

# Thyroid Function and Volume Changes in Patients with End Stage Renal Disease, Before and After Kidney Transplantation

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**D**isturbances of thyroid hormones metabolism and morphology are common in ESRD (End Stage Renal Disease) but data available shows discrepancies regarding the post transplantation status of kidney recipients. The aim of this study was to assess thyroid function and morphology after kidney transplantation surgery.

**Materials and Methods:** Thirty-two kidney recipient patients, without previous history of thyroid disorders, were enrolled. Serum levels of creatinine TT3, TT4, RT3U, TSH and thyroid staging were obtained and echogenicity were determined by ultrasonography one week before and 1, 3 and 6 months after kidney transplant surgery.

**Results:** Thirty-two patients (22 males, 10 females) with mean±SD of age 38.2±12.6 years were evaluated. TT3, TT4 and RT3U levels significantly increased by improvement of graft function ( $p < 0.05$ ) but in 7 patients with delayed graft function those values remained at lower levels. No cases with hyperthyroidism or hypothyroidism were detected. Thyroid volume decreased and echogenicity increased after transplantation ( $p < 0.05$ ). Six patients had thyroid nodules and cysts before surgery and 2 new cysts were detected after surgery. There was no relationship between age, sex, type and duration of dialysis and thyroid function after transplantation.

**Conclusion:** This study reveals a clear correlation be-

tween thyroid function and morphology (volume and echogenicity) and improvement of kidney function after transplantation; long-term follow-up is however required for evaluation of occurrence of thyroid nodules and malignancies following transplantation.

**Key Words:** Kidney transplantation, Thyroid Volume, Thyroid hormone, Goiter

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## Introduction

ESRD is a clinical situation in which the patient has a continuous dependency on dialysis due to improper functioning of the kidney. In most such cases, kidney transplant improves the life quality of the patient. Many studies have assessed changes in thyroid hormones and the related morphology in ESRD and a majority reported the hormonal changes to be TSH reduction, slow response of TSH to TRH injection, reduction or lack of diurnal rhythm, reduction in renal iodine excretion, disturbance in the clearance of hormones, serum level reduction for total and free T3 and T4, increase in rT3 and conspicuous augmentation in T3 sulfate concentration.<sup>1-4</sup> Moreover, some studies reveal

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more goiter and hypothyroidism incidence among ESRD patients than in the normal population;<sup>5-6</sup> there are some discrepancies in data on thyroid disorders (hypothyroidism in particular), volume changes and occurrence of thyroid neoplasms after graft transplantation. A few studies document changes in morphology and thyroid function after kidney transplantation and results show that during the first week after transplantation, total and free T3 is at its lowest level causing the patient to experience low T3 syndrome, a condition which recovers by improvement in transplanted kidney function and reduction of serum creatinine level.<sup>7-9</sup> However, in the case of chronic rejection of transplantation or delayed functioning of the transplanted kidney, hormone levels remain at their lowest. As a matter of fact, a significant and inverse relation between serum T3 and creatinine level (as an index of kidney function) has been justified.<sup>10-11</sup> Besides, transplant recipients undergo long term treatment with immunosuppressive medications, especially Cyclosporine that may reach toxic dose due to malfunctioning of thyroid which unfortunately could result in transplant rejection.<sup>12</sup> In addition, long term use of such medications may cause goiter and drug related tumors like benign and malignant neoplasm of the thyroid as well.<sup>13-15</sup>

Lebkowska et al performed a comparative study on the morphology and thyroid function of kidney transplant recipients, patients on peritoneal or hemodialysis and the normal population. The study showed that 100% of patients after kidney transplantation had goiter, 43% of the patients possessed thyroid nodule after transplantation of which 28% were diagnosed with thyroid cancer, and they also found a significant association interrelation between Cyclosporine level and the occurrence of goiter.<sup>16</sup> Furthermore, Tauchmanova et al studied 50 recipients during an average period of 23 months of follow-up in Italy, and reported 6% hypothyroidism, 24% thyroid nodule and 8% thyroid cyst.<sup>17</sup>

Considering the recent boom in kidney transplant in Iran, and existing controversies about thyroid function after surgery, this study was conducted to investigate the changes in hormone levels and assess thyroid function and morphologic changes prior to and during the early months following kidney transplantation.

## Materials and Methods

Between March 2004 and February 2005, all patients with chronic renal failure with GFR <10 cc/min, who were under observation at the Nephrology Clinic of Shaheed Modarres General Hospital and were candidates for kidney transplantation, were investigated. Exclusion criteria were previous history of thyroid diseases (hyperthyroidism-hypothyroidism), use of thyroid affecting medications (thiamides, thyroxine, steroids) or detection of thyroid disease by thyroid function test before, and acute graft rejection or death after surgery. All patients were fully informed regarding the research and rendered their written consent correspondingly.

At the beginning, a questionnaire was filled up for each patient to obtain personal demographic information, duration of the renal failure, duration and type of the supportive dialysis, and records of a systemic examination. Afterwards, patients were visited one week prior to the surgery, and after the first, third and sixth months following transplantation; at each visit, the patient was examined by an endocrinologist for clinical manifestations of hypothyroidism or hyperthyroidism; simultaneously size of the thyroid was classified according to WHO standards (Stage 0-I-II).<sup>18</sup> At this visit, 5 mL of venous blood samples were also obtained for laboratory examinations. Tests were conducted for TSH (0.3-4 mU/L) using IRMA method, RT3U (25%-35%), TT4 (4.5-12.5 µg/dL), TT3 (80-200 ng/dl) using RIA method by means of a Hungarian Lab Isotope kit, and Creatinine level (0.5-1.4 mg/dL) using Jaffe reaction method. Finally, each patient were examined by an

expert sonologist for the volume, echogenicity aspects and nodules of the thyroid using a Japanese sonography set, Fukuda Denshi UF 7700, and a 7.5 MHz probe.

Normal echogenicity was defined as a tissue echogenicity more than the strap muscle echogenicity of neck. An echogenicity equal to or less than the echogenicity of the aforementioned muscle is known as hypoecho-genicity.<sup>19</sup>

Thyroid volume was calculated by adding the volume of both lobes in cubic millimeters. Volume of each lobe could be calculated using the formula given, after measurement of anteroposterior (a), transversal (b) and longitudinal (c) dimensions:<sup>20</sup>

$$\text{Volume of each lobe} = a \times b \times c \times (\pi / 6)$$

After transplantation, each patient was put on a one month course of three distinctive medications. During the first three days, intravenous Methylprednisolone pulse (500 mg/day) was administered, followed by Prednisolone tablets (40–60 mg/day) for one month, tapered towards the end. Simultaneously, from the first day, Azathioprine tablets (100–150 mg/day) and Cyclosporine tablets (3–5 mg/kg/D) were administered as well. Based on renal activity, the patients were divided into two groups; group I included the patients with an appropriate primary graft function and group II, the patients with delayed graft function. In addition to the mentioned protocol of the above medications, these patients were also treated by supportive dialysis or high doses of immunosuppressives administered according to the nephrologist's corresponding diagnosis. If needed, keeping in mind the case conditions and requirements, insulin and antihypertensive drugs were also administered.

**Statistical Analysis:** Quantitative variables are given as mean±SD and qualitative ones by number and percentage. For the comparison of qualitative variables, before and after transplant, paired T-test has been used. To compare the thyroid stage before and after transplantation McNemar test was used,

P<0.05 being considered significant. Statistical analysis was done using SPSS V.13 software.

## Results

In this study, 35 patients with ESRD, kidney transplant candidates were enrolled; three died due to severe sepsis and myocardial infarction within few days of surgery and 32 ESRD (22 men and 10 women) patients were investigated following transplant until the end of the sixth month; mean±SD of age in this group was 38.2±12.6 years (18–60 years), 39.3±10.2 years for men and 38.1±8.1 years for women (P=NS).

Two patients had no history of dialysis before transplant; two patients had received peritoneal dialysis and the rest (87.5%) were hemodialysis patients; the mean ± SD for duration of dialysis was 18.2±8.1 months. Tests revealed no thyroid function disturbances, hyperthyroidism or hypothyroidism, in any of the patients before surgery. Twenty-five patients (78.1%), group I, demonstrated appropriate transplant renal function, seven patients (21.9%), group II, showed delayed graft function (Group II), and no case of kidney rejection was observed. One month after transplant, mean±SD of serum creatinine levels decreased remarkably compared to before surgery levels (p<0.001) and this trend continued in the following months (Table 1). Table 2 shows a comparison of mean±SD of thyroid hormone levels and their volume before and after transplantation.

**Table 1. Changes of serum creatinine level before and after first, third and sixth months of kidney transplantation**

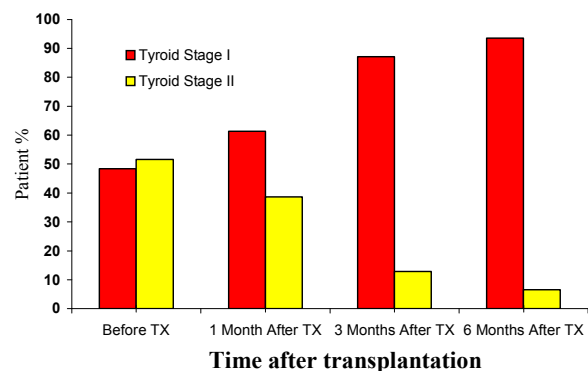
Time of surgery	Mean	SD
Before	8.393	3.34
First month	1.652	0.56
Third month	1.578	0.82
Sixth month	1.394	0.49

**Table 2. Comparison of mean±SD of thyroid hormones and volume before and after first, third and sixth months of kidney transplantation**

Time of surgery Variables	Before	First month	Third month	Sixth month
T3 (ng/dL)	89.6±40.9	96.3±29.3	109.6±35.0*	134.4±35.8*
T4 (µg/dL)	6.2±2.2	6.5±1.8	6.9±2.7	7.6±1.9*
RT3U (%)	28.3±3.3	32.4±2.0*	32.0±2.7*	32.3±2.7*
FTI	1.6±0.5	2.0±0.5*	2.1±0.7*	2.4±0.6*
TSH (mU/L)	1.6±0.9	0.3±0.1*	1.0±0.9*	1.0±0.4*
Thyroid volume (mm <sup>3</sup> )	12.1±6.0	10.6±5.3*	10.1±6.1*	10.2±8.1*

\* P < 0.05, compared to values before transplantation.

Mean±SD for TT3 level after transplant showed an escalating trend which after months 3 and 6 became statistically significant ( $p < 0.05$ ); the mean±SD of TT4 level also increased gradually after surgery and became statistically significant after the sixth month ( $p < 0.05$ ). Mean±SD of RT3U showed a statistically significant increase after transplant, compared to pre-transplant values, at all three stages of patient visits ( $p < 0.05$ ). Mean±SD of serum TSH level showed a notable decrease at all three visits in comparison with pre-transplant values. No case with hyperthyroidism or hypothyroidism was observed after surgery. In the study group, mean±SD of thyroid volume prior to transplant was  $12.6 \pm 6$  mm<sup>3</sup> which showed a significant decrease from the first month till the end of the study, compared with the pre-transplant values ( $p < 0.05$ ). Thyroid of one patient was not palpable (Stage=0), before and after the transplant. Among the rest of the recipients ( $n=31$ ), 48.4% were classified as stage I and 51.6% as stage II, prior to transplant surgery. After transplantation, there was a clear reduction in thyroid stage, the change being significant from the third month ( $p < 0.001$ ). After the sixth month 93.5% were classified as stage I and only 6.5% as stage II ( $p < 0.001$ ) (Fig. 1).



**Fig.1. Comparison of thyroid staging (based on WHO classification), before and after first, third and sixth months of kidney transplantation**

\* P=0.125 in comparison with the values before  
 \*\* P<0.001 in comparison with the values before

Before surgery, <sup>23</sup> (71.9%) showed normal thyroid echogenicity and 9 others (28.1%) had hypoechogenicity, which improved in the next few months, with 16.1% hypoechogenicity and 83.9% normal echogenicity being seen by the sixth month; changes however were not statistically significant.

Four patients had thyroid nodules and 2 cases had thyroid cysts, all less than 2 cm in dimension, with benign FNA results. At the first month examination, two new cysts (6 and 8 mm) were observed in two patients, a

condition that remained unchanged in number or dimensions at follows ups.

Patients of group II demonstrated a reduction in mean $\pm$ SD of T3 and T4 level in comparison to group I at the first month examination; both groups showed similar values at

the sixth month (Fig. 2). Due to the limited number of individuals in group II, no statistical analysis was performed. No significant relation was seen between age, sex, dialysis type and duration was found in relation to thyroid function, prior to and after transplantation.

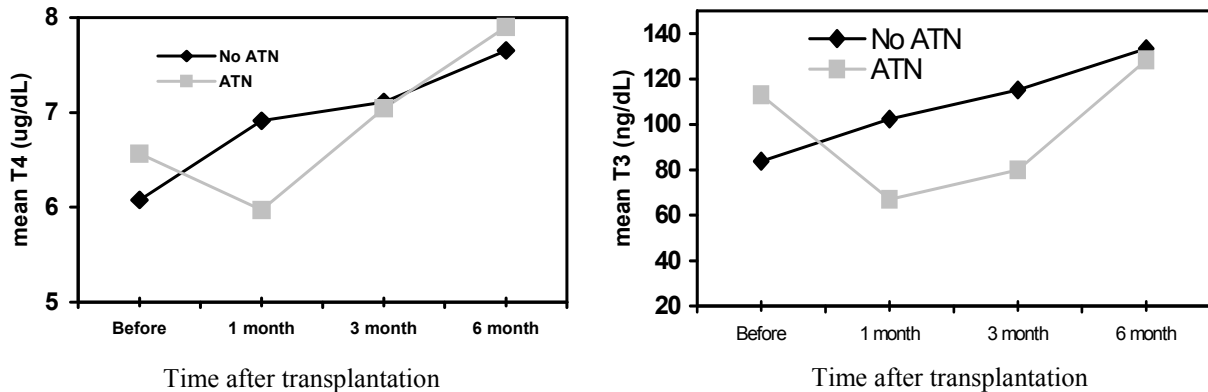


Fig. 2. Changes of mean serum T3 (ng/dL) and T4 ( $\mu$ g/dL) levels before and after surgery, in patients with and without post-transplant acute tubular necrosis(ATN)

## Discussion

While patients with ESRD demonstrate no signs of thyroidal disorders, mostly are afflicted with thyroidal hormone changes viz. non thyroidal illness which is caused by disturbances in hormone bindings due to increase of binding inhibitors such as Hippuric Acid in uremic serum or deiodinase inhibitors; kidney transplantation and restoration of normal clearance cause an obvious improvement of this disturbance.

Lebkowska et al studied<sup>17</sup> patients during the first 10 days after kidney transplantation and their comparison with 18 normal persons showed that free T3 serum level during the first 6 days after surgery dropped to the lower normal level and on the 10th day, following

improvement in kidney function, increased significantly.<sup>21</sup> Most of the studies after kidney transplantation, during the first month, showed a clear and inverse relationship between serum T3 and T4 and creatinine level as a kidney functioning index. It has also been confirmed that in case of acute graft rejection or delayed graft functioning, serum T3 remained at low levels and the patient experiences low T3 syndrome, and that by gradual improvement in kidney function, T3 level also increases.<sup>4</sup> Zarghami et al's study of 30 patients on the 10th and 30th days after transplant, reported that in the group of patients with rapid improvement in renal functioning, all hormones levels reached the normal values during the first 30 days. On the other hand, in the group, which demonstrated

delayed graft function, hormones levels consistently remained at low normal level with significant differences compared to the first group.<sup>22</sup>

Though our study initially assessed hormone levels from the first month, it confirmed that by improvement in thyroid functioning of the transplanted kidney and rapid decrease in serum creatinine, average levels of TT3, TT4 and RT3U showed significant increase in comparison with pre-transplant values. Serum TSH level also showed a marked fall caused by high dose corticosteroid administration during first month; that and a reduction in steroid dose during the next months, caused a considerable raise in TSH level (Table 2). Furthermore, comparison of hormones levels between group I (appropriate primary graft function) and group II (delayed graft function) showed that TT3 and TT4 levels in group II were lower, reaching levels similar to those of group I after improvement of transplanted kidney function (Fig. 2). In this project, neither hypothyroidism nor hyperthyroidism were observed. Other studies have reported conflicting results; majority of them did not report any specific functional disturbances while some reported increase in the incidence of hypothyroidism after kidney transplantation.<sup>17</sup>

The present study showed that kidney transplantation, not only results in only a decreasing trend in thyroid volume and stage, but also in thyroid echogenicity augmentation during the six month period, and that these changes, in particular for thyroid volume and staging were significant in comparison with pre-transplant conditions; this is in agreement with the results of previous studies<sup>23</sup> on thyroid morphology and function following transplant surgery.

Lebkowska et al, in a short-term investigation, assessed 32 patients during a 10 day-period after transplantation by focusing on thyroid morphology aspects, utilizing sonography. They showed a significant relation between mean thyroid volume changes and creatinine values.<sup>24</sup> In another survey, this

group studied 46 patients in a long-term follow-up (average period of  $45 \pm 37$  months) after transplantation and found a close association between thyroid volume and serum creatinine; the latter study found a close relationship between free serum T3 and creatinine levels as well.

In our study, 6 patients had thyroid nodules and single benign cysts before surgery and 2 cases of simple cyst were also observed after transplantation, which showed no notable size change during the study. A few studies have investigated long-term studies on thyroid morphology after transplantation, and they have reported increase in nodule incidence.<sup>12-13</sup> Concerning the pathological nature of nodules, contradictory information exists. Tauchmanova et al followed 50 cases of successful transplantations in Italy during an average period of 23 months and recorded 24% nodules and 8% cysts incidences; all benign in nature. They found out that nodule and cyst incidence were related to previous uremia and dialysis durations.<sup>17</sup> It should be mentioned that the majority of studies that reported the occurrence of malignant thyroid nodules after kidney transplantation, had long-term follow-ups. Use of immunosuppressive medications, in particular Cyclosporine has been mentioned as the reason which in turn causes not only thyroid cancer, but also increases the risk of malignancy among other organs such as skin, lymphatic system and liver.<sup>26-28</sup> A 50 month follow-up study kept 32 recipients under observation after transplantation; 17 cases (51%) had single or multiple nodules including 5 cases of papillary thyroid carcinoma. This research determined a positive correlation between cyclosporine levels and incidences of nodule and malignancy.<sup>13</sup> All of these studies had a long follow-up period with a minimum observation time of 2 years. Our study revealed only 2 cyst cases; hence, the 6 months follow-up period could be known as a major limitation of our study which does not give us an acceptable back-up for nodule incidence justification. Lack of feasibility for rT3 measure-

ment has been another limitation of this research.

Finally it could be concluded that after successful kidney transplantation, the changes in hormone levels, volume and echogenicity of thyroid indicate improvement; in addition, serum T3 and T4 levels are closely related to functioning of the transplanted kidney. It is worth mentioning that kidney transplantation was found to have no influence on the incidence of thyroid function disorders.

It is recommended that a research with long-term follow-up be designed focusing on the effect of immunosuppressive medications on thyroid morphological changes including nodule and cancer incidence probabilities.

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