only factor that accounted for the 18% decline found in the postoperative follow-up of the present study (37). This finding points out that target risks persist regardless of the cure of PHPT. Our data showed less kidney function impairment in those subjects who in the follow-up had dipper behavior and nocturnal normotension than in those with nondipper behavior and nocturnal hypertension. In this regard, previous studies have suggested that nondipper behavior and nocturnal hypertension are associated with a high risk of target organ damage evidence, including microalbuminuria and kidney damage progression, left ventricular hypertrophy, and silent cerebrovascular disease (38,39).

There were some limitations in the present study. The sample size of parathyroidectomized patients, whose circadian profile of blood pressure was evaluated with ABPM, was small and there was lack of a matched group of patients with essential hypertension to make a comparison.

In summary, we have found that parathyroidectomy does not change the high hypertension prevalence found in PHPT. Even more, PTH does not seem to play a unique role in the pathogenesis of hypertension, as its serum levels were normalized while BP remained elevated after a long-term follow-up. Renal impairment, a condition that did not ameliorate after parathyroidectomy, may be a link not only as a pathogenic mechanism but also in the post-operative increase in the prevalence of hypertension. Whether slight elevations of serum total calcium even in the normal range might effect the alterations of the circadian rhythm of BP that was found in the follow-up of parathyroidectomized patients, is one of the hypothesis that needs future research for confirmation.

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REFERENCES


