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Impact of autoimmune thyroiditis on primary hyperparathyroidism

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ABSTRACT

Aim. Primary hyperparathyroidism (PHPT) often coexists with thyroid diseases. Current guidelines advise preoperative ultrasound (US) examination of the thyroid gland for thyroid nodular disease or concomitant malignancy but not evaluation for autoimmune thyroiditis (AIT). The impact of autoimmune thyroiditis on the clinical presentation and intraoperative course of PHPT is not clear.

Material and methods. We retrospectively assessed the medical records of 21 patients with PHPT who underwent parathyroidectomy. Clinical, biochemical, ultrasonographic and intraoperative data were evaluated.

Results. There was a longer duration of parathyroidectomy in patients with AIT than in those without (113.3 min vs. 93.9 min, P = 0.03). A lower rate of kidney stones was noted in patients with autoimmune thyroiditis (44.4% vs. 0%, P = 0.03). Patients with AIT were more symptomatic, but this was not significant. There was no difference between the two groups in the prevalence of osteoporosis or thyroid nodular disease.

Conclusions. A significantly longer duration of parathyroidectomy was seen in PHPT patients with AIT. Patients with PHPT undergoing surgery should be investigated for autoimmune thyroiditis, as this may affect surgical planning.

Introduction

Primary hyperparathyroidism (PHPT) is characterized by elevated serum calcium levels along with elevated or paradoxically normal parathyroid hormone levels (PTH). It has varying incidence worldwide, ranging from 0.4 to 82 cases per 100,000 people [1]. When indicated, minimally invasive parathyroidectomy (MIP) is the surgical treatment of choice [2]. The American Association of Endocrine Surgeons (AAES) endorses the MIP approach due to its minimal operation length, fast recovery and rare intraoperative complications, and it provides a cure rate between 97% and 99% [2]. More than 85% of PHPT cases arise from solitary parathyroid adenomas, and the success of the operation depends on accurate imaging techniques that pinpoint the exact location of the adenoma, establish the probability that the adenoma is solitary or not and investigate the presence of concomitant thyroid nodular disease [2, 3].

Current guidelines suggest performing preoperative neck ultrasound to identify thyroid nodules and thyroid cancer [2, 4]. A study by M. Regal et al., showed that more than half of PHPT patients undergoing parathyroidectomy had concomitant thyroid disease [5]. Latina et al. showed that thyroid disease was present in 60% of PHPT patients, mostly thyroid nodular disease [6]. Even so, the current guidelines do not address preoperative screening for autoimmune thyroiditis, which is commonly present in patients with primary hyperparathyroidism.

Hashimoto's thyroiditis is the most common autoimmune thyroid disease and the most common cause of hypothyroidism in adults in the US, with an annual incidence worldwide of 0.3–1.5/1000 individuals/year and a much higher incidence [7]. It is characterized by chronic thyroid tissue inflammation, where the thyroid parenchyma is distorted by lymphocytic infiltration [7]. In a study by Ignjatovic et al., PHPT was more frequent in Hashimoto's thyroiditis patients, and it was postulated that chronically elevated TSH in the advanced stage of Hashimoto's thyroiditis may cause hyperplasia of the parathyroid gland [8].

Aim

The aim of this research study was to investigate the impact of autoimmune thyroiditis on PHPT and to evaluate the association of these two diseases in terms of symptoms, biochemical variables, and surgical outcomes.

Material and methods

Patient Recruitment

This was a retrospective review of the medical and surgical records of 21 patients with PHPT in the Thyroid & Endocrinology Center in Nicosia, Cyprus, a referral center for thyroid, parathyroid and endocrine diseases [9]. Inclusion criteria were primary hyperparathyroidism and parathyroidectomy. Patients with secondary or tertiary hyperparathyroidism were excluded. All patients underwent parathyroidectomy between 2016 and 2020 by a single endocrine surgeon. Eighteen patients underwent minimally invasive parathyroidectomy. One patient underwent concomitant hemithyroidectomy, and another patient underwent concomitant total thyroidectomy. A third patient did not undergo primary surgery but underwent reoperation for persistent disease. These three patients were excluded from the analysis of procedure length. Patients who had two parathyroid adenomas were also excluded from the analysis of procedure length. Data recorded were sex, age, weight, height, presence of symptoms, number and locations of parathyroid adenomas, presence or absence of concomitant nodular thyroid disease, thyroid cancer or autoimmune thyroid disease, calcium, phosphorus, PTH, TSH, FT4, 25-OH Vit. D, presence or absence nephrolithiasis, and dual energy X-ray absorptiometry (DEXA). Surgical data included the size and locations of the adenomas and the duration of the operation.

All patients underwent thyroid and neck ultrasound (US) by a GE Logiq E9 system with a ML 6–15 MHz linear transducer by a single endocrinologist experienced in endocrine neck US [10]. The possible parathyroid adenomas identified on US were mapped onto a detailed diagram, denoting the location and dimensions of each adenoma [11]. The diagnosis of autoimmune thyroiditis was based on a combination of detailed history taking, ultrasound findings and the presence of thyroid autoantibodies. All patients underwent abdominal ultrasound examination to evaluate the presence or absence of kidney stones and dual-energy X-ray absorptiometry (DEXA) to

assess bone mineral density (BMD) of the lumbar spine and femoral head.

The following parameters were examined regarding the impact on PHPT: sex, age, BMI, eGFR, number of adenomas, preoperative US dimensions, postoperative dimensions and vascularity, Hashimoto's thyroiditis/Graves' disease, nodular thyroid disease, serum calcium, phosphate, PTH, TSH, FT4, calcitonin, bone mineral density, and presence or absence of clinical symptoms.

Statistical Analysis

The data are presented as mean and standard deviation (SD) for numerical variables and absolute and percentage frequencies for categorical variables. The comparison of continuous variables between the two groups was done by performing an independent samples t test. To compare categorical variables with two possible outcomes, such as sex; the presence of nephrolithiasis, cancer, or thyroid nodules; the number of parathyroid adenomas; and the presence or absence of symptoms, Fisher's exact test was performed. For categorical variables with three possible outcomes (bone mineral density status: normal, osteopenia, osteoporosis), Pearson's chi-square was performed. A two-sided value of $P < 0.05$ was considered statistically significant. Statistical analysis was performed using the statistical analysis software package IBM-SPSS 20.

The study was approved by the Cyprus National Bioethics Committee. Patients' personal information and identities were kept fully confidential throughout the study.

Results

Table 1 lists the demographic characteristics, laboratory values and clinical data. Nine patients (42.9%) did not have concomitant autoimmune thyroiditis (Group 1). Twelve patients (57.1%) had autoimmune thyroiditis (Group 2), of whom 11 had Hashimoto's thyroiditis and 1 had Graves' disease that had progressed to hypothyroidism. The mean age was 56.2 ± 10.5 (range from 32 to 76 years). Eighteen patients (85.7%) were female. Of the 21 patients, one patient (4.8%) had concomitant differentiated thyroid cancer, while 12 patients (57.1%) had thyroid nodules. Seventeen patients (81.0%) had a solitary adenoma, whereas the other 4 patients (19.0%) had two. Four out of the 21 patients (19.0%) had nephrolithiasis or nephrocalcinosis. Fifteen patients (71.4%) reported symptoms of hyperparathyroidism, while 6 patients (28.6%) did not report any specific symptoms. The most common symptoms that were reported were bone pain, arthralgias, tiredness/fatigue and anxiety.

Preoperative serum calcium was 10.45 mg/dl ± 0.52, while preoperative PTH and phosphorus were 124.6 pg/ml ± 65.8 and 3.0 mg/dl ± 0.5, respectively. Thyroid-stimulating hormone (TSH), 25-OH-vitamin D (calcidiol), and creatinine were 1.85 μIU/ml ± 0.93, 26.8 ng/ml ± 10.08 and 0.74 ± 0.12, respectively. Six patients (28.6%) had normal bone mineral density, 10 patients had osteopenia (47.6%), and 5 patients (23.8%) had osteoporosis.

The mean age of Group 2 (autoimmune thyroiditis) was 59.2 ± 7.7, whereas Group 1 (non-autoimmune thyroiditis) had a mean age of 52.2 ± 12.3 (P = 0.15). There were 3 male patients (33.3%) and 6 female patients (66%) in Group 1, while Group 2 had no male patients (P = 0.06). The mean eGFR in Group 2 was 85.89 mL/min/1.73 m² ± 12.63, whereas in Group 1, the mean eGFR was 90.54 ± 11.59 mL/min/1.73 m² (P = 0.4). In Group 1, 4 out of 9 patients (44%) had nephrocalcinosis or nephrolithiasis compared to none of the 12 patients in Group 2 (P = 0.03). There was no significant difference between the groups regarding the presence of clinical symptoms (55.6% vs. 83.3%, P = 0.33). Thyroid nodular disease was similarly common in both groups (66.6% vs. 50%, P = 0.66).

There were no statistically significant differences between the groups in the level of PTH, calcium, TSH, phosphorus, 25-OH-vitamin D or creatinine. The mean serum PTH was 155.0 pg/ml ± 89.3 in Group 1 and 101.8 pg/ml ± 27.3 in Group 2 ($P = 0.06$). The serum calcium in Group 1 was 10.42 mg/dl ± 0.57 vs. 10.47 mg/dl ± 0.49 in Group 2 ($P = 0.82$). Bone mineral density did not differ between the two groups ($P = 0.65$).

In all Group 1 patients, preoperative US imaging found that all the adenomas were situated where the surgeon localized them intraoperatively. In 1 of the 12 (8.3%) Group 2 patients, the adenoma was found to be at a different location than shown preoperatively and bore a second adenoma that had not been identified by US preoperatively.

Table 1. Demographic characteristics, laboratory values and clinical data

Parameters	All Patients (n = 21)	Group 1 (n = 9)	Group 2 (Autoimmune Thyroiditis) (n = 12)	p value
Demographic Data				
Age	56.2 ± 10.5	52.2 ± 12.3	59.2 ± 7.7	0.15*
Male	3 (14.3%)	3 (33.3%)	0	0.06§
Female	18 (85.7%)	6 (66.6%)	12 (100%)	
BMI kg/m^2	26.8 ± 4.0	25.9 ± 3.5	27.5 ± 4.4	0.4*
eGFR ml/min/1.73 m²	87.89 ± 12.13	90.54 ± 11.59	85.89 ± 12.63	0.4*
Preoperative Ultrasonography				
Thyroid Nodules (%)	12 (57.1%)	6 (66.6%)	6 (50%)	0.66§
Number of Adenomas				
Solitary Adenoma	17 (81.0%)	8 (88.9%)	9 (75.0%)	1§
Two Adenomas	4 (19.0%)	1 (11.1%)	3 (25.0%)	
Adenoma Size (cm)	1.36 ± 0.61	1.49 ± 0.81	1.25 ± 0.40	0.39*
Abdominal Ultrasonography				
Nephrolithiasis/Nephrocalcinosis (%)	4 (19.0%)	4 (44.4%)	0	0.03§
Clinical Symptoms				
Symptomatic (%)	15 (71.4%)	5 (55.6%)	10 (83.3%)	0.33§
Asymptomatic (%)	6 (28.6%)	4 (44.4%)	2 (16.7%)	
Biochemical Laboratory Values				
Serum PTH (pg/ml)	124.6 ± 65.8	155.0 ± 89.3	101.8 ± 27.3	0.06*
Serum Ca (mg/dl)	10.45 ± 0.52	10.42 ± 0.57	10.47 ± 0.49	0.82*
Serum Phosphorus (mg/dl)	3.0 ± 0.5	2.90 ± 0.62	3.11 ± 0.33	0.37*
Serum TSH (µIU/ml)	1.85 ± 0.93	2.27 ± 0.78	1.54 ± 0.94	0.07*
Serum 25-OH-Vitamin D (ng/ml)	26.8 ± 10.08	30.32 ± 10.96	24.16 ± 8.90	0.17*
Serum Creatinine (mg/dl)	0.74 ± 0.12	0.77 ± 0.15	0.72 ± 0.09	0.30*
BMD (DEXA)				
Normal BMD (%)	6 (28.6%)	2 (22.2%)	4 (33.3%)	0.65†
Osteopenia On Any Site (%)	10 (47.6%)	4 (44.4%)	6 (50%)	
Osteoporosis On Any Site (%)	5 (23.8%)	3 (33.3%)	2 (16.7%)	
Surgical Data	All patients (n = 16)	Group 1 (n = 7)	Group 2 (Autoimmune Thyroiditis) (n = 9)	p value
Procedure Length (min) (Solitary adenomas)	104.8 ± 18.5	93.9 ± 20.7	113.3 ± 11.5	0,03*

Continuous variables expressed as mean ± SD, Categorical variable expressed as frequency and percentages
*Independent samples t test; §Fisher's exact test; †Pearson's chi-square

Procedure Length Results

After excluding from the procedure length analysis the patients who underwent concomitant thyroid surgery, reoperation for persistent disease and the patients with two parathyroid adenomas the mean duration of surgery of all the patients with solitary parathyroid adenoma (n = 16) was 104.8 min. ± 18.5 min. Group 1 had a mean duration of 93.9 min ± 20.7 min, whereas the mean duration in Group 2 was 113.3 min ± 11.5 min (P = 0.03).

Discussion

Our primary finding was that autoimmune thyroiditis increases the surgical time in patients with PHPT by an average of 19 min compared to the absence of autoimmune thyroiditis. As all but one of the patients in Group 2 had Hashimoto's thyroiditis, the effect on PHPT was primarily due to Hashimoto's thyroiditis. Thyroid pathologies, specifically Hashimoto's thyroiditis, are commonly found in patients with PHPT undergoing

parathyroidectomy. The incidence of Hashimoto's thyroiditis in patients undergoing parathyroidectomy has been reported to range from 2.2% to 42% [5, 12–17]. Our study, however, showed a higher rate (57.1%) of Hashimoto's thyroiditis in PHPT. Hashimoto's thyroiditis has been associated with a higher likelihood of transient complications during thyroidectomy, likely secondary to thyroid gland adherence to the surrounding tissues, increasing the risk of injury to the parathyroid glands and recurrent laryngeal nerves [18].

Current guidelines on preoperative work-up do not recommend screening for autoimmune thyroid disease prior to parathyroidectomy. Based on our research outcomes and the fact that Hashimoto's thyroiditis is a very prevalent disease, we can suggest that patients with PHPT scheduled to undergo parathyroidectomy be evaluated for autoimmune thyroiditis. As there is additional operative time needed in patients with autoimmune thyroiditis undergoing the MIP procedure, it is reasonable to suggest that in four-gland exploration procedures, the respective additional time would be disproportionately longer.

Our study found a high prevalence of concomitant thyroid disease in PHPT, either autoimmune thyroiditis or nodular thyroid disease or both. Wright et al. suggest that patients with thyroid pathologies undergoing surgery be investigated for parathyroid diseases and vice versa due to the high rate of coexistence of these two entities [19]. Similarly, the American Association of Endocrine Surgeons Guidelines for definite treatment of PHPT advises preoperative US screening of the thyroid gland to detect thyroid nodules and possible malignancies that can affect the course of the operation [2, 4, 19, 20]. These interventions are recommended on the grounds that unexpected concomitant thyroid pathology during parathyroidectomy would necessitate deviations from the preoperative surgical plan, increase postoperative complications, increase the discomfort caused to the patient and increase costs [3, 4, 19, 21].

Another important, unexpected finding of our study was that patients with autoimmune thyroiditis had significantly lower rates of kidney stones. Circulating thyroid hormones, more specifically hormones that alter the expression of certain ion channels and transporters, predispose patients to sodium equilibrium imbalances and are associated with alterations of the eGFR [22]. Patients with hypothyroidism can present with a significant reduction in GFR, which can be secondary to direct renal and systemic effects [22]. In our study, eGFR was lower in patients with AIT than in those without AIT, though this did not reach statistical significance. There is no clear explanation for the lower rate of kidney stones, but we assume that a lower GFR leads to lower calcium filtration to the kidney pelvis, therefore leading to less calcium aggregation and less nephrolithiasis or nephrocalcinosis.

Our study has several limitations. First, this was a retrospective study performed at a single center in Cyprus, and the small sampling size of only 21 patients inevitably led to sampling imprecision, which is common in endocrinological disease research but could have been mitigated if a larger sample had been available. Even so, to the best of our knowledge, this is the first study that has examined the intraoperative impact of autoimmune thyroid diseases in PHPT patients. As a second limitation, our study examined only patients with PHPT who underwent parathyroidectomy. Third, most patients with autoimmune thyroid disease had Hashimoto's thyroiditis, only one patient having Graves' disease. Considering this, a generalization to patients with Graves' disease cannot be made. Fourth, as US imaging was performed by a single examiner and operations were performed by a single surgeon, our results cannot be generalized.

In summary, our retrospective cohort study of 21 patients who underwent surgery for parathyroid adenomas showed a significantly longer duration of parathyroidectomy in PHPT patients with autoimmune thyroiditis. Patients with autoimmune thyroiditis had a significantly lower rate of kidney stones. Although not significant, patients with autoimmune thyroiditis were more symptomatic. Our results strongly suggest that patients with PHPT should undergo a complete investigation for autoimmune thyroiditis, as this may affect their surgical planning. More studies are needed to elucidate the clinical and surgical impact of autoimmune thyroid diseases on patients with PHPT.

Abbreviations

PHPT – primary hyperparathyroidism; AIT – autoimmune thyroiditis; PTH – parathyroid hormone levels; MIP – minimally invasive parathyroidism; US – ultrasound.

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Conflict of interest statement
The authors declare no conflict of interest.

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