大韓核醫學會誌：第28卷 第 2 號 1994

The Changes in Serum TSH-Binding Inhibiting Immunoglobulin (TBII) Activity and Thyroglobulin Level after Treatment with Radioactive Iodine (^{131}I) in Graves' Hyperthyroidism

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=국문초록=

그레이브스 갑상선기능항진증 환자에서 방사성 옥소(^{131}I) 투여 후 혈청 갑상선자극 면역글로불린 (Thyrotropin-Binding Inhibiting Immunoglobulin, TBII)활성도 및 Thyroglobulin의 변화

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그레이브스 갑상선기능항진증은 자가면역질환의 하나로 방사성 옥소가 간편하고 경제적이며 효과적인 치료법임이 알려져 있는데 방사성 옥소 투여 후 갑상선 조직의 자극 및 파괴에 따라 각종 항원의 노출의 증가와 이에 대한 자가항체의 변동이 예상된다. 저자들은 추정 갑상선 무게를 고려한 6-10 mCi의 방사성 옥소를 투여 받은 그레이브스 갑상선기능항진증 환자 90명을 2년간 추적하여 치료 전 후의 혈청 갑상선자극 면역글로불린(TBII)활성도와 thyroglobulin 및 antithyroglobulin antibody의 변화를 관찰하였다.

1) 대상환자 90명의 연령분포는 14-58세(중앙치 30)였으며 여자가 72명(80%)이었다.

2) 평가대상 환자 중 치료 전 TBII 활성도가 정상범위였던 경우는 15명(30%)이었고 증가된 경우는 35명(70%)이었다. 치료 전보다 치료 3개월 후에 TBII 활성도가 더 증가된 경우는 31명(62%)이었다.

3) TBII 활성도가 치료 전에 증가하였거나, 치료 전에 정상범위였다가 치료 3개월 후에 증가한 환자의 TBII 활성도의 동태는 치료 3개월 후에 가장 높았고 그 후 점차 감소하였다. 이들의 TBII 활성도가 15%이내로 정상화된 정도는 치료 후 6개월에 40%, 12개월에 82%였다.

4) 치료 전 antithyroglobulin antibody가 양성인 경우 80%에서 3개월 후에도 혈청 thyroglobulin의 동태는 치료 3개월 후에 높았다가 증가가 없었으며 치료 전 antithyroglobulin antibody가 음성인 경우 60%에서 치료 3개월 후에 혈청 thyroglobulin의 증가가 있었다.

5) antithyroglobulin antibody가 음성인 경우의 혈청 thyroglobulin의 동태는 치료 3개월 후에 높았다가 점차 감소하는 경향을 보였으며 antithyroglobulin antibody가 양성인 경우의 혈청 thyroglobulin의 동태는 치료 후 시간이 지남에 따라 점차 감소하였다.

6) 치료 전 antithyroglobulin antibody가 음성인 경우 치료 후 시간 경과에 따라 동시에 측정한 혈청 TBII 활성도와 thyroglobulin 사이에는 통계적으로 유의한 상관관계가 있었다($p<0.01$). 한편 치료 전 antithyroglobulin antibody가 양성인 경우 치료 후 시간 경과에 따라 동시에 측정한 혈

청 TBII 활성도와 thyroglobulin 사이에는 통계적으로 유의한 상관관계가 없었다(p=0.16).

이상의 결과로 방사성 옥소를 투여 받은 그레이브스 갑상선기능항진증 환자에서 혈청 TBII 활성도는 항갑상선제를 투여 받은 경우와는 달리 초기에 증가하였다가 시간이 지남에 따라 점차 감소함을 알 수 있었으며 그 감소 정도는 항갑상선제만을 쓴 경우보다 더 빠를 것으로 생각된다. 따라서 혈청 TBII 활성도와 thyroglobulin은 방사성 옥소 치료효과의 관찰에 중요한 역할을 할 것으로 생각되며 특히 antithyroglobulin antibody가 음성인 경우 혈청 thyroglobulin은 혈청 TBII 활성도를 반영할 것으로 사료된다.

Key Words: Hyperthyroidism, TBII, Radioactive Iodine

INTRODUCTION

Graves' hypethyroidism is an autoimmune disease characterized by high titers of autoantibody against thyropin(TSH) receptor or thyrotropin-binding inhibiting immunoglobulin(TBII).[1,2] With treatment with antithyroid drug, TBII activity decreases gradually[3,4,8] and the extent of decrease to normal range is greater in patients treated with higher dosages of antithyroid drug than in one with lower dosages[5]. On the othere hand, ther are some reports demonstrating further increase followed by decrease and normalization of TBII activity in patients treated with radioactive iodine[4,6].

Thyroglobulin is a major protein in thyroid follicles and it can be elevated not only by destruction of thyroid follicles but also by stimulation of TSH or TBII[7]. Thus thyroglobulin can reflect the activity of autoimmune process. But the autoantibody against the thyroglobuin in the serum may affect the serum throglobulin level.

We measured TBII activity and thyroglubulin level after treatment with radioactive iodine in Graves' hyperthyroidism to evaluate the effect of radioactive iodine on the TBII activity and thryoglobulin level and to observe whether thyroglobulin level can reflect the elevated TBII activity, or not.

MATERIALS AND METHODS

Patients

90 patients who were diagnosed as Graves' hyperthyroidism in Korea Cancer Center Hospital from July 1991 to March 1992 by clinical symptoms in conjunction with appropriate laboratory examination including thyroid scan, TBII activity, and titers of TSH, T3, T4, or free T4 were enrolled(Table 1).

Dose of ^{131}I

Selected dose of ^{131}I according to the thyroid weight which did not reflect thyroid uptake(modified fixed dose)was administered to patients (Table 2). Thyroid function was evaluated every 3 months for 2 or more years after radioactive iodine therapy.

Measurement of TBII Activity and Thyroglobulin Level

TBII activity was measured by radioreceptor assay and was calculated as percentage of inhibition of the binding of radiolabeled TSH to the TSH receptors by

Table 1. Patients' Characteristics

Characteristics	(%)
· Patients No.	90
male	18(20)
female	72(80)
· Age(Median)	14-58(30)

Table 2. Treatment Scheme

- Dose of ^{131}I : modified fixed dose method
- Dose according to estimated weight which does not reflect RAI uptake of thyroid
  - 60 gm → 6 mCi
  - 80 gm → 8 mCi
  - 100 gm → 10 mCi
- Duration of follow up
  : every 3 months for 2 years

the following equation. TBII activity was considered as increased or positive if it exceeds 15%.

$$\text{TBII activity}(\%) = \frac{\text{labeled TSH specifically bound in the presence of test sample}}{\text{labeled TSH specifically bound in the presence of negative serum}} \times 100$$

Thyroglobulin level was measured by the sandwich radioimmunossay method and was considered as increased if it exceeds 60 ng/mL. Statistical analysis of significant differences between groups was performed by means of Student's t test and a p value of less than 0.05 was considered statistically significant.

RESULTS

Trends of TBII Activity

Before treatment, 15 patients(30%) showed normal range of TBII activity, and 35 patients(70%) showed elevated TBII acitvity. Further increase in TBII activity was demonstrated in 31 patients(62%) after treatment(Table 3). The TBII activity after radioactive iodine treatment increased maximally in 3 months and gradually declined to normal range. 40% of patients had the normalized serum TBII activity in 6 months after treament, and 82% in 12 months(Fig. 1).

Trends of Thyroglobulin Level

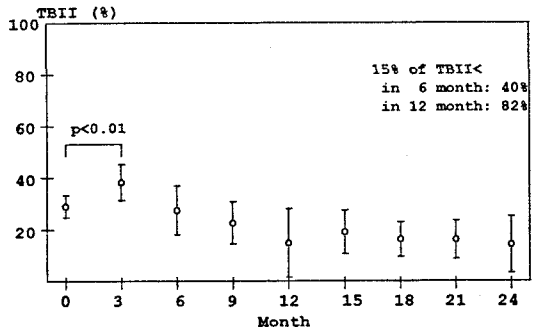
In 30 patients with positive antithyroglobulin antibody, 25 patients(80%) showed no significant change in the serum thyroglobulin level in 3 months after radioactive iodine therapy. In 12 patients without antithyroglobulin antibody, the initial serum thyroglubulin levels were higher than those of patients with positive antithyroglobulin antibody, and

Table 3. Trend of TBII Activity

Before Treatment	3Months after Treatment		Total
	No change or Decrease	Further Increase	
Normal range	2	13	15
Increased	17	18	35(70%)
Total	19	31(62%)	50

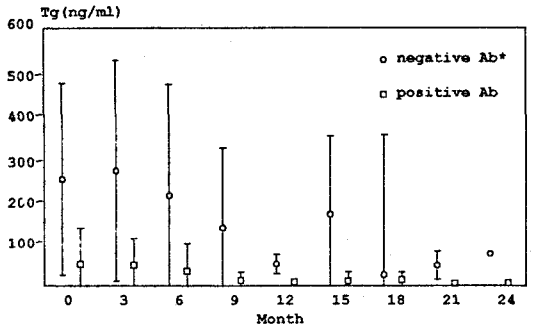
Table 4. Trend of Thyroglobulin

Before Treatment	3Months after Treatment		Total
	No change or Decrease	Further Increase	
TaAb*(+)	25(80%)	5	30
TgAb(—)	5	7(60%)	12
Total	30	12	42



* antithyroglobulin antibody

Fig. 1. The trends of the serum TBII activity after radioactive iodine treatment demonstrated maximal increase in 3 months and gradual declining to normal range, and the extent of normalization was 40% in 6 months and 82 % in 12 months.



* antithyroglobulin antibody

Fig. 2. The trends of thyroglobulin in patients with negative antithyrogl obulin antibody demonstrated maximal increase in 3 monkths and gradual declining to normal range, but, on the other hand, those in patients with positive antithyroglobulin antibody showed gradual declining and normalization without further increase.

there were 7 patients(60%) with further increased serum thyroglobulin level in 3 months after radioactive iodine therapy(Table 4). The trend of thyroglobulin in patients without antithyroglobulin antibody demonstrated maximal increase in 3 months and gradual declining to normal range. On the other hand, the trend of thyroglobulin in patients with positive antithyroglobulin antibody showed gradual declining and normalization without further increase(Fig. 2).

Correlation between TBII Activity and Thyroglobulin Level

In patients without antithroglobulin antobody, the serum thyroglobulin level correlated with the corresponding TBII activity($r=0.645$, $p<0.01$) (Fig. 3).

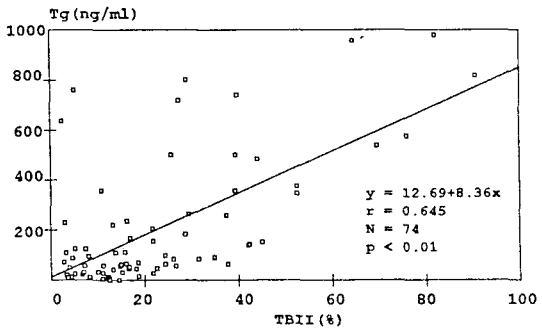


Fig. 3. In patients with negative antithyroglobulin antibody, the serm thyroglobulin level correlated with the corresponding TBII activityt($r=0.645$, $p<0.01$).

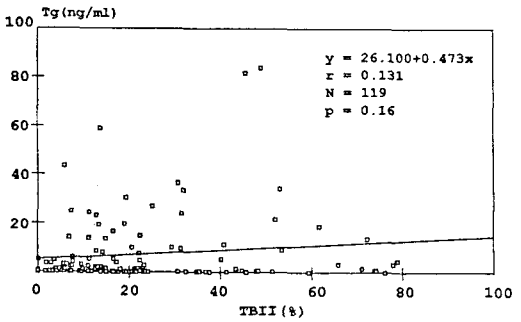


Fig. 4. In patients with positive antithyroglobulin antibody, the serum thyroglobulin level did not correlate with the corresponding TBII activity($p=0.16$).

But in patients with positive antithyroglobulin antibody, thyroglobulin level did not correlate with the corresponding TBII activity($p=0.16$) (Fig. 4).

DISCUSSION

The TSH-binding inhibiting immunoglobulin(TBII) is now being considered to be implicated in the pathogenesis of Graves' hyperthyroidism[1,2] and, therefore, lead to it may stimulate TSH receptors causing stimulation of thyroid function[8,9] and thyrotoxic state. We measured the binding of this stimulating antibody to TSH receptor by radioreceptor assay and it may represent the extent of stimulation of TSH receptor causing thyrotoxic state[10]. So it is possible that the TBII activity would represent the extent of stimulation of thyroid function[10-12].

With treatment with antithyroid drug, progressive decrease and normalization of serm TBII activity without transient elevation was reported in many studies[4,8,10]. Although the mechanism of this response in relation to antithyroid drug is not clear, there are some evidences that antithyroid drug may have immunosuppressive activity[2-4,13]. Radioactive iodine has ablative effect to thyroid follicles and, thus, it may damage thyroid follicles and may result in release and exposure of TSH receptors, causing production of autoantibody against it(TBII)[4]. In fact, after the radioactive iodine threatment, our study showed thransient further increase in the serum TBII activity followed by gradual normalization, which was not in cases treated with antithyroid drug.

In our data the high serum TBII activities go through for some prolonged period without declining, and, thus, the assay of TBII activity during treatment may give a valuable guide to decision about the time to cease the antithyroid medicaition[3,10].

The changes of the serum thyroid hormones after the radioactive iodine treatment without the medication effect were not evaluated because of concomitant administration of radioactive iodine, but it is possible that desturcted and/or stimulated thyroid follicles can produce or release thyroid hormones and thyroglobulin[4,14]. It, therefore, may cause transient increase in serum thyroid hormone level before their decrease to normal range[15,16].

Some reports of long term follow up evaluation after radioactive iodine therapy showed later increase in TBII activity after remission which can also be found in cases treated with antithyroid drug, which seems to be the result of reactivation of the autoimmune process in the thyroid[17]. This finding suggests the TBII activity as a valuable indicator for subclinical hyperthyroidism, that is recurrence[17].

Thyroglobulin, a major protein in thyroid follicles, can be also increased in patients treated with radioactive iodine[18]. It is reasonable to think that thyroid follicles are destroyed by radioactive iodine and release thyroglobulin. In our study, the elevated serum thyroglobulin level in 3 months after treatment suggests that the serum thyroglobulin level may increse just after treatment despite the lack of measurement of thyroglobolin level within 3 months after treatment. In general, the duration of increased release of thyroglobulin by destruction of follicles is so brief as observed in thyroiditis. The increase in the serum thyroglobulin level in 3 months after ther radioactive iodine treatmemt suggested that it might be the result of stimulation of thyroid follicles to produce thyroglobulin by increased serum TBII activity after radioactive iodine therapy. So the increased serum thyroglobulin level may reflect increased TBII activity.

There can be a situation in that antithyroglobulin antibody causes falsely low serum level of thyroglobulin measeured by radioimmunoassay[19,20]. In our result, the surum thyroglobulin levels were lower in patients with corresponding TBII activity in patients with positive antithyroglobulin antibody. This can be due either to the clearance of the thyroglobulin *in vivo* or interference in the radilimmunoassay procedure by the antithyroglobulin antibody.

In conclusion, the serum TBII activity increased after radioactive iodine therapy and normalized faster than after treatment with antithyroid drug only, and in patients with negative antithyroglobulin antibody, the serum thyroglobulin level may reflect the corresponding TBII activity.

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