Thyroid Hormone Changes in Early Kidney Transplantation and Its Correlation with Delayed Graft Function

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Introduction: Thyroid hormones affect kidney function and may alter with changes in kidney function, as well. We evaluated changes in serum levels of triiodothyronine (T3), thyroxin (T4), and thyroid-stimulating hormone (TSH) early after kidney transplantation and their relationship with delayed graft function (DGF).

Materials and Methods: Fifty-five consecutive kidney allograft recipients were enrolled in the study. Serum levels of T3, T4, and TSH were measured on the day before transplantation, and also on posttransplant days 1, 3, 7, 14, and 21. Results were compared between patients with a normal allograft function and those with DGF.

Results: The mean T3 level decreased from 110.41 ± 49.79 ng/dL before transplantation to 80.78 ± 51.42 ng/dL on the 1st day after transplantation (P = .04), while T4 reduction reached a significant level on the 3rd day after transplantation (8.27 ± 3.27μg/dL to 5.50 ± 2.57 μg/dL, P = .004). Patients with DGF experienced a significantly greater decrease in the serum level of T3 at the end of the 1st week after transplantation compared with patients with normal kidney function (P = .02). This significant decrease in T3 continued until the end of the 2nd week. Serum levels of T4 reduced comparably in the two groups, until the end of the 1st week, when it showed a significantly more reduction in the patients with DGF (P = .04).

Conclusion: Both T3 and T4 reduced early after kidney transplantation, and this reduction was significantly more prominent in those with DGF. This is compatible with a consequence rather than a cause of DGF, explained in the setting of sick euthyroid syndrome.

Urol J. 2010;7:30-4.
www.uj.unrc.ir

Keywords: delayed graft function, kidney transplantation, thyroid function tests

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Received February 2009
Accepted November 2009

INTRODUCTION

Thyroid hormones affect the functions of a number of organs, and these may alter the kidney function, as well. On the other hand, the thyroid gland function may be influenced by kidney dysfunction.[1-3] Patients with end-stage renal disease may suffer from elevated thyroid-stimulating hormone (TSH) levels, reduced TSH response to thyroid-releasing hormone, and reduced serum total and free triiodothyronine (T3) and thyroxine (T4) values, in the absence of a primary thyroid disease.[1,2] Then again, these patients may develop goiter, thyroid nodules, thyroid carcinoma, and hypothyroidism.[2]

Kidney transplantation alleviates these changes, but it can also affect thyroid function in the presence of different conditions a kidney transplant recipient may experience.[4]

In this study, we evaluated T3, T4, and TSH changes early after kidney transplantation, and the relationship of these changes with the occurrence of delayed graft function (DGF). In hope of finding a correlation between DGF and thyroid hormone changes measured by routine and simple thyroid function assessment tests available in all laboratories, we purposefully decided not to perform more complicated thyroid function tests such as reverse T3 and T3 resin uptake.

MATERIALS AND METHODS

Fifty-five kidney transplant candidates were consecutively selected to enroll in this cross-sectional study. Thirty-seven patients were living donor allograft recipients and the remaining 18 received a cadaveric kidney graft. The study was approved by the ethics committee of the university and the patients provided informed consent.

Before transplantation, all of the patients were on hemodialysis. Immunosuppression after transplantation consisted of cyclosporine, mycophenolate mofetil, and prednisone. Serum levels of T3, T4, and TSH were measured on the day before transplantation, and also on the 1st and 3rd days and at the end of the 1st, 2nd, and 3rd weeks after transplantation, using radioimmunoassay method. In search of the relationship between kidney allograft function and thyroid hormone changes, serum levels of T3, T4, and TSH on the day before transplantation (baseline) were compared with each consequent posttransplant measurement in all patients. Also, T3, T4, and TSH levels were compared between patients with normal immediate kidney function and those with DGF. Delayed graft function was defined as a decrease in the serum creatinine level of at least 10% per day for at least 3 consecutive days during the first week after transplantation.

We used the paired *t* test for comparisons of the T3 and T4 levels in patients with and without DGF in each subsequent measurement in relation with before transplantation. Due to non-normal distribution of TSH serum levels, the Mann Whitney *U* test and the Wilcoxon sum rank test were used for comparing its serum level in the two groups and its changes in each measurement after transplantation in comparison with those before transplantation, respectively. General linear model repeated measurement analysis was used for overall significance of T3, T4, and TSH changes in the six measurements.

RESULTS

A total of 55 kidney recipients (34 men and 21 women), with a mean age of 34.41 ± 15.47 years, were included in the study. The kidney allograft resumed normal function in 47 patients (85.5%), while in 8 patients (14.5%), its function was delayed due to acute rejection in 2 and acute tubular necrosis (ATN) in 6. Baseline thyroid function studies, including serum levels of T3, T4, and TSH, were similar between the two groups of patients with normal graft function and DGF.

Repeated measurement analysis showed highly significant changes in T3, T4, and TSH through the 6 measurements ($P < .001$). The mean T3 level decreased from 110.41 ± 49.79 ng/dL on the day before transplantation to 80.78 ± 51.42 ng/dL on the 1st day after transplantation ($P = .04$). This trend continued until the end of the 2nd week after transplantation. Serum level of T4 decreased from 8.27 ± 3.27μg/dL before transplantation to 6.92 ± 3.72 μg/dL on the 1st posttransplant day ($P = .09$). This trend in T4 concentrations reached a significant level on the 3rd day after transplantation (4.55 ± 2.57 μg/dL, $P = .004$); however, T4 levels reached the pretransplant levels at the end of the 3rd week after transplantation.

Patients with DGF experienced a significantly greater decrease in the serum level of T3 at the end of the 1st week after transplantation compared with patients with normal kidney function ($P = .02$; Table 1). This significant decrease in T3 continued until the end of the 2nd week. Serum levels of T4 reduced comparably in the two groups, until the end of the 1st week, when it showed a significantly more reduction in the patients with DGF (Table 1).

Table 1. Changes in Triiodothyronine (T3) and Thyroxin (T4) After Kidney Transplantation in Recipients With and Without Delayed Graft Function

	Delayed Graft Function		
Laboratory Study	No	Yes	*P*
T3, ng/dL			
Baseline	106.2 ± 40.85	121.62 ± 30.99	.33
Day 1	90.64 ± 41.64	85.00 ± 43.49	.71
Day 3	86.53 ± 35.06	83.05 ± 21.09	.77
Day 7	85.18 ± 35.39	57.90 ± 15.86	.02
Day 14	82.54 ± 26.44	78.75 ± 23.81	.67
Day 21	91.13 ± 28.79	93.79 ± 34.57	.81
T4, µg/dL			
Baseline	8.36 ± 3.06	8.55 ± 3.25	.88
Day 1	7.68 ± 2.84	7.24 ± 3.75	.68
Day 3	6.80 ± 2.94	5.49 ± 1.90	.16
Day 7	6.41 ± 2.32	4.69 ± 2.86	.04
Day 14	6.54 ± 2.28	5.03 ± 1.13	.04
Day 21	7.88 ± 3.35	6.56 ± 2.72	.23

Serum levels of TSH began to decrease significantly from the 1st day after transplantation compared with the baseline values ($P < .001$; Table 2). This trend continued to the end of the 3rd week after transplantation when serum TSH level returned to the pretransplantation level. Comparing TSH levels in patients with and without DGF, TSH levels decreased on the 1st day after transplantation in both groups, but significantly reduced TSH level continued until the end of the 3rd week after transplantation only in the kidney allograft recipients with normal kidney function, but returned to normal in the patients with DGF on the 3rd day after transplantation (Table 3).

We compared serum TSH levels between the patients who received antithymocyte globulin (ATG) and those with no ATG administration; The significant reduction of TSH level in those with ATG continued to the end of the 3rd week, while in patients who received ATG, TSH returned to the pretransplantation levels after 1 week. There were no associations between donor source, age, gender, and the underlying disease and the thyroid hormones before transplantation and their changes after transplantation.

Table 2. Thyroid-Stimulating Hormone (TSH) Levels Before and After Transplantation

TSH Measurement	TSH, IU/mL	*P**
Baseline	1.94 ± 0.89	…
Day 1	1.09 ± 0.76	< .001
Day 3	0.95 ± 0.90	< .001
Day 7	1.04 ± 0.79	.01
Day 14	1.86 ± 2.89	.02
Day 21	1.78 ± 0.40	.15

**P* values are related to the comparisons between TSH level of that measurement (the respective row) with the previous one.

Table 3. Changes in Serum Thyroid-Stimulating Hormone (TSH) Levels Compared to Baseline Level Before Kidney Transplantation in Recipients With and Without Delayed Graft Function

	Normal Kidney Function		Delayed Graft Function	
TSH Measurement	Mean Change, IU/mL	*P*	Mean Change, IU/mL	*P*
Day 1	-3.18	.001	-2.11	.04
Day 3	-4.17	< .001	-1.76	.08
Day 7	-3.97	< .001	-0.94	.35
Day 14	-2.28	.02	-0.92	.36
Day 21	-2.96	.003	-0.54	.59

DISCUSSION

Our finding, the moderate reduction of serum T3 and T4 levels on the 1st and 3rd days after transplantation, is compatible with sick euthyroid syndrome (SES). Due to the rather shorter T3 half-life in comparison with the half-life of T4, reduction of T3 began earlier than T4.[3] Using the same way of reasoning, earlier return of T3 serum level (at the end of the 1st week) compared with T4 can be explained. In the SES (low serum levels of T3, T4, TSH, or all the three), high endogenous catecholamine levels may stimulate preferential tissue conversion of T4 to the nonactive reverse T3 rather than to the active free T3.[4] Plasma T3 levels, therefore, drop precipitously. There is evidence that low T3 states occur immediately after kidney transplant due to the stress of the operation, infusion of high-dose intravenous methylprednisolone, and hypothermia. The continuation of significantly reduced T3 in patients with DGF into the second week after transplantation may be regarded as a cause or consequent of failed graft function; regarding the nonsignificant difference in T3 serum level between the two groups before transplantation, we hypothesize that DGF leads to continuation of uremic state, administration of higher doses of methylprednisolone, more severe reperfusion injury, and inflammation, all impairing conversion of T4 to T3.

Lebkowska and colleagues found that the free T3 concentration correlated with function of the kidney allograft.[6] They suggested that in transplant patients, the supplementary thyroid hormone therapy should be considered.[6] In another study, a positive correlation was found between changes in serum concentration of free T4 and changes in serum creatinine ($r = 0.73$; $P < .001$).[7] Reinhardt and colleagues showed that T3 concentrations reflected kidney allograft function after kidney transplantation. Serum T3 was below the normal limit in patients with DGF (acute kidney failure or acute rejection). The postoperative period (up to 3 days after transplantation) was associated with a low T3 syndrome. Thyroid-stimulating hormone did not return to the pre-operative values, even in patients with primary graft function.[8] Recovery in the hormonal status did not start in the first week of posttransplant period. A significant transient decrease in TSH, free T3, and free T4 concentrations following kidney transplantation has been reported in kidney allograft recipients.[9] However, comparing thyroid hormone changes in donors and recipients immediately after transplantation, T3 changes observed in donors and recipients were similar, indicating that the hormonal changes observed are mostly due to surgical stress.[10]

In our study, acute tubular necrosis was the prevalent cause of DGF (in 6 cases). Regarding TSH serum level changes, reduced TSH level continued until the end of the 3rd week after transplantation only in the kidney recipients with normal kidney function, but returned to normal in patients with DGF on the 3rd day after transplantation. This cannot be due to relative smallness of the DGF group (type 2 error), regarding the reversed results obtained when comparing T3 in the two groups, also this fact that in all patients, significantly reduced TSH serum level in those who had received no ATG continued to the end of the third week, while in ATG-administered ones returned to the pretransplantation level after 1 week. We hypothesize this may be a falsely elevated level due to ATG administration and the presence of antimouse or antihorse antibodies in the serum of these patients results in falsely elevated TSH values when using radioimmunoassay method for TSH measurement. Indeed, 4 patients in the DGF group had received ATG. The same reason for falsely elevated TSH serum level in transplanted patients was proposed by Seghers and colleagues.[11] We were not able to repeat the TSH determination in the presence of normal horse serum and obtain a true TSH value. Fractionation of the serum with protein-A chromatography, to detect the falsely elevated TSH measured by immunoreactivity, was not performed either.[11]

CONCLUSION

Both T3 and T4 levels decreased early after kidney transplantation. When considering the effect of DGF on thyroid hormones changes, T3 and T4 significantly reduced in patients with DGF compared with normal-functioning kidney transplant group. This significantly greater reduction in T3 and T4 in the DGF group, despite no significant difference between the two groups before transplantation, is more compatible with a consequence rather than a cause of DGF occurrence, explained in the setting of SES. Continuation of the reduction in TSH level in patients with normal kidney function early after transplantation until the end of the 3rd week in spite of its return to normal level in DGF-inflicted patients can be ascribed a falsely elevated level due to ATG administration and the presence of antimouse or antihorse antibodies in the serum of these patients with DGF, resulting in falsely elevated TSH values, when using radioimmunoassay method for TSH measurement.

CONFLICT OF INTEREST

None declared.

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