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The Recurrence Rate of Graves' Disease among Patients with Subclinical Thyrotoxicosis after Initial Remission with Antithyroid Agents

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Background and Objectives: The recurrence rate of patients with Graves' disease (GD) is estimated to be 50-55% after withdrawal of antithyroid drug therapy, and relapse is frequent in the first year after discontinuing the medication. Follow-up examination of these patients frequently reveals laboratory findings consistent with subclinical thyrotoxicosis in the first year after stopping the antithyroid agents. We investigated the risk of recurrence of GD among patients with resurfacing subclinical thyrotoxicosis state after remission of initial GD with antithyroid treatments. **Materials and Methods:** We reviewed the patients diagnosed with GD who visited the Department of Endocrinology at two tertiary medical centers: Wonju Severance Christian Hospital and Gangneung Asan Hospital. We enrolled patients whose GD was completely treated after initial treatment with antithyroid agents who then developed subclinical thyrotoxicosis after discontinuation of antithyroid agents. **Results:** We reviewed a total of 44 patients (29 females, 15 males; age, 48.93±18.04; range, 17-85 years). The recurrence rate was 27.3% (12/44 patients), and recurrence occurred 3 months to 12 months later resurfacing of subclinical thyrotoxicosis. Patients with recurred GD was significantly older than non-recurred patients (44.63±17.75 years vs. 58.58±15.48 years, p=0.02). Other clinical parameters measured at the time of initial diagnosis were not different between the two groups. **Conclusion:** The recurrence rate of GD in patients with resurfacing subclinical thyrotoxicosis after initial remission of the disease was less than 30%. A close monitoring is recommended in these subgroup patients, especially in older patients.

Key Words: Graves' disease, Antithyroid agents, Recurrence

Introduction

The most common cause of hyperthyroidism is known to be Graves' disease (GD). Antithyroid drug therapy is primarily used as first-line therapy for GD in many Asian countries, including Korea.[1,2] If patients with GD experience adverse effects of antithyroid agents or if remission is not achieved despite prolonged antithyroid drug therapy, thyroidectomy or radioactive iodine therapy can also be considered. When ingested, antithyroid drug immediately enters the thyroid gland and inhibits the oxidation and organizing of iodine involved in thyroid hormone production process while also inhibiting the formation of thyroxine (T4) and triiodothyronine (T3) by interfering with the coupling of iodotyrosines.[3] Recently, it has also been known that antithyroid drug has anti-inflammatory and

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immunosuppressive effects which can suppress thyroid stimulation hormone receptor antibody (thyroid-stimulating immunoglubulin, TSI).[1,3] Although the reported recurrence rate of GD varies, discontinuation of antithyroid agents leads to recurrence in 50 to 55% of cases.[4] Factors especially associated with higher recurrence rate include severe hyperthyroidism, large goiters, and high titers of TSI at the time of initial diagnosis.[1,4] Periodic assessment of thyroid hormone, thyroid stimulating hormone (TSH), and TSI after treatment with antithyroid agents in patients with GD occasionally finds subclinical thyrotoxicosis state with only reduced TSH level and normal thyroid hormones. These patients are not considered to have recurred GD and therefore are not considered as candidates for resumption of antithyroid drug therapy or initiation of definitive treatment such as surgery or radioactive iodine therapy. According to Kubota et al.,[5,6] 41.2% of the patients showed subclinical thyrotoxicosis state after abortion of antithyroid agents, of which only few developed actually recurred GD; TSH was returned to normal in most cases. However, treatment guidelines for patients with transient subclinical thyrotoxicosis after treatment with antithyroid agents in GD are not yet available. The aim of this study was to investigate the recurrence of GD among patients with resurfacing subclinical thyrotoxicosis state after remission of initial GD with antithyroid treatments.

Materials and Methods

We reviewed the patients diagnosed with GD who visited the Department of Endocrinology at two tertiary medical centers: Wonju Severance Christian Hospital and Gangneung Asan Hospital. This study was approved by the local Institutional Review Board, Yonsei University Wonju College of Medicine, Wonju, Korea (YWMR-14-5-046). We enrolled patients whose GD was completely treated after initial treatment with antithyroid agents (methimazol or propylthiouracil) who then developed subclinical thyrotoxicosis after discontinuation of antithyroid agents. Subclinical thyrotoxicosis was defined as suppressed TSH level with normal thyroid hormone level. Serum levels of free T4 (Siemens, Munich, Germany, Wonju Severance Christian Hospital, normal range 0.83-1.76 ng/dL; Immunotech, Czech, Gangneung Asan Hospital, normal range 0.8-1.9 ng/dL), TSH (Siemens, Munich, Germany, Wonju Severance Christian Hospital, normal range 0.35-5.5 μU/L; Gangneung Asan Hospital, Brahms, Germany, normal range 0.4-5.0 μU/L), and TSI (Siemens, Munich, Germany, Wonju Severance Christian Hospital, normal range 0-1.58 U/L; Gangneung Asan Hospital, Medipian, Gmbh, Germany, normal range 0-2.0 U/L) were measured at the time of initial antithyroid drug treatment, antithyroid drug withdrawal, and 3, 6, and 12 months after withdrawal. Transient subclinical thyrotoxicosis was diagnosed when thyroid function was normalized without antithyroid drug resumption in patients who developed subclinical thyrotoxicosis following antithyroid drug withdrawal. Patients who remained euthyroid for more than 1 year without addition of antithyroid drug after transient hyperthyroidism were regarded as remission of GD. Those with increased thyroid hormone and decreased TSH levels leading to antithyroid drug resumption were diagnosed with GD recurrence. Data were expressed as mean$\pm$standard deviation. Student's t-test was used for the comparison of thyroid hormone and TSH receptor levels between patients with remission and relapse state from GD after antithyroid drug treatment. All analyses were performed using Windows-based SPSS statistical package (version 20.0, Chicago). The p value <0.05 was considered to be significant.

Results

A total of 44 patients with resurfacing subclinical thyrotoxicosis after remission of initial GD with antithyroid treatments (29 females, 15 males; age, 48.93$\pm$18.04; range, 17-85 years) were enrolled. Only 27.3% (12/44 patients) of these patients had recurrence of GD: remission was achieved in remaining patients. The recurrence of GD occurred at 3 months to 12 months after resurfacing of subclinical thyrotoxicosis. Table 1 shows the clinical data, level of free T4, TSH, and TSI at initial diagnosis of GD and at subclinical thyrotoxicosis state. The level of TSI at time of initial di-

Table 1. Comparison of variables in patients with subclinical thyrotoxicosis following initial Graves' disease remission

	Remission group (n=32)	Recurrence group (n=12)	p value
Age (year, mean±SD)	44.63±17.75	58.58±15.48	0.020
Sex (male %)	31.3 (10/32)	41.7 (5/12)	0.406
Duration of antithyroid agents therapy (months)	31.59±16.61	35.42±16.11	0.507
Free T4 at initial diagnosis (ng/dL)	3.57±1.67	3.20±1.92	0.571
TSH at initial diagnosis (μU/L)	0.04±0.10	0.06±0.10	0.666
TSI at initial diagnosis (U/L)	13.59±19.21	18.31±19.26	0.504
Percentage of patients with positive for initial TSI (%)	93.5	83.3	0.308
Free T4 at subclinical thyrotoxicosis state	1.44±0.38	1.49±0.43	0.707
TSH at subclinical thyrotoxicosis	0.26±0.92	0.15±0.29	0.533
TSI at subclinical thyrotoxicosis state	1.76±1.55	2.46±2.83	0.459
Percentage of patients with positive for TSI at subclinical thyrotoxicosis state (%)	33.3	66.7	0.092

SD: standard deviation, TSH: thyroid stimulating hormone, TSI: thyroid stimulating immunoglobulin

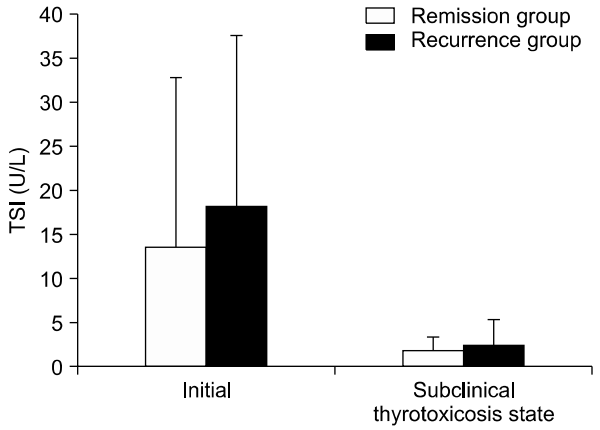

Fig. 1. The level of TSI at initial diagnosis of Graves' disease and subclinical thyrotoxicosis state after withdrawl of antithyroid agents. TSI: thyroid stimulating immunoglobulin

agnosis and subclinical thyrotoxicosis state was showed at Fig. 1. Patients with recurred GD were significantly older than non-recurred patients (44.63±17.75 years vs. 58.58±15.48 years, p=0.02). Other clinical parameters measured at the time of initial diagnosis, such as thyroid hormone, TSH, and TSI, were not different between the two groups. The duration of antithyroid drug therapy or the level of free T4 and TSI at the time of subclinical thyrotoxicosis state also did not differ between the two groups.

Discussion

In our study, only 27.3% of the patients with resurfacing subclinical thyrotoxicosis after discontinuation of antithyroid drug therapy due to Graves' disease experienced recurrence of the disease. Transient subclinical thyrotoxicosis occurred mostly 3 months (median, 3 months; range, 1-12 months) after withdrawal of antithyroid drug therapy. In Japanese data, 11.8% of 28 patients with subclinical thyrotoxicosis state after abortion of antithyroid agents showed recurrence of GD and they reported the transient thyrotoxicosis was occurred mostly 3-6 months after antithyroid drug therapy withdrawal. Our data was similar pattern compared to former studies.[5,6]

We have not been able to investigate the extent to which patients with GD treated with antithyroid drug therapy shows transient subclinical thyrotoxicosis state, but such patients are frequently encountered in clinical setting. Although these patients may have a high likelihood of GD recurrence, the present study showed that remission was achieved again in a substantial number of patients. Subclinical thyrotoxicosis after discontinuation of antithyroid drug therapy may be a transient finding, with follow-up of the thyroid function test usually showing benign findings.

We investigated the risk factors of GD recurrence in patients with subclinical thyrotoxicosis treated with antithyroid drug therapy for GD. The rate of GD recurrence after subclinical thyrotoxicosis state was higher in older patients. In recent meta-analysis report, risk factors of relapse in GD were goiter size, smoking, and

TSI levels and the age or sex did not show significant associations with recurrence.[7] In another studies showed average age at diagnosis was significantly younger at non-remission group compared with remission group after antithyroid drug therapy for GD.[8,9] But, our data showed opposite result. We guess the reasons of this differences may be due to the differences of compliance or amount of iodide intake. But we could not prove this results, so, further evaluation about age factor for recurrence of GD in patients with subclinical thyrotoxicosis state after antithyroid drug therapy withdrawal is needed.

TSI values at initial diagnosis were not significantly different between remission and recurrence group. It is generally known that higher TSI level at the time of diagnosis of GD is associated with higher likelihood of GD recurrence.[10,11] Although most studies suggest the decision to discontinue antithyroid agents should be made based on TSI level,[1,2] there is no significant difference in TSI level between patients who developed GD recurrence and those who remained disease-free in our study. We guess the reason of no differences of initial TSI level between patients with recurrence and remission in our study is because we did not investigate all patients treated with antithyroid agents for GD but only those who temporarily developed subclinical thyrotoxicosis state. However, TSI level at the time of GD diagnosis were high in patients with relapsed GD, although statistically not significant, which suggests its value in predicting the recurrence at least indirectly. TSI levels were significantly lowered at the time of subclinical thyrotoxicosis state after drug withdrawal than at the time of diagnosis of GD. This may have been because the decision to complete treatment with antithyroid agents was made based on TSI levels.

We suggest that patients with older age at the time of diagnosis of GD are more likely to develop recurrence, and therefore, this subset of patients requires closer monitoring following completion of antithyroid drug therapy.

This study was a retrospective study performed through a chart survey, and there was a limit to the degree in which the data could be analyzed. Another limitation of this study is that the data were collected across two hospitals uses different testing machines and reagents for measuring free T4, T3, and TSI. However, the normal range was not significantly different and the unit of laboratory data was same, so the data were combined. This study is a small-scale, simple-design retrospective study. However, no study has reported the rate of GD recurrence among patients who develops subclinical thyrotoxicosis following antithyroid drug therapy for GD, at least in Korea, and this data may serve as a base for future large-scale prospective study.

In summary, close laboratory monitoring rather than resumption of antithyroid drug therapy is recommended in patients with resurfacing subclinical thyrotoxicosis after initial remission of GD achieved with antithyroid drug therapy because the actual GD recurrence rate is low in such population.

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Conflicts of Interest

The authors have nothing to disclaim.

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