Review Article

Primary hyperparathyroidism and hypertension

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Abstract: Although untreated primary hyperparathyroidism is associated with increased cardiovascular mortality, controversy exists regarding the therapeutic effects of parathyroidectomy on cardiovascular health. This review will examine the evidence linking primary hyperparathyroidism (PHPT) and cardiovascular disease, specifically hypertension, and evaluate the available literature regarding the natural history of hypertension after successful parathyroidectomy.

Keywords: Primary hyperparathyroidism (PHPT); hypertension; cardiovascular mortality; parathyroidectomy; parathyroid

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Introduction

Hypertension, defined as systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥80 mmHg, is present in almost half of the United States' population and represents a significant number of patients with a potentially modifiable major risk factor for cardiovascular mortality. With every 20 mmHg increase in systolic blood pressure above normal, the risk of death from stroke, heart disease, or other vascular disease doubles (1). Of those with hypertension, about 10% will have a secondary, often endocrine-related, cause. Although primary hyperaldosteronism is the most common endocrine-related source of hypertension, primary hyperparathyroidism (PHPT) has also been linked.

Untreated hyperparathyroidism is associated with increased cardiovascular mortality (2-6), yet data supporting improvement or resolution of cardiovascular morbidity and/or mortality after parathyroidectomy is less consistent. Some studies support improvement of cardiovascular parameters whereas other studies report persistent increased risk of cardiovascular morbidity and/or mortality even after successful parathyroidectomy. Variation in patient population, severity of disease (hyperparathyroidism and cardiovascular disease), and choice of measure and timepoint (systolic or diastolic pressure, determination of hypertension or other surrogate measures of cardiovascular illness such as arterial stiffness or ventricular hypertrophy) likely contribute to the difficulty assessing the relationship. For example, surrogate markers of cardiac dysfunction such as carotid stiffness, left ventricular mass, and interventricular septal thickness have been documented to improve after parathyroidectomy at varying timepoints (typically 3–6 months) (7-9). In contrast, improvement or resolution of hypertension or the cardiovascular risk index was not observed in retrospective observational studies of patients undergoing successful parathyroidectomy (10,11). Additionally, the multifactorial etiology of cardiovascular disease and frequent overlap with essential hypertension, obesity, hyperlipidemia, and diabetes mellitus potentially confound assessments.

In 2014 the consensus from the Fourth International Workshop on Asymptomatic Primary Hyperparathyroidism did not support consideration of cardiovascular morbidity as an indicator for parathyroidectomy in patients with PHPT, and concluded that parathyroidectomy for the

purpose of improving cardiovascular disease was not appropriate (12). In contrast, as the understanding of cardiovascular disease and PHPT evolves, the more recently released American Association of Endocrine Surgeons guidelines for the management of asymptomatic PHPT support the consideration of parathyroidectomy for possible mitigation of cardiovascular risk factors on a case-by-case basis (13). Patients with PHPT represent a group of patients with a wide spectrum of disease severity, in whom a relatively simple and well tolerated operation can result in biochemical cure, often with relief of multiple long term sequelae. An improved understanding of the association between PHPT and hypertension and thus the potential for improving cardiovascular health and/or mortality after parathyroidectomy requires further attention.

This review will examine the evidence linking PHPT and cardiovascular disease, specifically hypertension, and evaluate the available literature regarding the natural history of hypertension after successful parathyroidectomy.

Prevalence of hypertension amongst patients with PHPT

Between 40% to 60% of patients with PHPT have concomitant hypertension (14,15). It should be noted that other potentially confounding cardiovascular risk factors are also more frequently observed in patients with PHPT, including diabetes mellitus [8–15.9% of PHPT patients (15-17)], metabolic syndrome [from 8–59% of patients with PHPT (15,18,19)], hyperlipidemia [52.3% of PHPT patients as compared to 3.7% in a Northeast US population (15)], and coronary artery disease (6.95% of PHPT patients as compared to 3.7% in a Northeast US population) (15). A matched Scandinavian case-control study of 123 patients with PHPT demonstrated that patients with PHPT were more likely to require antihypertensive medication, and more commonly had a history of congestive heart failure, thromboembolic disease, cerebrovascular accident, or diabetes mellitus than control patients undergoing unrelated surgical procedures (20). A recent Nationwide Inpatient Sample study confirmed these increased rates of comorbidities with an increased prevalence of hypertension (63% *vs.* 39%, P<0.0001), diabetes, hyperlipidemia, obesity, chronic kidney disease, heart failure, and established coronary artery disease in patients with PHPT (n=37,922) as compared to the general population (n=33,094,451). Interestingly, after controlling for age, sex, and the afore-mentioned cardiac risk factors, the presence of PHPT remained strongly correlated with hypertension (OR 1.3, P<0.001) (21). It is impossible to establish causality, although the evidence supports an increased prevalence of cardiovascular disease, including hypertension, amongst patients with PHPT.

Potential mechanisms

First recognized as a cardiovascular hormone by Collip and Clark in 1925 (22), parathyroid hormone (PTH) has far-reaching effects, although exact cellular mechanisms are not clearly understood and are outside the scope of this article. In brief, PTH activates protein kinase C, augments cellular calcium influx, and indirectly inhibits the contractile effect of beta-adrenergic stimulation in the adult cardiomyocyte. PTH also acts as a vasodilator on vascular smooth muscle cells (23). Although *in vitro* studies support this vasodilatory mechanism, *in vivo* studies are paradoxical, with hypertension (as well as hypercalcemia) resulting from the infusion of physiologic doses of PTH in otherwise healthy adults (24,25). Others have described increased levels of, and enhanced cardiovascular reactivity to, norepinephrine in patients with both hyperparathyroidism and hypertension, and shown resolution of the noradrenergic excess after parathyroidectomy (26). Other potential mechanisms to explain hypertension as a result of PTH include mediation by the resulting hypercalcemia [although this does not explain observed correlations between hypertension and normocalcemic PHPT (27,28)] amplified effects of the renin-angiotensin system, increased endothelin levels (22), and production of reactive-oxygen species (29). Finally, clinically observed end-organ effects include lack of arterial distensibility, which appears to be independent of endothelial signals and related to reactivity within the arterial media (30), increased end diastolic volume, and left ventricular hypertrophy (31-34).

Population-based studies

Relationship between PTH and hypertension

Several large scale population based studies have examined the impact of PTH levels on the incidence of hypertension independent of the diagnosis of parathyroid disease (35-41). Although these studies did not report calcium levels and were not designed to identify or discriminate between primary and/or secondary hyperparathyroidism, their findings remain of interest. Most have found a modest

relationship between the risk of hypertension and increasing PTH levels, independent of PHPT (RR =1.35, P=0.006 in a recent meta-analysis) (42). One study in an American population of 3,002 patients, which included only 17 (<1%) patients with known PHPT, demonstrated that higher levels of PTH were associated with increased risk of incident hypertension over a follow-up period of 9 years. This relationship was attenuated but remained significant after adjusting for covariates and was most pronounced at higher PTH levels (adjusted HR 1.27; 95% CI: 1.01–1.59, for PTH ≥65 pg/mL). The authors also observed an association between lower 25-hydroxyvitamin D levels and risk of hypertension, but it was lost after adjustment for covariates including PTH (39). Others have also noted the impact of 25-hydroxyvitamin D on hypertension, with lower levels correlating with increased risk (35,37,40,41), but with differing conclusions regarding the interactions between PTH and 25-hydroxyvitamin D. Interestingly, it appears that in the studies in which the relationship between PTH and risk of hypertension is weakest, the driving force of 25-hydroxyvitamin D appears strongest. One Korean cohort, in which 64.5% of study participants developed hypertension, found that PTH levels did not correlate with either systolic or diastolic blood pressure and showed only a weak relationship with hypertension, which disappeared after correction for covariates such as age, gender, and body mass index. This study showed a relationship between lower levels of serum 25-hydroxyvitamin D and increased risk of incident hypertension, which remained significant after adjustments for potentially confounding variables (OR 2.74; 95% CI: 1.4–5.34 in patients with serum 25-hydroxyvitamin D levels less than the median) (37).

Differences within study population may also impact the role of PTH on the incidence of hypertension. The abovementioned studies encompass different international populations that vary by race, age, and geography as well as likely other factors. At least one large population based study has shown that 25-hydroxyvitamin D levels and PTH levels vary by race (43), as does the risk of hypertension (44,45). The Atherosclerosis Risk in Communities Study specifically examined the impact of race on PTH and incident hypertension. In this study of 7,504 participants from 4 communities across the United States, an association between PTH levels and risk of hypertension was not observed overall, after correcting for race, age, sex, body mass index, renal function, and low vitamin D status. However, in the 1,264 subjects who were black, PTH levels were on average higher at baseline and associated with greater risk for incident hypertension (HR 1.38; 95% CI: 1.01–1.89, P=0.003 for patients with PTH >50.1 mpg/mL), leading the authors to suggest interaction with race (40).

Another potential variable in the struggle to correlate PTH and blood pressure is the possible impact of circadian rhythms. One analysis of 292 patients in the Styrian Hypertension Study demonstrated that higher PTH levels correlated with higher nocturnal blood pressure readings, but not daytime readings (46). A smaller study showed both low 25-hydroxyvitamin D levels and higher PTH levels were associated with patients with hypertension and lack of nocturnal decline in blood pressure ("nondippers") (47). It is possible that PTH may have a larger influence on blood pressure variation and/or control amongst patients with established hypertension whereas only modest relationships have been identified with the *development* of hypertension.

Relationship between PTH and hypertension in patients with PHPT

In contrast to the population based studies described above, Lundgren and colleagues (2) used population-based screenings to show that in patients with untreated PHPT, mortality was increased as compared to healthy controls and the cause of death was disproportionately related to cardiovascular disease. Although initial studies suggested that the increased risk of mortality persisted after parathyroidectomy (3,48), the same Scandinavian group later suggested that the detrimental effect diminished with time from the operation (3) and was ultimately reversible (49). Whether the potential change in mortality is directly related to treatment of PHPT associated hypertension is unclear and causality cannot be established.

More recently, Vaidya and colleagues (50) used the Nurses' Health Study to identify patients who did not have PHPT at baseline and were diagnosed with PHPT during the study period. In this population of largely white and postmenopausal women, the age-adjusted relative risk (RR) for PHPT in women with hypertension compared to those without was 1.8 (95% CI: 1.43–2.26), an effect that persisted after correction for body mass index, race, smoking status, menopausal status, postmenopausal hormone use, physical activity, dietary intake (of calcium, vitamins D and A, magnesium, protein, and alcohol), or medical comorbidity (diabetes, congestive heart failure, osteoporosis or bisphosphonate use). Interestingly, when the use of specific antihypertensive medication class was considered, only furosemide (and not thiazide diuretics) was significantly

associated with increased risk of incident PHPT (RR 1.71; 95% CI: 1.08–2.71). In contrast to the other population studies in which higher PTH levels were associated with the risk of hypertension, this analysis implies that pre-existing hypertension was a risk factor for PHPT. Given the often delayed diagnosis of PHPT it is possible that the diagnosis of hypertension did not actually precede development of PHPT, but this study lends further support to the link between the two and prompts the interesting question of causality.

The Parathyroid Epidemiology and Audit Research Study is a retrospective population based observational study in Tayside, Scotland that focused on 2,097 adults with untreated mild PHPT over a 9-year time period (51-54). Patients with PHPT were more likely than the general population to have multiple cardiovascular related comorbidities, including hypertension, even when corrected for pre-existing conditions (standardized incidence ratio for hypertension 3.77; 95% CI: 3.21–4.41). Higher PTH levels (but not calcium levels) correlated with higher all-cause and cardiovascular mortality and cardiovascular morbidity (53); these effects persisted when compared to a cohort matched by age, sex, and year of diagnosis (55) and long term outcomes were independent of serum calcium concentration (53). Critics of the study note that PTH levels and vitamin D levels were not available for all study participants and the high mortality rate (30%) may limit the applicability of the data (12). These studies describe the natural history of untreated PHPT and underline the importance of parathyroidectomy in management of seemingly "mild" PHPT.

In addition to potential differences in study population, variation in blood pressure measurement, and inherent differences in laboratory technique, each of the aforementioned studies used study-specific and variable ranges for classifying both 25-hydroxyvitamin D and PTH levels, with some analyzing them as continuous variables and others stratifying by quartile or standard deviation. Given the established relationship between vitamin D levels and PTH, the authors suspect that differences in measurement and variable categorization may lead to some of the observed heterogeneity in effect.

Hypertension and parathyroidectomy

In aggregate the current population-based data support an association between PTH and hypertension. Yet if a relationship exists between PTH and hypertension, one would expect hypertension to improve after successful parathyroidectomy. To date evidence regarding blood pressure after parathyroidectomy is inconclusive, with some reporting no improvement (56-60) and others reporting improvement (11,28,33,61-65). Heterogeneity in study population, methodology, duration of follow-up, and definition of hypertension contribute to the discordance.

In a large study of 1,020 patients with PHPT matched on sex, age, body mass index, and smoking status to 1,020 patients who were receiving outpatient healthcare at the same institution, hypertension was more prevalent in the PHPT group (72.1% versus 45.9% in women, 67.4% versus 49.9% in men, P<0.001 for both). Parathyroidectomy was associated with a decrease in systolic blood pressure regardless of pre-existing hypertension (150 versus 138 mmHg postoperatively in patients with hypertension, P<0.01), whereas a decrease in diastolic blood pressure was observed only in patients with hypertension (n=663) (61). Although in this large study effects were observed in both hypertensive and nonhypertensive patients, it is possible that either sample size or the underlying prevalence of hypertension within the study population may contribute to the heterogeneity of results seen in other studies. For example, a clinically relevant impact on blood pressure was not observed in a smaller cohort study restricted to patients without hypertension. In this study 49 patients with PHPT were matched by sex, age, and geographic region to 49 healthy controls. As compared to the controls, patient with PHPT had slightly higher blood pressure at baseline (systolic 127.2 versus 119.3 mmHg, respectively, P<0.05; diastolic 80.4 *vs.* 76.0 mmHg, respectively, P=NS). At a mean of 15 months after surgery all patients had normal calcium and a statistically significant, but perhaps not clinically relevant, decline in both systolic and diastolic blood pressure (127.2 versus 124.4 mmHg, and 80.4 versus 78.4 mmHg, respectively, P<0.05) (66). It is plausible that in an otherwise healthy population blood pressure may change only minimally post-parathyroidectomy. In support of this theory, a single institution study of 368 patients with PHPT undergoing parathyroidectomy demonstrated a statistically significant decrease in both systolic and diastolic blood pressure measurements (a change of ≥10 mmHg, P<0.001) at 6 months postoperatively in the 147 patients with pre-existing hypertension, but not in the 145 patients without hypertension (62). Another cohort study by Luigi and colleagues (63) compared 30 patients with PHPT treated with parathyroidectomy to 30 controls with hypertension and 30 normal subjects, with a higher prevalence of hypertension (81%) amongst the PHPT group. The study also noted

a higher frequency of altered circadian rhythm of blood pressure, or nocturnal "nondipping", in the PHPT group as compared to the hypertension group (57% versus 35%, P=0.02). At 1 year follow-up, all patients in the PHPT group had a normal calcium with a significant decrease in the prevalence of hypertension (62% versus 81% preoperatively, P<0.05), an improvement in the nondipping pattern (decreased to 38%, P<0.05), a lower frequency of metabolic syndrome (28% *vs.* 38% preoperatively, P<0.05), and a significant reduction in the use of antihypertensive agents.

A particular strength of the study by Luigi and colleagues (63) is the long follow-up period, which is not only sufficient to document biochemical cure of PHPT (13), but in this incidence sufficient to demonstrate change in blood pressure. It is reasonable to assume that blood pressure regulation requires sufficient time for vascular remodeling, and the optimal length of time is unknown. Short follow-up after parathyroidectomy may explain lack of observed changes in blood pressure. For example, a recent Scandinavian study randomized 79 patients with mild PHPT (as defined by serum ionized calcium < 1.7 mmol/L) to parathyroidectomy or observation, and did not observe improvement in systolic or diastolic blood pressure at 3 months postoperatively (56). The authors concluded longer follow-up time should be considered when assessing cardiovascular changes after parathyroidectomy. In a perhaps a more nihilistic approach, some have proposed that the effects of elevated PTH either persist long after parathyroidectomy or are not correctable surgically, with two small series (n=56 and n=62) noting that none of the patients with pre-existing hypertension corrected after parathyroidectomy (21% and 29%) and in fact 32% to 45% of the patients who were normotensive preoperatively developed hypertension during follow-up of 5 and 2.9 years, respectively (57,58). Both of these studies were conducted prior to 1990, which may limit their applicability to more modern populations.

In addition to the abovementioned sources of heterogeneity, antihypertensive medication noncompliance, dosage changes, or regimen changes are difficult to account for outside of a clinical trial and likely influence assessments of blood pressure control in both the pre- and post-operative setting. The potential asymmetric impact of PTH on either diastolic blood pressure or diurnal blood pressure patterns may improve after parathyroidectomy, but remain masked by a persistent diagnosis of hypertension as mediated by systolic blood pressure. Additionally, blood pressure can be influenced by multiple other factors, including chronic pain. In a novel study design, one group documented a substantial decrease in total number of medications required after parathyroidectomy for PHPT (11% as compared to 4% of patients undergoing thyroidectomy in a similar time period, P=0.01). Of the medications stopped, antihypertensives comprised a small subset and chronic analgesics (exclusive of perioperative requirements) were the most common (67). The interplay between the myalgias of PHPT, pain management, and blood pressure is unknown, but it is plausible that chronic pain elevates blood pressure in patients with PHPT. The study highlights the complex interplay between PTH and psychiatric and neurocognitive manifestations, and draws into question the concept of other factors influencing blood pressure in patients with PHPT.

Conclusions

The systemic impact of PHPT is far reaching, and surgical correction of PHPT offers chance for durable cure. As summarized in this article, population based studies support an association between increasing PTH levels and the incidence of hypertension, independent of the diagnosis of PHPT, although exact mechanism and causality are not clearly understood. Few large scale population studies focus on PHPT, but of those, data further support a link between PHPT, PTH levels, and hypertension. Although causality cannot be assigned, patients with PHPT are more likely to have concomitant cardiovascular morbidity, including hypertension, and have increased risk of cardiovascular mortality. Results of selected studies support improvement in blood pressure and/or the presence of hypertension after parathyroidectomy, whereas others fail to show change. The possibility of inadequate sample size or a misguided study population, variable follow-up time, and an asymmetric or nonlinear effect of PTH amongst patients with or without hypertension are only a few of the many potential confounders, in addition to the multifactorial nature of hypertension and cardiovascular disease. The authors propose that the observed increased cardiovascular risk in patients with PHPT is a combination of traditional cardiovascular risk factors and effects of elevated calcium and PTH. It is plausible that the driving force of traditional cardiovascular risk factors in patients with PHPT may mask or diminish any treatment effect of parathyroidectomy, particularly in those patients with mild disease.

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Footnote

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