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ORIGINAL ARTICLE

Thyroid autotransplantation after total thyroidectomy in multi-nodular goiter—a case series analysis

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Abstract

Background Following the success of parathyroid autotransplantation, thyroid autotransplantation was introduced, aiming to avoid or reduce the severity of post-thyroidectomy hypothyroidism in noncompliant patients.

Aim While our primary aim was to assess the survival and function of heterotopic autotransplanted thyroid tissue after total thyroidectomy, our secondary aim was to establish a relationship between autotransplanted volume and euthyroid state.

Methods We conducted a case series analysis, including 40 women diagnosed with multinodular goiter for whom total thyroidectomy was considered. Patients were randomized into two groups: group A (20 patients) who received 15 g and group B (20 patients) who received 10 g of healthy non-nodular thyroid tissue.

Survival and function of heterotopic autotransplanted thyroid tissue was assessed by hormonal profile and thigh ultrasound scan (site of autotransplanted thyroid graft) 2, 6, and 12 months postoperatively.

Results We have included 40 ladies divided into two groups: group A < 50 years and group B > 50 years. There was no statistically significant difference between group A and group B regarding radioactive iodine uptake after the 2nd, 6th, and 12th months. There was a statistically significant difference between results after the 2nd, 6th, and 12th months regarding free T3 (FT3; tri-iodothyronine), free T4 (FT4; thyroxine), thyroid-stimulating hormone, and pulse ($p \leq 0.001$). The study revealed a highly statistically significant difference between the 2nd, 6th, and 12th months in FT3, FT4, and TSH levels and pulse ($p \leq 0.001$) as well as highly statistically significant difference between group A and group B regarding FT3 and FT4 after the 2nd, 6th, and 12th months ($p \leq 0.001$) (Tables 2 and 3).

Autotransplanted thyroid tissue processing and injection time range was 18–20 min, and none of the patients had immediate or delayed complications.

Conclusion We found the procedure to be safe, successful, and not time-consuming; we also found that better results were achieved when larger volumes were implanted in younger patients.

Keywords Multinodular goiter · Goiter · Thyroidectomy · Autotransplantation

Introduction

Multinodular goiter is considered the most common endocrine disease that requires surgery; with the innovation of medical and surgical facilities, thyroidectomy became a safe procedure with a low complication rate and nearly negligible mortality rate. Type of surgery was controversial till the European and American guidelines recommended total thyroidectomy as a reliable approach in preventing recurrence [1]. Unfortunately, total thyroidectomy inevitably makes patients dependent on replacement therapy for life, an issue which can be challenging not only for patients but clinicians as well as efficacy of replacement therapy is strongly dependent on the form of TH used, timing of the blood tests to assess TSH concentrations as, well as other factors such as biologic availability and absorption of the medications [2]. Thyroid replacement therapy may also lead to various long-term side effects like weight gain, subclinical depression, headaches, cardiovascular disorders, and alteration in lipid profile [3].

Autotransplantation of thyroid tissue following total thyroidectomy not only helps in avoiding lifetime thyroid hormone replacement therapy but also maintains the auto-

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regulatory mechanism of thyroxin production [4] and avoid local recurrence in the neck which is associated with a high rate of complications if neck re-exploration is needed [5].

Only a few studies with small number of patients have looked into the efficacy and safety of thyroid autotransplantation, yet the adequate volume of thyroid graft which can achieve a postoperative euthyroid state is not ascertained. In our study, we have assessed the survival and function of autotransplanted thyroid tissue after total thyroidectomy in patients with multinodular goiter as an alternative method to lifelong hormonal replacement therapy.

Patients and Methods

Study Setting

The study was conducted in Faculty of Medicine at Fayoum University hospitals in Egypt.

Ethical Considerations

We have obtained the approval of the Ethical Committee of the Faculty of Medicine at Fayoum University in Egypt before conducting the study.

Study Design

We have conducted a case series analysis on patients who presented to our department with multinodular goiters for whom total thyroidectomy was indicated between January 2017 and August 2018.

We have included all women scheduled for total thyroidectomy due to simple multinodular goiter and with euthyroid state who are fit (American Society of Anesthesiologists (ASA) 1 and 2) and willing to take part in the study and excluded patients with suspicion of malignancy, patients with a history of previous neck irradiation, patients with malignant or recurrent goiter, and patients who have no sufficient healthy thyroid tissue for transplantation.

Preoperative assessment included history taking to rule out coagulopathy and neck irradiation, also assessing family history of thyroid malignancy, clinical examination of the head and neck, laboratory tests including routine bloods and thyroid functions to ensure euthyroid status, neck ultrasound scan, and indirect laryngoscopy as well as fine needle aspiration cytology of the dominant nodule or suspicious nodule, and only patients with benign findings were included in the study.

The patients were randomly allocated into two groups using flip coin method: group A, 20 patients who received 15 g, and group B, 20 patients who received 10 g of healthy non-nodular thyroid tissue.

Operative Technique

Following total thyroidectomy, the specimen was grossly examined to identify a healthy non-nodular area for which frozen section was carried out to exclude malignancy, and then sliced and mixed with saline and injected using a 20 cc syringe attached to 1 mm blunt tip fat transfer needle into the anterolateral aspect of the left thigh in multiple pockets through tiny skin puncture (Fig. 1).

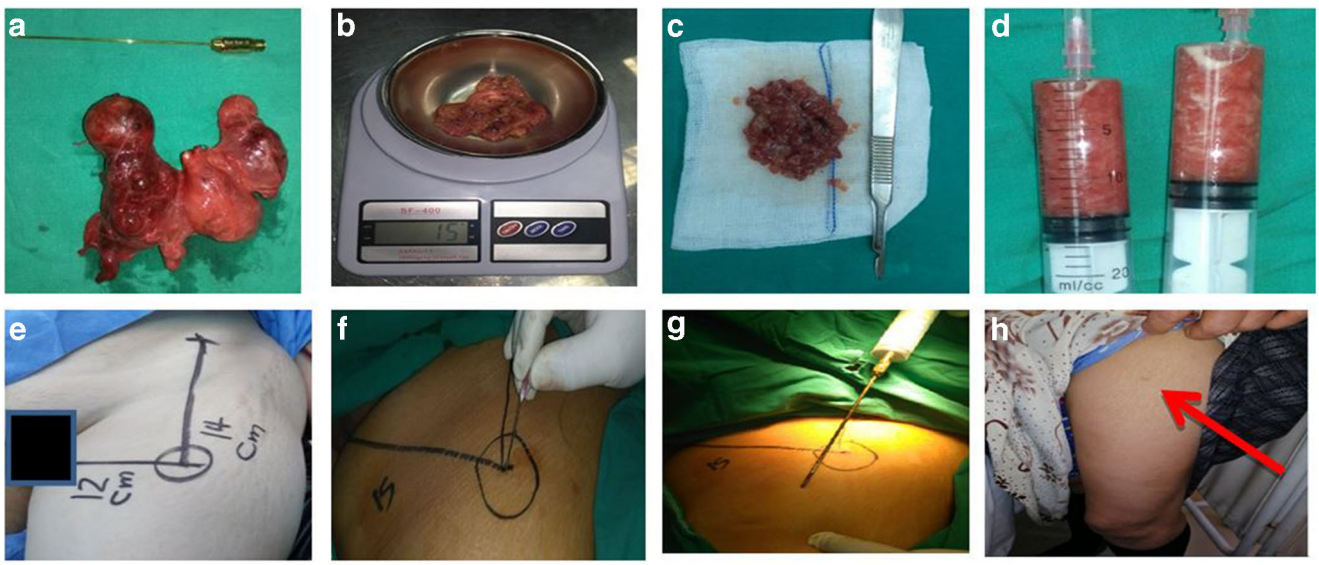

Fig. 1 Operative steps. **a** Totally thyroidectomy specimen. **b** Healthy non nodular thyroid tissue prior to preparation. **c** Sliced thyroid tissue. **d** Thyroid tissue mixed with saline, ready for injection. **e** Marking site of transplantation. **f** Sharp needle puncture at marked transplantation site. **g** Fat transfer needle used in thyroid tissue autotransplantation. **h** Puncture site one year after transplantation (red arrow)

Follow-up

Postoperatively, 50 μg/d L-thyroxine was prescribed; till the implanted thyroid tissues start functioning adequately only then it was stopped. Clinical assessment including pulse, thyroid function tests including free T3 (FT3; tri-iodothyronine) (FT3), free T4 (FT4; thyroxine) (FT4), thyroid-stimulating hormone (TSH), thigh ultrasound scan (US) (site of autotransplanted thyroid graft), and isotope scan of the implantation site were carried out at 2 months, 6 months, and 12 months after the operation. Replacement therapy was withheld 3 weeks before each occasion in order to assess the function of the implanted tissues.

Statistical Methods

Collected data were organized and statistically analyzed using the SPSS software statistical computer package version 22 (SPSS Inc., USA). For quantitative data, the mean, standard deviation (SD), and range were calculated; independent *t* test was used in comparing between the two groups. Qualitative data collected were presented as numbers and percentages, and chi-squared test was used as a test of significance. For interpretation of the results of tests of significance, significance was adopted at $p < 0.05$.

Results

We have included 40 patients divided into two groups: group A which was further divided into two subgroups, the first group included 16 patients younger than 50 years, and their age range was 24 to 46 years (mean 35.94 SD 7.66), while the second group included four patients older than 50 years which age ranged from 51 to 53 years (mean 52 SD 1.41). Group B was also divided into two subgroups: the first group included 15 patients younger than 50 years, and their age ranged from 24 to 48 years (mean 39.70 SD 7.93), and a second group comprised five patients older than 50 years, and their age ranged from 50 to 55 years (mean 52.67 SD2.52) (Table 1).

Autotransplanted thyroid tissue processing and injection time range was 18–20 min (mean 19 min. SD 1) for group A and 12–15 min (mean 13.5 min. SD 1.5) for group B.

None of the patients had immediate or delayed complications neither related to thyroidectomy nor the autotransplantation site.

There was no statistically significant difference between group A and group B regarding radioactive iodine uptake after the 2nd, 6th, and 12th months. There was a statistically significant difference between results after the 2nd, 6th, and 12th months regarding FT3, FT4, TSH, and pulse ($p \leq 0.001$). The study revealed a highly statistically significant difference between the 2nd, 6th, and 12th months in FT3, FT4, TSH levels, and pulse ($p \leq 0.001$) as well as highly statistically significant difference between group A and group B regarding FT3 and FT4 after the 2nd, 6th, and 12th months ($p \leq 0.001$) (Tables 2 and 3).

Table 1 Demographic data: age and sex distribution among groups

			Groups			
			Group A		Group B	
Age	> 50 years	Range	51–53		50–55	
		Mean ± SD	52.00 ± 1.41		52.67 ± 2.52	
	< 50 years	Range	24–46		24–48	
		Mean ± SD	35.94 ± 7.66		39.70 ± 7.93	
			N	%	*N*	%
Age	> 50 years		4	20	5	25
	< 50 years		16	80	15	75

The study revealed a highly statistically significant difference between results after the 2nd, 6th, and 12th months regarding FT3, FT4, TSH, and pulse ($p \leq 0.001$) in group A < 50 years.

The study revealed a highly statistically significant difference between group A and group B regarding FT3 and FT4 after the 2nd, 6th, and 12th months ($p \leq 0.001$) < 50 years.

The study revealed a highly statistically significant difference between group A and group B regarding TSH and pulse at the 2nd, 6th, and 12th months < 50 years ($p \leq 0.001$) (Table 2).

In patients older than 50 years, we have noted a statistically significant difference between group A and group B regarding FT3, FT4, TSH levels, and pulse after the 2nd, 6th, and 12th months ($p \leq 0.001$). We found no statistically significant difference after the 2nd, 6th, and 12th months regarding FT3, FT4, TSH, and pulse in group A > 50 years ($p > 0.05$), but there was a statistically significant difference after the 2nd, 6th, and 12th months regarding FT3 and FT4 ($p \leq 0.05$), while there was no statistically significant difference between the 2nd, 6th, and 12th months regarding TSH and pulse in group B > 50 years. All patients in both groups had positive thyroid scan at the site of implantation starting from the 2nd month denoting good isotope uptake, which indicates survival of implanted thyroid tissue, even though the thyroid profile was not still euthyroid indicating that the graft is not fully functioning yet (Table 3).

All patients in both groups below the age of 50 years old continued to be euthyroid and did not require levothyroxine (L-T4) replacement therapy while patients in both groups older than 50 years required a small dose (25–50 μg/day) of levothyroxine.

Patients in group B younger than 50 years old reached euthyroid profile in longer time compared to the same age group in group A, but patients above 50 years old in both

Table 2 Comparison between groups A and B < 50 years as regards fT3, fT4, TSH, and pulse after 2, 6, and 12 months

		Groups at < 50		*p* value
		Group A	Group B	
FT3 at 2nd month	Mean ± SD	1.18 ± 0.28	0.85 ± 0.09	< 0.001
FT3 at 6th month	Mean ± SD	1.77 ± 0.20	1.33 ± 0.25	< 0.001 HS
FT3 at 12th month	Mean ± SD	2.46 ± 0.46	1.89 ± 0.51	0.001 HS
FT4 at 2nd month	Mean ± SD	0.69 ± 0.10	0.60 ± 0.13	0.007 S
FT4 at 6th month	Mean ± SD	0.89 ± 0.07	0.72 ± 0.09	< 0.001 HS
FT4 at 12th month	Mean ± SD	1.12 ± 0.18	1.03 ± 0.20	0.032 S
TSH at 2nd month	Mean ± SD	22.94 ± 2.26	30.64 ± 4.59	< 0.001 HS
TSH at 6th month	Mean ± SD	16.01 ± 4.38	26 ± 4.67	< 0.001 HS
TSH at 12th month	Mean ± SD	9.72 ± 3.37	22.20 ± 5.05	< 0.001 HS
Pulse at 2nd month	Mean ± SD	77.83 ± 6.93	72.47 ± 6.66	0.124 NS
Pulse at 6th month	Mean ± SD	85.11 ± 2.87	80 ± 3.27	0.064 NS
Pulse at 12th month	Mean ± SD	92.38 ± 1.33	93.47 ± 1.46	0.068 NS

HS highly specific, *S* specific, *NS* non-specific

groups showed no significant difference in thyroid profile throughout the follow-up period.

We have noted that young patients and those who received 15 g of thyroid tissue reached euthyroid status earlier than older patients and those who received 10 g of thyroid tissue. It is worth noting that the latter patients may still reach euthyroid status after a long time or might need a larger volume to be transplanted; they might also benefit from multiple sites transplantation.

Discussion

Total thyroidectomy is still the cornerstone for treatment of multinodular goiter and Graves' disease. Unfortunately, hypothyroidism is inevitable following total thyroidectomy, so thyroid replacement therapy is always prescribed to maintain thyroxin level. Still, this simple task is not without complication; also, the dose of levothyroxine needs to be closely monitored [2, 6, 7].

Thyroid replacement therapy medications are associated with concerns related to product stability (shelflife): formulation consistency over time and bioequivalence studies between brands; also, levothyroxine degrades quickly with exposure to light, moisture, oxygen, and carbohydrate excipients [8, 9].

Thyroid tissue autotransplantation has been introduced following the success and establishment of parathyroid gland autotransplantation [10]. Although the autotransplantation of the thyroid gland is still controversial in clinical practice [11],

Table 3 Comparison between groups A and B > 50 years as regards fT3, fT4, TSH, and pulse after 2, 6, and 12 months

		Groups at > 50		*p* value
		Group A	Group B	
FT3 at 2nd month	Mean ± SD	0.85 ± 0.07	0.97 ± 0.01	0.200 NS
FT3 at 6th month	Mean ± SD	1.04 ± 0.08	1.23 ± 0.21	0.317 NS
FT3 at 12th month	Mean ± SD	1.30 ± 0.13	1.50 ± 0.10	0.154 NS
FT4 at 2nd month	Mean ± SD	0.64 ± 0.06	0.45 ± 0.05	0.200 NS
FT4 at 6th month	Mean ± SD	0.73 ± 0.04	0.80 ± 0.02	0.200 NS
FT4 at 12th month	Mean ± SD	0.90 ± 0.11	0.88 ± 0.16	0.859 NS
TSH at 2nd month	Mean ± SD	35.50 ± 0.71	36.00 ± 1.00	0.591 NS
TSH at 6th month	Mean ± SD	31.33 ± 4.72	34.50 ± 0.71	0.437 NS
TSH at 12th month	Mean ± SD	25.33 ± 7.57	31.00 ± 1.41	0.326 NS
Pulse at 2nd month	Mean ± SD	68.00 ± 7.21	61.00 ± 1.41	0.287 NS
Pulse at 6th month	Mean ± SD	76.00 ± 8.54	71.50 ± 7.78	0.594 NS
Pulse at 12th month	Mean ± SD	80.67 ± 12.70	69.50 ± 0.71	0.208 NS

there is reassuring evidence that it is a safe and secure procedure that provides survival and function of the thyroid graft achieving a postoperative euthyroid state in selected patients without the need for further administration of L-T4 replacement therapy [12].

Autotransplantation of thyroid tissue does not only avoid thyroid hormone replacement therapy but also maintain the auto-regulatory mechanism of thyroxin production [4], and it does not carry the risk of neck re-exploration in case of recurrence [5].

Since the volume of a healthy thyroid gland varies from 15 to 25 g, it is sensible to autotransplant not less than 10 g [13–15]. Studies reported variable degree of graft function which can be linked to preoperative gland pathology, weight of the transplanted tissue, and status of the graft (cell density and potential regeneration power), as well as the survival of cells in the transplant bed, its size, and the duration of long-term stimulation [15].

Mohsen et al. found that all autotransplanted thyroid tissue showed uptake of technetium (99mTc), and TSH was elevated in the majority to maintain normal or near-normal thyroid hormones; they concluded that 10-g implants showed higher isotope uptake than 5 g. However, this difference was not reflected by thyroid hormone profile. They also noted that the implant function improves with time [5].

In spite of the fact that influences of estrogen on the development, physiology, and histology of the thyroid gland have been demonstrated before in the literature, the effects of estrogen replacement therapy on the thyroid diseases is not established yet [16]. That may explain why older patients in our cohort did not reach euthyroid status after thyroid transplantation, the fact which could be avoided by estrogen/progesterone replacement therapy after thyroid transplantation.

In our cohort follow-up, isotope scan showed uptake in both groups from the 2nd month; even though thyroid profile was not still euthyroid, this was a good indicator for survival of implanted thyroid tissue even it is not fully functioning. Also, ultrasound scan of implantation site did not detect any abnormalities. Thyroid profile carried out at the 2nd, 6th, and 12th months showed that young patients and those who received 15 g of thyroid tissue showed early euthyroid state, indicating successful thyroid transplantation process, while older patients and those who received 10 g of thyroid tissue failed to reach euthyroid state all through our follow-up period. Yet, these patients might reach normal thyroid profile after a long period of time in line with El Hadad et al findings [17],or they might need more transplantation tissue volume or may get the benefit of transplantation in multiple sites not only left thigh.

All our patients received 50 μg/d L-thyroxine to replace the removed thyroid gland meanwhile maintaining a low level of TSH release by the pituitary gland to stimulate the growth of implanted thyroid tissue. Yet, long-term follow-up of patients is essential, especially the TSH level to guard against pituitary hyperfunctioning and also of the implantation site to detect any change in the implanted tissue [12].

Neither our study nor recent studies in the literature reported postoperative complications related to the thyroidectomy or the recipient site, confirming that thyroid autotransplantation is a quite safe procedure [17, 18].

Limitations

Our follow-up was relatively short; we think that longer follow-up is mandatory for all patients, either those who stopped the replacement therapy after sufficient function to the thyroid graft or those who still on low dose replacement therapy, as some patients take longer time to regain normal thyroid functions [17].

SPECT-CT is one of the valuable objective imaging modalities for evaluation of the functional capacity of the transplanted thyroid tissue; unfortunately, we were not able to perform complementary postoperative SPECT-CT as carried out in other studies [18].

Group B contains a little bit greater number of patients > 50 years, which could have affected the study results especially with small sample size.

Conclusion

Heterotopic thyroid autotransplantation process is a safe, short, simple procedure.

We achieved better results in younger patients; we also found that the more cell load and volume of thyroid tissue used, the earlier the results and normalization of thyroid profile and clinical status, yet optimum volume which lead to euthyroid status is yet to be established.

We recommend a larger sample size study with longer follow-up comparing different transplanted volumes in relation to thyroid functions.

Author Contributions MI was responsible for the surgery and ongoing patient's care and provided the data as well as result of the analysis. SM and HH researched, drafted, and conceived the manuscript. All authors read and approved the final manuscript.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Ethical Approval We have obtained the approval of the Ethical Committee of the Faculty of Medicine at Fayoum University in Egypt prior to conducting the study.

Patients' Consent Written informed consent was obtained from all patients.

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