

# Outcome and Technique of Auto Transplanting Thyroid Tissue after Total Thyroidectomy for Simple Multinodular Goiters

Mohamed Salah Yousif<sup>1\*</sup>, Mahmoud Abdallah Abdelrazik<sup>1</sup>, Basma Ahmed Mohamed<sup>1</sup>

<sup>1</sup>Department of General Surgery, Faculty of Medicine for Girls, Al-Azhar University,

Cairo, Egypt.

## \*Email: drmohamedsalah9292@gmail.com

#### Abstract

The procedure of thyroidectomy was developed by Theodore Kocher and William Halsted. Thyroid auto transplantation offers an attractive alternative to subtotal thyroidectomy and replacement therapy. However, it has not been sufficiently clinically investigated. Aim of this work evaluates the role of thyroid auto transplantation of fresh thyroid tissue done in the same session of total thyroidectomy (TT) for benign goiters to achieve a postoperative euthyroid state without the need for administration of life-long L-T4 replacement therapy. A prospective study was carried out on 40 patients with benign thyroid disorder where a small piece of healthy thyroid tissue about 15 gram is sliced by scissor and implanted in the Antero - lateral aspect of the non-dominant thigh. Demographic data of these patients include age, sex, evaluation of preoperative symptoms and signs, 32 thyroid tissue implants survived and showed variable degree of function as all the patients showed viability and new vascular formations at 1-month postoperatively and most of the patients had normal thyroid hormones levels at 6-months postoperatively. The best results in this study were achieved in young patients with preoperative pathology of simple nodular disease in whom maximum weight of non-nodular healthy thyroid tissue was implanted. Clinical application of thyroid autotransplantation is an easy, safe and worthy technique to be adopted in selected patients after TT for benign goiter to achieve a postoperative euthyroid state without the need for administration of postoperative life-long L-T4 replacement therapy.

Key words: Auto transplanting thyroid tissue, Total thyroidectomy, Multinodular goiters.

## 1. Introduction

The concept of endocrinal tissue auto transplantation has been largely investigated in the case of parathyroid glands, and to a lesser extent for pancreatic islets. Although both the experimental studies of thyroid auto transplantations and the early case reports of lingual thyroid auto transplantations have shown encouraging results, a very limited number of clinical studies investigated thyroid auto transplantation in adult patients with benign thyroid disorders. Moreover, the discrepancy in the patients' characteristics and thyroid auto transplantation technique in these studies hinders the standardization of thyroid auto transplantation for clinical practice. Hypothetically, thyroid auto transplantation offers an attractive

alternative for subtotal thyroidectomy, as it enables the preservation of native responsive thyroid tissue in an accessible location, and, thus, evades the risk of possible regrowth in the neck region (Sakr et al., 2018) [1]. Whenever surgery is indicated for a simple multinodular goiter, trend is the current to do total thyroidectomy (Agarwal et,al 2008) [2]. Inevitably this makes the patient dependent on replacement therapy for life. Although it seems relatively easy to control hypothyroidism by levo-thyroxine, from the patient's point of view, a daily dependence on it and regular visits to hospital to check hormone levels are burdensome. Other problems that may interfere with reaching an euthyroid status replacement therapy using are and noncompliance malabsorption of patients. (Mohamed El Hadad et al., 2020) [3]. Objective and aim of the study will be auto transplantation of normal thyroid tissue after TT is to avoid postoperative hypothyroidism. permanent Another advantage of thyroid auto-transplantation maintaining the autoregulatory is mechanism of thyroxin production inside according the body to its needs. Heterotopic thyroid auto transplantation was proposed to avoid reoperation at the site of previous neck surgery in cases of goiters recurrent or recurrent hyperthyroidism. (Gamal et al., 2019) [4]. Before applying the same principles on the thyroid gland in humans, studies have been done on animals. Autologous transplantations were found to be successful in 70% of cases and histological examinations showed normal thyroid architecture (Mohsen et al., 2015) [5].

# 2. Patients and Methods

In this study we tried to evaluate auto transplantation of thyroid gland after total thyroidectomy for benign thyroid diseases, transplanted thyroid tissue was implanted in quadriceps femoris muscle and implanted thyroid tissue was followed for 6 months as shown into results. This study was conducted at AL-Zahraa university hospital including 40 patients with a diagnosis of simple nodular goiter. This study continued from May 2021 to December 2021.

# 2.1 Patients

The present study was carried out among patients presented to the outpatient clinic and the department of general surgery by simple multi-nodular goiters that have been picked up on clinical examination as well as the ultrasound of the thyroid. All the patients included in the study after they have been informed about the details of possible the procedures and all complications of total thyroidectomy and thyroid implantation; a written consent entails that were taken.

# 2.2 Inclusion criteria

This study included patients with ages from 18-50 years, patients with simple multi nodular goiters who were indicated for total thyroidectomy because of compression manifestations, cosmetic concerns, and where nodularity extended to both lobes.

# 2.3 Exclusion criteria

patients with ages below 18 years old, Unwilling patients, patients with malignant, toxic or recurrent goiter, patients showing any clinical or ultrasound suspicion of malignancy were excluded, pregnancy, those with family history of cancer thyroid, history of neck irradiation will be excluded because they constitute a high risk of developing thyroid cancer, clinically morbid patients or patients un-fit for surgery.

# **2.4 All patients included in the study were subjected to.**

Detailed history taking specially age, sex, full general examination, local examination specially (neck swelling, dyspnea, dysphagia) with no toxic symptoms and laboratory investigations were done for all patients mainly (TSH, free T3, free T4). Ultrasonography (US), FNAC was done for all patients and plain

X-ray on thoracic inlet. Total thyroidectomy was done for all patients.

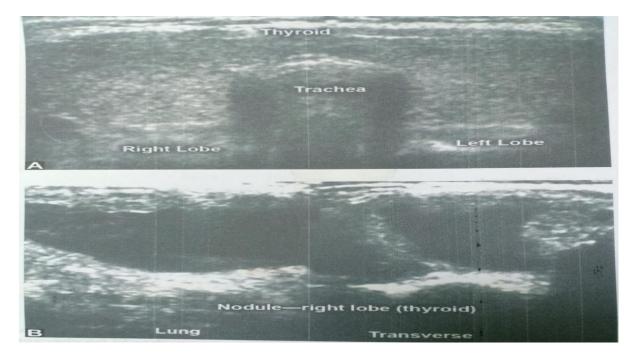


Figure (1): A- US on thyroid gland & B- show nodule in right lobe of thyroid gland.



Figure (2): Chest X-ray show retro-sternal goiter with tracheal deviation toward the right side.

#### 2.5 Methods (Operative technique):

All patients undergoing total thyroidectomy. All patients should be ideally euthyroid at the time of operation.

## 2.6 Anesthesia and position:

Thyroidectomy is performed under general anesthesia with endotracheal intubation. The patient is placed supine in a 20-degree reverse Trendelenburg position, with both arms tucked. The neck is hyperextended by placing a beanbag or soft roll behind the scapulae and a foam ring under the head. This position places the thyroid gland in a more anterior position. The head must be well supported to prevent postoperative posterior neck pain. The surgical area is prepared with 10% iodine and sterilely draped.

## 2.6 Description of the procedure

Apparently normal part of the gland weighting about 10-15 gm. without palpable nodules was cut into 5-6 slices which had been put in 50cc ringer lactate solution. A small incision about 2 cm was done by scalpel in the antero lateral part of the middle of the thigh, rectus femoris muscle sheath was exposed well and opened and separate muscle fibers. Then



Figure (3): Ligation of middle thyroid vein during total thyroidectomy.



Figure (4): Thyroid gland after total thyroidectomy.

we put the slices of the thyroid tissue in the muscle and close the muscle sheath by vicryl 2/0 simple sutures. Skin of the thigh was closed by using subcuticular 2-0 prolene sutures and covered by clean sterile dressing. The sutures of the neck were removed one week postoperatively while the sutures of the thigh were removed 10 days postoperatively.

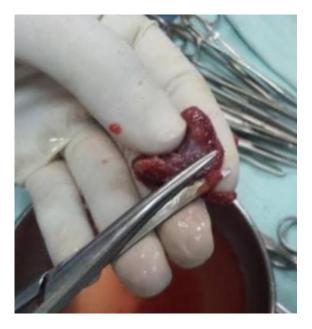


Figure (5): Slicing thyroid implant before implantation



Figure (6): Thigh incision for thyroid implant.



Figure (7): Slice of thyroid implant during transplantation.

#### 2.7 Follow up

Post-operative evaluations include (clinical symptoms and signs, laboratory investigations, imaging and post-operative complications mainly: (bleeding, hypocalcemia, recurrent laryngeal nerve injury, wound infection and seroma). Postoperative assessment by the anesthetic to assess vocal cords mobility. Evaluation of complications related to implantation process in the form of:

- o Thigh numbness.
- o Muscular hematoma.
- o Wound seroma.
- o Muscle fibroma.

Histological examination of excised thyroid tissue to confirm diagnosis and to exclude other pathological thyroid diseases (there is histo-pathological department in Al-Zahra hospital available when needed). Duplex ultrasound to evaluate viability, growth and new vascularization of the implanted thyroid tissue after one month of implantation. Measurement of serum FT3, FT4 and TSH at one, two, four and six months postoperatively to monitor the function of the auto-transplanted thyroid tissue. Patients received minimum dose of replacement therapy (50 µg L T4) at variable time intervals during the followup period according to the thyroid function tests and this dose is stopped three weeks before the next follow-up thyroid function tests. A 99mTechnetium (Tc)-scintigraphy will be done after 2 months of thyroid auto transplantation to assess its proper engraftment and function. Follow-up visits were scheduled one week at postoperatively for detection of any postoperative complications and at one, two, four and six months postoperatively thereafter to monitor the survival and function of the thyroid auto-transplanted cells.

## 3. Results

This study includes forty (40) patients with age ranged from 18-50 years old (average 38). The sex of the patients was 32 females (80%) & 8 males (20%).

 Table (1): Demographic data of the studied patients.

		No. = 40
Age	Range Mean ± SD	18 - 50 $38.41 \pm 10.02$
Sex	Males Females	8 (20.0%) 32 (80.0%)

 Table (2): Clinical presentation of the studied patients.

Clinical presentation	No.	Percentage
Neck swelling	36	90.0%
Compression Manifestations	4	10.0%

In this study most of the patients 36 (90%) presented by neck swelling and cosmetic concern with no toxic manifestation while

3.1 Preoperative thyroid pathology

The study included 40 patients with benign thyroid pathology all patients had undergone FNAC from any suspicious or dominant nodule and were all diagnosed pathologically as Bethesda II lesions

 Table (3): Early post total thyroidectomy complications.

4 (10%) of the patients presented by compression manifestation as dyspnea and dysphagia as shown in Table. 2.

simple multi nodular goiter (SMNG). In this study early post total thyroidectomy complications shows one patient with RLN injury and four patients with hypocalcemia as shown in Table. 3.

Post total thyroidectomy complications	No.	Percentage
Recurrent laryngeal nerve injury	1	2.5%
Hypoparathyroidism (hypocalcemia)	4	10%
	histopathology	result as shown in th

The most complication occurred in the thigh muscle post transplantation is thigh numbress it occurred in ten patients (25%) while muscle fibroma occurs in two patients (5%), muscle hematoma in one patient (2.5) % and wound infection in one patient (2.5%). Post-operative

histopathology result as shown in the following as shown in Table. 4. Post transplantation follow-up of total 99m technetium uptake as shown in as shown in Table. 6.

Table (4): Post transplantation complications among the studied patients in the thigh muscle

Post transplantation complications	No	%
Wound infection	1	2.5%
Muscle hematoma	1	2.5%
Muscle fibroma	2	5.0%
Thigh numbness	10	25.0%

Table (5): Postoperative histopathological results of the studied patients.

Postoperative pathology	Ν	%
Colloid nodular goiter	30	75.0%
Nodular thyroid hyperplasia	8	20.0%
Hyperplastic nodular goiter	2	5.0%
Total	40	100.0%

**Table (6):** Follow-up of the studied patients.

		<b>No.</b> = 40
Thyroid hormones	Normal	32 (80.0%)
Thyroid normones	Hypothyroidism	8 (20.0%)
Duplex ultrasound on thyroid	Growth	32 (80.0%)
transplant	No growth	8 (20.0%)

 Table (7): post-transplantation technetium uptake by thyroid implant.

	Uptake	Number	Percentage
At 2 months	Mean $\pm$ SD 1.07 $\pm$ 0.28	16	40%
At 4 months	Mean $\pm$ SD 1.18 $\pm$ 0.29	24	60%
At 6 months	Mean $\pm$ SD 1.28 $\pm$ 0.42	32	80%



Figure (8): Technetium scan of thyroid tissue and implant.

Level of TSH increased post-operative and decreased gradually by time to reach the normal level at 2,4,6 months postoperative as shown in Table. 8. Level of free T3 decreased post-operative and gradually increase by time to reach normal level at 2,4,6 months post-operative. as shown in Table. 9.

Follow-up at 1 month	Range	29.5-104.1
	Mean $\pm$ SD	49.090±17.202
Fellow up at 2 months	Range	17.4-90.1
Follow-up at 2 months	Mean $\pm$ SD	33.780±16.758
Eallow up at 4 months	Range	10.1-100.2
Follow-up at 4 months	Mean $\pm$ SD	22.024±20.491
Follow-up at 6 months	Range	2.5-98.4
	Mean $\pm$ SD	12.410±22.834

Table (8): Postoperative follow-up of TSH levels.

 Table (9): Postoperative follow-up of FT3 (pg/ml) levels.

Follow-up at 1 month	Range Mean ± SD	0.46 - 2.51 $1.47 \pm 0.48$
Follow-up at 2 months	Range Mean ± SD	0.85 - 3.1 $1.79 \pm 0.50$
Follow-up at 4 months	Range Mean ± SD	0.93 - 3.21 1.92 ± 0.59
Follow-up at 6 months	Range Mean ± SD	0.9 - 4.12 2.44 ± 0.85

Follow-up at 1 month	Range Mean ± SD	0.42 - 1.31 $0.94 \pm 0.22$
Follow-up at 2 months	Range Mean ± SD	0.45 - 1.6 1.11 ± 0.33
Follow-up at 4 months	Range Mean ± SD	0.53 - 1.64 $1.22 \pm 0.34$
Follow-up at 6 months	Range Mean ± SD	0.55 - 1.7 1.31 ± 0.39

Table (10): Post-Operative follow-up of FT4 (pg/ml) levels.

Table (11): Shows outcome of the studied patients.

Outcome	No.	%
Success	32	80.0%
Failure	8	20.0%

#### 4. Discussion

There was a significant negative correlation between age and serum levels of FT3 and FT4 and a positive correlation with serums levels at 12 months post transplantation. A negative correlation was also found between age and final graft outcome (fully functioning graft, minimally insufficient graft, or insufficient graft. No significant correlation was found between age and the need for replacement therapy. However, when a cutoff point was set at 50 years old, a significantly higher need for replacement was found in the older age group (Sakr et al., 2018) [1]. In this study age of the patients was an important factor affecting the overall graft function. Although results of this work regarding the relation between the patients' age and the need for replacement therapy was insignificant, yet this relation was significant when considering 50 years as a cut off age. Thus, we can conclude that younger patients have better chances of complete graft function without the need for further replacement therapy. During the follow-up period (six months) for all the patients, an obvious improvement of the overall functions of the transplant was detected with time passage reflected by the improvement of mean FT3, FT4 and TSH. This is a point of importance to consider in the assurance of the patient during the

follow-up period. Thyroid nodules are common clinical findings and have a reported prevalence of 4% to 7% in the adult population. Discrete thyroid swellings are common and are present in 3-4% population in UK and USA. Thyroid swellings are four times more common in females (Padmawar et al., 2014) [6]. In this study most of clinical presentation of patients was neck swelling 36 patients (90%). Total thyroidectomy is now accepted worldwide as the standard surgical procedure for the management of benign bilateral nodular thyroid disease. Hypocalcemia is the most common complication of that procedure and a variety of strategies for diagnosing and managing post-thyroidectomy hypocalcemia have been advocated (Grodski et al., 2008) [7]. Two hundred twenty-one patients undergoing thyroidectomy were analyzed for factors increasing the risk of postoperative hypocalcemia. Eighty three percent of all patients experienced hypocalcemia postoperatively, with 13 percent requiring some treatment for symptoms. Patients with advanced thyroid cancer, Graves' other manifestations disease, or of preoperative hyperthyroidism had significantly increased rates of hypocalcemia compared with patients with small cancers or benign euthyroid disease (Wingert et al, 1986) [8].

In this study there is 4 (10%) patients developed hypocalcemic manifestations and total & ionized calcium were at low level (below normal level) and treated by calcium gluconate 10% IV and manifestations started to improve rapidly after infusion.

The study of Okamoto et al. in 1990 [9], who underwent thyroid autotransplantation for five patients with Graves' disease after STT and followed them by technetium 99 uptake; they stated that: four of these patients (80%) showed normal Tc uptake at sites of implantation and none of them fell into overt hypothyroidism.

Also, the work of Shimizu et al., in 2002 [10]. Involved four patients with Graves' disease, who underwent autotransplantation of their own cryopreserved thyroid tissue after STT, only one patient (25%) developed recurrent hypothyroidism six months after autotransplantation.

In this study 80% (32 patients) of implants survived and functioned at variable times of follow up period as nine patients (22.5%)started functionalize to completely after one month of implantation and complete function with no need for further replacement therapy was encountered in thirty-two patients at 6 months of follow up. Another important work, which showed to some extent near results to those of this study, was the one performed by Roy et al. in 2003 [11] and involved 15 patients (eight with nodular goiter and seven with Graves' disease), six of the patients with nodular goiter (75%) became euthyroid, while only one of the patients with Graves' disease (14.3%) became euthyroid and did not need further postoperative replacement therapy.

Regarding the transplantation technique, some modifications were adopted similar to the pioneering work of Gauger et al. in 2000 [12], who invented a facilitated technique for parathyroid transplantation

inside the sternomastoid muscle (Gauger et al., 2000) [12]. The main principles of parathyroid transplantation were followed, which are slicing the gland and its implantation inside the muscles. The average parathyroid implant weight is about 40 mg only as compared to the thyroid auto-transplanted which weighed at least 10 g in this study. The usual technique of slicing and implanting the gland inside muscle pockets will result in too much amount of transplanted tissue per muscle pocket causing overcrowding of the implanted tissue that may hinder the transplanted tissue take and its survival. For this reason, the thyroid tissue to be transplanted is finely sliced and inserted into large muscle (the rectus femoris muscle). This large muscle would accommodate for the transplantation of this relatively large amount of transplanted tissue without overcrowding of the transplanted thyroid tissue. This modified technique of transplantation, which was also adopted by Mohsen et al. in 2015 [5] resulted in an obvious positive effect on the graft take and function.

In this study the effect of several factors as operative time, patient's age and time passage play an important role on the overall graft survival and function.

Duplex ultrasound as a follow up tool for detecting survival viability of the implanted thyroid at one month after implantation and as routine follow up also is a new tool experienced at this study. unlike other previous studies done for transplantation in which technetium 99 uptake was used to detect functional and viability of the implanted tissue as study done by Roy et al. 2003 [11] and study done by Mohsen et al., 2015 [5].

During the one-year follow-up period of the patients, thyroid function tests (FT3, FT4 and TSH) were assessed every two months. When clinical hypothyroidism developed for any patient, a minimum dose of 50 ug L-T4 replacement therapy was started for only one month and stopped one month prior to the next follow-up test. This minimum dose of replacement therapy improves the clinical manifestations of hypothyroidism without normalizing the patient's TSH level which is thought to play the most important role in enhancing growth and function of the transplanted tissue (Swan et al., 1967) [13].

In this study stoppage of this minimum dose of replacement therapy one month prior to the next follow up tests is very reasonable as the half-life of T4 is one week, T3 is one day and TSH is one hour, i.e., at this time of discontinuation, the patient is completely dependent on the function of the implanted thyroid tissue. By analyzing the results of this study, it is conceived that most of the patients had reached a clinical euthyroid state but with a state of subclinical hypothyroidism and hyperactivity of the pituitary gland.

In (Sakr et al., 2018) [1] one of the main concerns regarding thyroid auto transplantation is the risk of implanting malignant thyroid tissue. Despite the thorough preoperative clinical assessment, ultrasound guided FNAC, and intraoperative assessment of gland texture and color, the final pathological analysis showed papillary thyroid carcinoma (PTC) in 2 patients (12.5% of patients with Bethesda II score).

Campbell et, al 2015 [14] recently reported the presence of thyroid malignancy in 23.1% of multinodular goiters with benign preoperative FNAC. These 2 patients were readmitted to the hospital and the grafts were excised with a cuff of muscle tissue.

In this study post-operative (TT) histopathological examination of thyroid gland show no malignancy in all patients.

The two most common early complications of thyroid surgery are hypocalcemia (20–30%) and recurrent laryngeal nerve injury (5–11%). Bilateral recurrent nerve paralysis resulting in

adduction of the vocal cords is a rare lifethreatening complication (occurring in less than 0.1% of cases that requires emergency management (christou et,al 2013) [15].

In this study there was four patients developed hypocalcemia (10%) while one patient (2.5%) developed recurrent laryngeal nerve injury.

# 5. Future perspectives in this study

Clinical trial of thyroid auto transplantation is not a very famous technique, and more follow-up intervals of the patients must be considered to ensure more improvement of thyroid function tests specially TSH level and to determine whether the TSH level will improve by time or hyper functioning of the pituitary gland will be the terminal pathway.

Moreover, a proper follow-up of the implantation site must be done. to detect any change in the nature of the implanted tissue. Yearly US may detect goiter recurrence in the muscle, which although if happened, will be less likely to appear or compress any vital structures in the implantation relatively roomy site. Reoperation, if indicated, for removal of any future pathology of the transplant will definitely less hazardous than be reoperation in the neck.

The major issue raised in our study was whether to apply this transplantation technique for patients with Graves' disease or not. Further studies need to be done on larger populations of patients to document a proper statistically analyzed data.

# 6. Conclusion

Thyroid auto-transplantation is a safe and easy technique that provides survival and function of the thyroid graft achieving a postoperative euthyroid state in the majority of selected patients undergoing need TT without the for further administration L-T4 of replacement therapy.

Degree of graft function was variable and affected by different parameters; most important were age of the patient, preoperative gland pathology, and the operative time of the whole process. Best results were achieved in young patients with preoperative nodular disease in whom maximum weight of non-nodular healthy thyroid tissue was auto transplanted within a short period of time during the same session of TT.

Long-term follow-up of these patients is important specially the TSH level to guard against pituitary hyper-functioning and also of the implantation site to detect any change in the nature of the implanted tissue with time passage. For more evaluation in need higher numbers of patients and more follow-up.

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