Primary hyperparathyroidism predicts hypertension: Results from the National Inpatient Sample.

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Primary hyperparathyroidism predicts hypertension: Results from the National Inpatient Sample

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ABSTRACT

Introduction: Primary hyperparathyroidism (pHPT), most commonly caused by solitary parathyroid adenomas, leads to mobilization of calcium and is known to result in nephrolithiasis and osteoporosis. To date, studies of pHPT and cardiovascular risk factors and events have produced discrepant findings, likely due to small sample sizes and enrolling populations with varying disease severity.
Hypothesis: We utilized a national registry, hypothesizing an association between pHPT and cardiovascular risk factors and events.
Methods: Patients >18 years with a diagnosis of pHPT were identified in the Nationwide Inpatient Sample 2009–2010 database using the Ninth Revision of International Classification of Diseases code 252.01. Demographics, risk factors, and cardiovascular event rates were collected and compared to general population data.
Results: pHPT was present in 0.1% ($n = 37{,}922$) of hospital admissions. There was a significant increase in the prevalence of most cardiac risk factors including hypertension (HTN), diabetes mellitus, hyperlipidemia, obesity, and chronic kidney disease. The rates of heart failure (HF) and coronary artery disease (CAD) were higher in the pHPT population. However, after performing multivariate regression for age and cardiac risk factors, pHPT did not independently predict HF or CAD. The risk of HTN, however, was independently predicted by pHPT (OR 1.3; $p < 0.001$).
Conclusions: Primary hyperparathyroidism independently predicted the risk of hypertension in a patient population from a large national database. Despite significant differences in univariate analysis of cardiac risk factors and events, pHPT did not independently predict risk of HF or CAD after multivariate regression analysis. Future studies should explore potential mechanisms relating hypertension to pHPT.

1. Introduction

Primary hyperparathyroidism (pHPT) is a disease characterized by a normal or elevated parathyroid hormone level in the setting of elevated serum calcium. pHPT is one of the more common endocrine disorders [1] and its prevalence is rising in the United States [2]. Most frequently caused by solitary parathyroid adenomas, pHPT leads to calcium mobilization from skeletal stores [3] and increased calcium reabsorption in renal tubules [4]. Consequently, osteoporosis and nephrolithiasis are considered classic sequelae of pHPT. pHPT patients are routinely assessed for these complications, as their presence increases the justification of surgical intervention.

Recently, an association between pHPT and cardiovascular morbidity and mortality has been suggested [5,6]. However, most studies thus far have been limited due to small sample sizes. Thus, cardiovascular manifestations are not included in current guidelines on pHPT management. The aim of the present study was to utilize a national patient registry with a larger sample size to assess the association between pHPT and cardiovascular risk factors and events.

2. Methods

2.1. National Inpatient Sample Database

We analyzed data from the National Inpatient Sample (NIS) database for the year 2009–2010 which contains data on inpatient hospital stays from states participating in Healthcare Cost and Utilization project. Each year, NIS provides data on roughly 8 million hospitalizations from about 1000 hospitals. The NIS is designed to approximate a 20% sample of U.S. community hospitals, defined as "all non-federal, short-term, general, and other specialty hospitals, excluding hospital units of institutions," representing >95% of the U.S. population. Criteria used for stratified sampling of hospitals into the NIS include

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ownership, bed size, teaching status, urban/rural location, and U.S. region. All discharges from sampled hospitals are included in the NIS database. The NIS is an all-payer database that covers all patients, including those covered by Medicare, Medicaid, or private insurance, and those who are uninsured. Inpatient stay records in the NIS include clinical and resource use information available from discharge abstracts derived from state-mandated hospital discharge reports. Discharge weights provided by the NIS allow extrapolation to calculate expected national hospitalization rates [NIS online overview].

2.2. Study population

In 2009–2010, a total of 7,807,930 hospital records corresponding to a national estimate of 33,094,451 hospital discharges in the United States were analyzed. We extracted all patients >18 years with all listed diagnosis of pHPT using the International Classification of Diseases-Ninth Edition-Clinical Modification (ICD-9-CM) code 252.01 (n = 37,922). We chose all listed diagnosis to include all patients with a diagnosis of pHPT. Patient characteristics, demographics, cardiovascular risk factors, and cardiovascular event rates were collected on these patients and compared to general population data.

2.3. Statistical analysis

Categorical variable were presented as number (percentage), while continuous variables were presented as mean ± SD for normally distributed variables and median (IQR) for others. Multivariate logistic regression analysis was done to determine predictors of HF, CAD, and hypertension in pHPT, after adjusting for demographic factors and cardiac risk factors. P value was calculated by chi-square test for categorical variables and t-test for continuous variable. P value < 0.05 was considered statistical significant. All statistical analysis was performed using STATA 10.0.

3. Results

pHPT was present in 0.1% (n = 37,922) of all hospital admissions. Patients were older and more likely to be females in the pHPT group. There was a significant increase in the prevalence of most cardiac risk factors including hypertension (HTN), diabetes mellitus, hyperlipidemia, obesity, and chronic kidney disease in patients with pHPT when compared to the general population (Table 1). The rate of heart failure (HF) and established coronary artery disease (CAD) were also higher in the pHPT population with no significant difference in acute coronary syndrome between both the groups.

After performing a multivariate regression analysis adjusted for age, gender, and other risk factors including DM, hyperlipidemia, obesity, hypertension, tobacco use, and chronic kidney disease, pHPT was associated with increased risk of hypertension with an OR of 1.3 (1.2–1.5; p < 0.001).

Table 1
Demographic and cardiovascular risk factors in patients with primary hyperparathyroidism.

Variables	Primary PTH n = 37,922 (0.1%)	No primary PTH n = 33,056,529 (99.9%)	P value*
Demographic factors			
Age	67.4 ± 0.3	48 ± 0.01	<0.001
Female (%)	75	58	<0.0001
Cardiac comorbidities			
Heart failure (%)	8.2	6.4	<0.0001
Established CAD (%)	21	18	<0.0001
Acute coronary syndrome (%)	3.3	3.3	0.96
Risk factors			
Diabetes mellitus (%)	19.1	15	<0.0001
Hypertension (%)	63	39	<0.0001
Hyperlipidemia (%)	31.2	20.6	<0.0001
Tobacco use (%)	7.8	10.8	<0.0001
Obesity	10.6	7.7	<0.0001
Chronic kidney disease (%)	18.3	8.4	<0.0001

* P value calculated by chi-square test for categorical variables and t-test for continuous variable.

4. Discussion

The present study demonstrates that pHPT is an independent risk factor for hypertension using a large national patient database. That pHPT is associated with hypertension remains controversial, and data have only been reported previously in small studies, the largest of which was comprised of 123 pHPT patients [7–11].

Several mechanisms have been proposed in the pathogenesis of hypertension in pHPT, including activation of the renin-angiotensin system and alterations of vascular function and structure. PTH stimulates renin production via specific receptors independent of baroreceptors [7]. Activation of the renin-angiotensin system contributes not only to increased blood pressure (BP), but also vessel sensitization to vasopressors [8]. Brinton et al. found that patients with pHPT and hypertension had higher plasma renin activity (PRA) compared to patients with pHPT who were normotensive, patients with secondary hyperparathyroidism, or patients who were hypercalcemic due to other causes [9]. The authors also reported a decrease in both PRA levels and BP post parathyroidectomy, though these results were not reproduced in other studies [8,9].

The effect of PTH on vascular smooth muscle cells is controversial as PTH infusion has been reported to cause a reduction in BP in hypertensive patients [12], but an increase in BP in normotensive patients [13]. On a molecular level, PTH binding to PTH/PTHrP receptors found on vascular smooth muscles increases cyclic adenosine monophosphate (cAMP) levels which results in reduced influx of calcium and, thus, decreased smooth muscle contraction [14]. However, prolonged PTH exposure desensitizes PTH receptors [14]. As a result, investigators in the past have suggested that the variation in BP response may be related to differing PTH levels in individual patients [15]. Contradictory findings have also been reported on the associations between pHPT and impairment of endothelial flow-mediated vasodilation [16,17], as well as intima-media thickness [18,19].

We observed no increase in the rate of CAD and HF in the pHPT population from this large patient national database after multivariate analysis. Past reports in the literature suggest an increase in cardiovascular events in pHPT patients [20]. However, Kepez et al. reported no significant difference in coronary artery calcification scores between patients with pHPT and age-gender-matched controls [21]. Similarly, several studies assessing left ventricular ejection fraction found no significant difference between pHPT patients and the general population [22–25]. An increased incidence of left ventricular hypertrophy, on the other hand, has been reported among the pHPT population [26–30].

Limitations of this study include the use of ICD-9 codes, which allows for the possibility of incorrect coding. Additionally, certain disease processes, including left ventricular hypertrophy, could not be assessed for, as a specific ICD-9 code does not exist. Also, the severity of pHPT in terms of serum calcium concentration, PTH level, and presence of symptoms could not be obtained and thus subgroup analysis could not be performed. Lastly, the retrospective observational design of the study can only demonstrate association, and hence causation cannot be determined. Despite limitations of a registry analysis, the large sample size and inclusion of patients from all geographical regions in the country are strengths of this study.

5. Conclusions

Primary hyperparathyroidism independently predicted the risk of hypertension in a patient population from a large national database. Despite significant differences in univariate analysis of cardiac risk factors and events, pHPT did not independently predict risk of HF or CAD after multivariate regression analysis. Future studies should explore potential mechanisms relating hypertension to pHPT.

Conflicts of interests

None.

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