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ORIGINAL ARTICLE

Failure of fragmented parathyroid gland autotransplantation to prevent permanent hypoparathyroidism after total thyroidectomy

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Abstract
Purpose Parathyroid autotransplantation during total thyroidectomy leads to higher rates of postoperative hypocalcaemia. It has been argued, however, that it prevents permanent hypoparathyroidism. The impact of autografted normal parathyroid gland fragments on long-term parathyroid status has not been assessed properly. To clarify this, the short- and long-term parathyroid function was assessed in patients with three glands remaining in situ after total thyroidectomy, in whom the fourth gland was either autotransplanted (Tx) or accidentally resected (AR).
Methods Consecutive patients ($n = 669$) undergoing first-time total thyroidectomy were prospectively studied recording the number of parathyroid glands remaining in situ: PGRIS =4—(glands autografted + glands in the specimen). The study was focused on the subgroup of 186 patients with three parathyroid glands remaining in situ as a result of either accidental resection (*AR,* $n = 76$) or autotransplantation into the sternocleidomastoid muscle (*Tx,* $n = 110$). Prevalence of postoperative hypocalcaemia, protracted, and permanent hypoparathyroidism were compared between the two groups. Demographic, disease-related, laboratory, and surgical variables were recorded. All patients were followed for at least 1 year.
Results Both groups were comparable in terms of disease and extent of surgery. Mean postoperative serum calcium was the same (AR: 1.97 ± 0.2 vs Tx: 1.97 ± 0.22 mmol/L). Rates of protracted (AR: 24% vs Tx: 25.5%) and permanent hypoparathyroidism (AR: 5.3% vs Tx: 7.3%) were similar in both groups.
Conclusions The prevalence of parathyroid failure syndromes after total thyroidectomy was similar whether a parathyroid gland was inadvertently excised or autotransplanted. Autotransplantation did not influence the permanent hypoparathyroidism rate.

Keywords Parathyroid autotransplantation · Permanent hypoparathyroidism · Postoperative hypocalcaemia · Total thyroidectomy

Introduction

Permanent hypoparathyroidism is the most common long-term complication after total thyroidectomy [1–4]. In a recent review and meta-analysis, the prevalence of transient hypocalcaemia was estimated to range between 19 and 38% and that of permanent hypoparathyroidism between 0 and 3% [5]. Pragmatic multi-center studies, independently audited and without conflicts of interest, however, have reported permanent hypoparathyroidism rates well over 5% [6–9].

Hypocalcaemia after total thyroidectomy is mainly caused by a decrease in circulating PTH [10, 11] resulting from a reduction of the parathyroid parenchyma due to intraoperative injury to the parathyroid glands secondary to mechanical or thermal trauma, gland devascularization, or accidental excision of parathyroid tissue. The general recommendation to prevent postoperative parathyroid failure is a meticulous surgical technique in order to identify and preserve the parathyroid glands in situ and, when felt not possible, due to the anatomic disposition or possible devascularization, perform

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the autotransplantation of a finely fragmented normal gland(s). Thus, the threshold for parathyroid autotransplantation is highly subjective and is influenced by the belief of the surgeon in the viability and functional capacity of the grafted tissue. In fact, a very liberal and even a routine approach to parathyroid autografting has been recommended hypothesizing that this would be the final solution to prevent permanent hypoparathyroidism [4, 12–17].

Some studies, however, have found a clear-cut association between parathyroid autotransplantation and temporary and permanent hypoparathyroidism [1, 18–20]. We reported that both accidental parathyroidectomy and parathyroid autotransplantation, increase the prevalence of all parathyroid failure syndromes [21] because they both result in less than four parathyroid glands preserved in situ which is a very powerful predictive factor for both protracted and permanent hypoparathyroidism [19].

The present study was designed to assess the outcome of parathyroid autotransplantation by analyzing the long-term parathyroid function in a group of patients with three parathyroid glands preserved in situ after total thyroidectomy, in whom the fourth gland was either inadvertently resected or autografted.

Subjects and methods

The study was designed as a review of consecutive patients undergoing first-time total thyroidectomy for goiter or thyroid carcinoma during the period 2000–2014 whose records were collected in a prospectively maintained clinical database. Exclusion criteria were Dunhill procedures, less than total thyroidectomies performed for Graves' disease, reoperations, and associated parathyroidectomy for either primary or secondary hyperparathyroidism.

The number of parathyroid glands remaining in situ (PGRIS) was calculated by using the formula: 4—(parathyroid glands autografted + parathyroid glands found in the specimen) as previously described [19]. Patients were then classified according to the number of PGRIS as Group 1–2 (one or two parathyroid glands in situ), Group 3 (three parathyroid glands in situ), and Group 4 (all four glands remaining in situ). The present study focuses on the PGRIS 3 subset of patients in whom the fourth parathyroid gland was either autotransplanted (Group Tx, test group) or accidentally resected (Group AR, control group) and subsequently found in the specimen by the pathologist.

All the procedures were performed by the same team of experienced endocrine surgeons at a tertiary referral center for endocrine surgery. In every case, the surgical report contained precise information on the number of identified parathyroid glands and those eventually autografted. The same dedicated pathologist assessed the presence of parathyroid glands in all surgical specimens.

Surgical technique

Total thyroidectomy was performed for either multinodular goiter or thyroid cancer; the latter was associated with routine central compartment dissection and modified radical lateral neck dissection when required.

Parathyroid glands were looked for in their orthotopic position and when necessary were mobilized using a fine disposable electrosurgical electrode needle with straight tip (UTAH Optimicro™, Utah Medical Products, Midvale, Utah, USA). No effort was made to identify parathyroids hiding in non-orthotopic places and, if not identified or found by the pathologist, were assumed to remain in situ. Autotransplantation was carried out on the basis of doubtful vascular integrity or presumed difficult mobilization regardless of the status of the remaining identified parathyroid glands. Before, autotransplantation parathyroid frozen biopsies were performed selectively when in doubt.

The technique of autotransplantation employed was that reported by Olson et al. [4]. The resected normal parathyroid glands were maintained on a saline humidified gauze on a frozen surface until the end of the procedure, approximately 20–30 min. The glands were then chopped into 1 mm^3 fragments and buried into several pockets in the ipsilateral sternocleidomastoid muscle.

Patient management and follow-up

Serum calcium and iPTH levels (chemoluminescence; normal range 13–65 pg/mL, detection limit 3 pg/mL) were measured 24 h after surgery. For iPTH determination either an immunoradiometric second-generation assay using a Total Intact PTH IRMA assay (Scantibodies Laboratory, Santee, California, USA) or a solid-phase, two-site chemiluminescent enzyme-labeled assay, IMMULITE® 2000 Intact PTH assay (Siemens Healthcare Diagnostics Spain, Madrid, Spain) were utilized. If the total serum calcium concentration was <2 mmol/L 24 h after thyroidectomy, treatment with calcium salts (1.5–3 g of element calcium/day) and calcitriol (0.5–1.0 μg/day) was started to prevent clinical symptoms.

Patients were usually discharged on the second postoperative day and seen in a follow-up visit the following week. Thyroid stimulating hormone, serum calcium, serum phosphate, iPTH, and vitamin D levels were determined within 4–6 weeks of total thyroidectomy. Dosages of calcium supplements and calcitriol remained unchanged between hospital discharge and the second follow-up visit. Patients with benign disease and with normal parathyroid function were sent to the referring physicians, whereas all patients with thyroid cancer and/or postoperative serum calcium levels lower than 2 mmol/

L or iPTH levels below 13 pg/mL were controlled by the surgical team for at least 1 year.

Definitions

Postoperative hypocalcaemia was defined as a serum calcium concentration lower than 2 mmol/L at 24 h after total thyroidectomy; protracted hypoparathyroidism if iPTH concentration was <13 pg/mL and calcium replacement with or without calcitriol was required at 4–6 weeks after thyroidectomy; finally, permanent hypoparathyroidism was defined as a subnormal iPTH concentration (<13 pg/mL) and need for calcium replacement with or without calcitriol for more than 1 year after total thyroidectomy [21]. The extension of the surgical procedure was classified as isolated total thyroidectomy for multinodular goiter or total thyroidectomy plus central neck dissection for carcinoma (eventually associated to lateral compartment modified radical dissection).

Statistical analysis

A database created with FileMaker Pro 8 software (Santa Clara, CA, USA) was prospectively maintained. Clinical, surgical, pathology, and biochemical variables related to parathyroid function were recorded. Statistical analyses were performed using SPSS IBM Statistics v.22.0 ® (Armonk, NY, USA). The Kolmogorov–Smirnov test was utilized to assess the normal distribution of quantitative variables. Either $\chi 2$ or Fisher exact tests were used to investigate comparison of proportions as required. For quantitative variables, the unpaired Student's *t*-test and or U Mann-Whitney test were utilized. Values are expressed as mean (standard deviation). Statistical significance was set at $P < 0.05$.

Results

From a series of 669 total thyroidectomies, 186 were PGRIS 3 (Fig. 1). In these cases, the fourth parathyroid gland had been accidentally resected (Group AR) in 76 patients (41%), whereas in 110 (59%) it was autotransplanted (Group Tx). Thyroidectomy was performed for multinodular goiter in 132 patients (71%) and for thyroid cancer in 54 (29%). There were 28 men (15%) and 158 women (85%) with a mean age of 55.5 ± 15 years (range 12–86 years).

Both groups were comparable regarding clinical variables (Table 1). There were no statistical differences regarding the extent of surgery, the weight of the specimen, and number of retrieved nodes. As expected, more parathyroid glands were identified in Group Tx than in Group AR. At the time of hospital discharge, patients developing hypocalcaemia in any of the two groups were prescribed similar doses of calcium salts and calcitriol.

Postoperative and long-term parathyroid function

Biochemical variables at 24 h, 1 month, and at 1 year after total thyroidectomy were similar in both groups. Thus, the prevalence of postoperative hypocalcaemia, protracted, and permanent hypoparathyroidism was similarly independent of whether the fourth gland was accidentally resected or autotransplanted (Table 2).

Discussion

At the end of the last century, total thyroidectomy became the preferred surgical option for a variety of thyroid disorders, both benign and malignant. Seminal papers proposing this more radical approach were published in the 1980s by Clark et al. [22] for differentiated thyroid carcinoma and Reeve et al. [23] for benign goiter.

Paralleling these proposals, the prevalence of postoperative hypocalcaemia and permanent hypoparathyroidism during the next decades increased, and parathyroid failure is currently recognized as the most common adverse effect of total thyroidectomy. Several recent multi-center anonymized surveys have reported a prevalence of permanent hypoparathyroidism ranging from 5 to over 20% [6–9, 24].

Experts in thyroid surgery writing on postoperative hypocalcaemia during the 1970s and1980s emphasized that all efforts had to be done to preserve the parathyroid glands in situ through meticulous dissection in order to maintain their blood supply and to avoid accidental resection [25, 26].

A new approach to the prevention of parathyroid failure was proposed by Wells et al. [27] after describing that small fragments of hyperplastic parathyroid tissue transplanted into muscle pockets would function and prevent hypoparathyroidism in MEN 1 patients after total parathyroidectomy. The idea that autotransplanted normal parathyroid tissue could also survive and secrete parathormone and prevent hypoparathyroidism was thereafter supported not only by Wells' group[4] but also by other influential surgeons [16, 28, 29] despite scientific proof for this was very week.

In fact, there are no good evidence studies proving that transplanted normal parathyroid tissue fragments do in fact prevent permanent hypoparathyroidism. Even Wells' group has backed from routine autotransplantation of the four parathyroid glands in patients undergoing preventive thyroidectomy for MEN 2 [30]. The Sydney group has reported the need for chronic calcium replacement in a cohort of patients after total thyroidectomy and liberal parathyroid autografting (mean of 1.4 transplanted glands per patient) [31].

Currently, there is large consensus that parathyroid autotransplantation during total thyroidectomy is associated with higher rates of postoperative hypocalcaemia [5, 13, 14, 16, 18–20, 32–34]. Thus, the controversy mainly centers

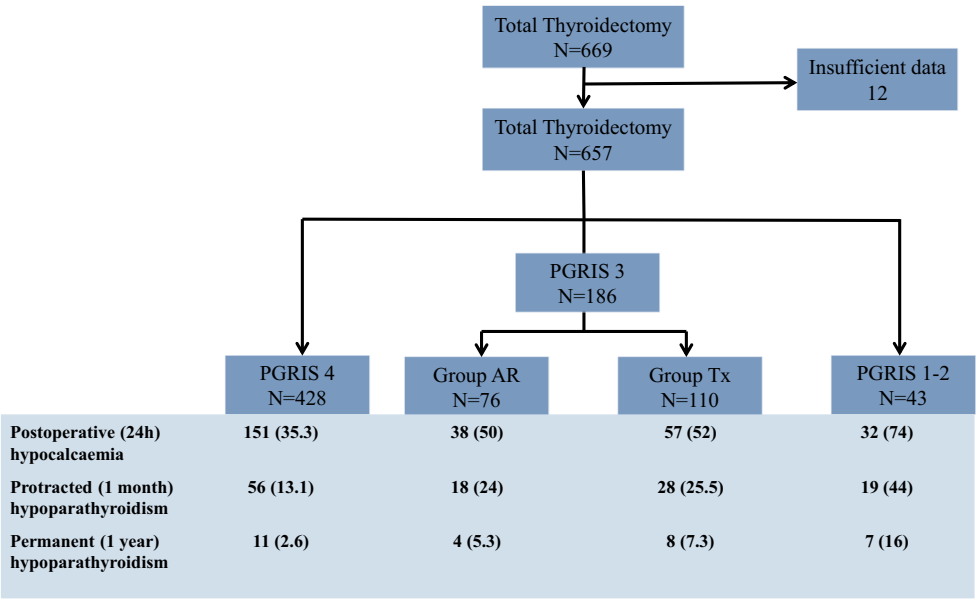

Fig. 1 Patients' flow chart showing the different outcome of parathyroid failure syndromes depending on the number or parathyroid glands remaining in situ (PGRIS). *Group AR* accidentally resected. *Group Tx* autotransplanted, *iPTH* intact parathyroid hormone. Values in parentheses are percentages

around whether it can prevent permanent hypoparathyroidism. According to our previous studies, autotransplantation is associated not only with higher rates of postoperative hypocalcaemia, but also with a three-fold increase of permanent hypoparathyroidism rates [19]. Moreover, the number of parathyroid glands remaining in situ was identified as a crucial variable influencing the prevalence of permanent parathyroid failure.

Since no randomized trial can be ethically designed to prove the value of autotransplantation, the present study addresses this controversy using an observational innovative indirect method that compares the short- and long-term parathyroid function of PGRIS 3 in patients in whom the fourth gland was transplanted with a control group of clinically similar patients in whom the fourth gland was excised inadvertently and found in the specimen by the pathologist. As expected, the only

Table 1 Clinical and surgical variables in patients with three parathyroid glands preserved in situ whose fourth parathyroid gland was either autotransplanted (Group Tx) or accidentally resected (Group AR)

	Total (n = 186)	Group Tx (n = 110)	Group AR (n = 76)	P
Age (years)		54.5 (15)	53.1 (18)	0.544*
Sex ratio (M/F)	28/158	15/95	13/63	0.515**
Indication for surgery				0.196**
Goiter	132	82 (74.5)	50 (66)	
Cancer	54	28 (25.5)	26 (34)	
Extent of surgery				0.831**
TT	142	85 (77)	57 (75)	
TT+ CCND	25	15 (14)	10 (13)	
TT+ CCND+ LCND	19	10 (9)	9 (12)	
Specimen weight (g)[a]		87.7 (78)	72.4 (64)	0.159*
No. of resected lymph nodes (if cancer)[a]		3.57 (0.8)	4.15 (0.9)	0.664*
No. of parathyroid glands identified[a]		3.29 (0.7)	2.77 (0.7)	<0.001*
Calcium dosage (g/day)[b]		2.72 (0.5)	2.64 (0.57)	0.590§
Calcitriol dosage (mcg/day)[b]		0.33 (0.5)	0.57 (0.5)	0.076§

Values in parentheses are percentages unless indicated otherwise. *TT* total thyroidectomy, *CCND* central compartment node dissection *LCND* lateral compartment node dissection

*Student's t-test; **χ^2 test; §Mann-Whitney U test

[a] Values are mean (s.d.)

[b] Only in patients developing postoperative hypocalcemia

Table 2 Parathyroid function parameters in patients with three parathyroid glands in situ whose fourth gland was either autotransplanted (Group Tx) or accidentally resected (Group AR)

	Group Tx (n = 110)	Group AR (n = 76)	P
Postoperative hypocalcaemia (s-Calcium^{24hours} <2.0 mmol/L)	57 (52)	38 (50)	0.807*
Protracted hypoparathyroidism	28 (25.5)	18 (24)	0.783*
Permanent hypoparathyroidism	8 (7.3)	4 (5.3)	0.764**
s-Calcium^{24hours} (mmol/L)[a]	1.97 (0.22)	1.98 (0.2)	0.810***
iPTH^{24hours} (ng/L)[a]	3.6 (2.4)	7.9 (9.5)	0.475****
s-Calcium^{1month} (mmol/L)[a]	2.28 (0.2)	2.29 (0.2)	0.850***
s-Phosphate^{1month} (mmol/L)[a]	1.29 (0.23)	1.29 (0.29)	0.730***
iPTH^{1month} (ng/L)[a]	26 (24)	30.6 (28)	0.409****
iPTH^{1year} (ng/L)[a]	39.5 (27)	25.48 (21)	0.179****

Values in parentheses are percentages unless indicated otherwise. *iPTH* intact parathyroid hormone

*χ2 test; **Fisher test; ***Student's *t*-test; ****Mann-Whitney U test

[a] Values are mean (s.d.)

factor significantly different between Group Tx and Group AR was fewer parathyroid glands identified intraoperatively in the latter. Although some authors have suggested that no effort should be made to identify the parathyroid glands to prevent their accidental removal [35, 36], the present study suggests that accidental parathyroidectomy is associated with a risk of permanent hypoparathyroidism in the 5–7% range, well above the 2–3% observed in PGRIS 4 patients [19].

Supporters of autotransplantation claim that parathyroid tissue takes well on a muscular bed [33] but most of these reports deal with implanted hyperplastic glands [27, 37]; evidence of function of autografted normal parathyroid tissue is very limited [38, 39]. Lo C et al. [39] demonstrated a 1.5-fold gradient of parathyroid hormone measurements between grafted and non-grafted forearms after autotransplantation of normal parathyroid tissue. These measurements, however, were performed only in seven patients at 3 months after total thyroidectomy and no data were provided concerning hypoparathyroidism prevention. In the study of El-Sharaky et al., function of parathyroid graft was assessed 1 month after surgery but not at 1 year [38]. A recent prospective study on parathyroid forearm reimplantation [40], documented a gradient (range ×1.5–5) between grafted and non-grafted forearms at 3 months, but failed to properly document the long-term parathyroid function. In addition, the authors report only 2/25 cases of postoperative hypocalcaemia, at variance with almost all studies. Our interpretation of these reports is that although some endocrine function coming from grafted parathyroid fragments may be detectable, it does not follow that it is enough to prevent permanent hypoparathyroidism.

A limitation of the present study is that a unique uniform technique of parathyroid reimplantation was used throughout. It might be that our technical approach fails to appropriately preserve the viability of the implanted tissue despite it is currently used by over 80% of endocrine surgeons according to a recent European survey [41]. It is difficult to assess whether differences in one of the steps of the procedure can make a substantial difference. For instance, whether the gland is immediately autografted [15–17] or at the end of the thyroidectomy [4, 14, 18–20, 33], the autotransplantation technique chosen (fragmented versus injected) and specially the surgeon criteria to carry out the autotransplantation (routine versus selective).

Another limitation of the study is that the viability of the remaining glands could not be assessed. We feel, however, that there are no good reasons to suspect that there were significant differences between the resected and the transplanted groups in terms of injury of the three remaining glands and this is supported by similar parathyroid failure rates. Parathyroid autotransplantation is very often successful when grafted glands are diseased as happens in hereditary primary or in secondary renal hyperparathyroidism. In these cases, however, there is an intrinsic proliferative stimulus that may enhance both the successful implantation of the tissue and the progressive growth of even minute viable fragments. When normal parathyroid tissue is implanted, however, the lack of this proliferative drive may be responsible for the failure of the graft to produce enough PTH to prevent permanent hypoparathyroidism.

In conclusion, autotransplantation of fragmented parathyroid glands did not prevent permanent hypoparathyroidism after total thyroidectomy in PGRIS 3 patients. The prevalence of parathyroid failure was similar whether the fourth gland was autografted or accidentally resected. Our current view is that both parathyroid autotransplantation and inadvertent parathyroidectomy [42] should be avoided and all efforts made to preserve the parathyroid glands in situ. Even taking into account the methodological limitations of the present study, its message of caution is clinically relevant since parathyroid autotransplantation during total thyroidectomy is still performed in many institutions despite lack of proof of its capacity to prevent hypoparathyroidism.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical considerations The authors of the present study state that the protocol for the research project has been approved by a suitably constituted Ethics Committee of the Hospital del Mar within which the work was undertaken and that it conforms to the provisions of in accordance with the Helsinki Declaration as revised in 2013. The study outcomes will affect the future management of our patients since the use of parathyroid autotransplantation will become restrictive.

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