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Does levothyroxine administration impact parathyroid localization?

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ABSTRACT

Background: Proper localization is crucial in performing minimally invasive parathyroidectomy for primary hyperparathyroidism. Ultrasonography (US) and Tc-99m sestamibi (MIBI) scintigraphy are common methods used for localization. As the appearance and activity of the thyroid gland may impact parathyroid localization, the purpose of this study was to determine how exogenous use of the thyroid hormone, levothyroxine (LT), affects parathyroid localization.

Methods: Adult patients with non–familial primary hyperparathyroidism who underwent initial parathyroidectomy from 2000–2014 were retrospectively identified. LT (+LT) and non-LT (–LT) patients were matched 1:3 based on age, gender, goiter status, and preoperative parathyroid hormone levels. Subgroup analysis was performed on patients previously treated with radioactive iodine and patients undergoing single adenoma resection.

Results: Of the 1737 patients that met inclusion criteria, 286 were on LT at the time of their parathyroid localization scan. Use of LT did not impact the percentage of correct MIBI localization scans when compared with –LT patients ($P = 0.83$). Interestingly, use of LT significantly hindered localization by US in comparison with the –LT group (48.4 *versus* 62.2%, $P < 0.01$). When examining only patients where a single upper gland was removed, the +LT group was less likely to have a correct US compared with the –LT group (50 *versus* 72.8%, $P < 0.01$). However, there was no difference in US accuracy for patients who only had a single lower gland removed ($P = 0.51$).

Conclusions: Exogenous LT is associated with impaired parathyroid localization with US but not MIBI. Surgeons should be aware of localization efficiency for this subset of patients in the era of personalized medicine and cost effectiveness.

1. Introduction

Primary hyperparathyroidism (PHPT) is a common endocrine disorder characterized by oversecreting parathyroid glands, which affects approximately 1% of the population. Surgery is the only curative treatment for PHPT with success rates of 95% in the hands of an experienced endocrine surgeon [1–3]. Although the traditional surgical approach was a bilateral neck exploration

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with subsequent identification of all four parathyroid glands, imaging techniques and intraoperative parathyroid hormone (PTH) monitoring have now allowed surgeons to offer a unilateral, minimally invasive parathyroidectomy. The key to a minimally invasive approach is proper localization of the parathyroid glands before surgery [4–6].

Two common methods of localization include ultrasonography (US) of the anterior neck and Tc-99m sestamibi (MIBI) scintigraphy. MIBI is a lipophilic monovalent cation that has an increased uptake in epithelial cells rich in mitochondria, such as parathyroid adenomas. However, MIBI retention is not specific to the parathyroids, and uptake is observed in mitochondrial rich thyroid tissue, especially in the case of hypermetabolic thyroid nodules [7]. Therefore, the metabolic activity of the thyroid and its uptake of MIBI affects parathyroid localization. Furthermore, thyroid gland size and echotexture affect US localization of the parathyroids [8].

Conditions which alter thyroid appearance and activity, such as hypothyroidism, may impact parathyroid localization. The most common cause of hypothyroidism is the autoimmune disease, Hashimoto thyroiditis, which destroys thyroid follicles and gives the thyroid a nodular, stippled appearance on US. Hypothyroid patients require exogenous use of the thyroid hormone, levothyroxine (LT), to maintain a euthyroid state. However, LT inhibits the patient's natural thyroid activity. Therefore, we hypothesized that compared with patients not taking LT, PHPT patients who are on LT may have improved MIBI localization because of diminished thyroid uptake but impaired US localization from an abnormal thyroid echotexture. As the impact of hypothyroidism and thyroid hormone on MIBI and US localization has not been well studied, the purpose of this research was to determine LT's effect on parathyroid localization.

2. Methods

We performed a retrospective review of a prospectively collected database of patients who underwent parathyroidectomy at the University of Wisconsin Hospital between 2000 to May 2014. Included in the study were adult patients with PHPT who underwent an initial parathyroid operation. Familial disease, secondary, tertiary or reoperative cases were excluded. Additionally, we excluded patients who underwent a concurrent thyroid operation. Finally, because of lithium's association with hyperparathyroidism, patients with prior lithium exposure were not included in the study. Patients were stratified into two groups, patients on LT (+LT) and patients not on LT (−LT). Because −LT patients far outnumbered +LT patients, +LT patients were matched 1:3 to −LT patients based on age, gender, presence of goiter, and baseline PTH levels.

Preoperative patient characteristics and clinical parameters were recorded. Additionally, parathyroid operation findings were contrasted. Finally, number and correctness of MIBI and US parathyroid localization studies were evaluated. In >90% of cases, US was performed and interpreted by the operating endocrine surgeon. Additionally, interpretation of the MIBI scan preoperatively was confirmed by the surgeon. An MIBI scan was considered correct if the gland removed was on the same side as the gland identified by MIBI. An US was defined as correct if the gland removed was the same gland (laterality and upper *versus* lower) identified on US. A negative MIBI or US was correct only if the patient was found to have hyperplasia (three or more enlarged glands).

At our institution, parathyroidectomies are performed using intraoperative PTH testing. A 50% decline in PTH from the peak PTH level measured at 5, 10, or 15 min after excision is required. Additionally, gamma probe radiation counts are used, which include background counts read at the thyroid isthmus and *ex vivo* counts read outside the body. A percent of background value, defined as *ex vivo* and/or background count, is calculated with a ratio above 20% indicating an abnormal parathyroid has been removed [9].

Subgroup analysis was conducted on patients who had previous radioactive iodine (RAI) and on patients who had a single adenoma removed, including further analysis comparing upper and lower single adenoma patients. Subset analysis was also performed on +LT patients to determine the effect of an LT dose ≥100 mcg. Gamma probe radiation counts were obtained for subset analysis.

The data were analyzed using SPSS statistical software (IBM Corp 2013, Armonk, NY). Continuous variables were compared using Student *t*-tests or Wilcoxon rank-sum tests where appropriate. Categorical variables were compared using chi-squared tests or Fisher exact tests where appropriate. *P* value <0.05 was considered significant.

3. Results

3.1. Patient characteristics and operative findings

From January 2000–May 2014, 1737 patients underwent parathyroidectomy meeting inclusion criteria for this study. Of these patients, 286 were on LT (+LT) at the time of their localization study and were matched to 858 patients not on LT (−LT). Patients in the +LT and −LT group had no significant differences in terms of demographics, comorbidities, and disease features (Table 1). −LT patients had more thyroid nodules than patients on LT (20.3% *versus* 14.0%, $P = 0.02$). No difference was found between the +LT and −LT patients in terms of operative findings (Table 2).

3.2. Localization accuracy

A similar number of patients had a MIBI scan or US performed in each group (Table 3). The percentage of correct MIBI scans was not significantly different between the +LT and −LT patients (64.3% *versus* 65.0%, $P = 0.82$, Table 3). +LT patients had a significantly lower percentage of correct US studies compared with patients not on LT (48.4% *versus* 62.2%, $P < 0.01$; Table 3).

3.3. RAI subgroup analysis

Next, we performed subset analysis for patients on LT due to previous RAI therapy. Thirty-one patients with previous RAI treatment on LT were matched to 93 −LT patients. Patient demographics, preoperative clinical parameters, and parathyroid