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Original Article

Management of thyrotoxicosis in children and adolescence: a Turkish multi-center experience

Running Head: Thyrotoxicosis in children and adolescence

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Abstract

Objective: To determine demographic and biochemical features of childhood and juvenile thyrotoxicosis and determine the treatment outcomes in them.

Methods: We reviewed records of 503 children from in 12 different cities of Turkey who were diagnosed with thyrotoxicosis between 2007 to 2017.

Results: In all, 375 (74.6%) patients had been diagnosed with Graves' disease (GD) and 75 (14.9%) had hashitoxicosis, and 53 (10.5%) had been diagnosed with uncommon causes of thyrotoxicosis. Commonest presenting features in children with GD or hashitoxicosis were tachycardia and/or palpitation, weight loss and excessive sweating. The cumulative remission rate was 17.6% in 370 patients with GD who received ATDs for initial treatment, and were treated for a median of 22.8 months (range 0.3 – 127 months). No variables predictive of the achievement of remission were identified. Twenty-seven patients with GD received second-line treatment for poor disease control and adverse events associated with antithyroid drugs. Total thyroidectomy was reported in 17 patients with no recurrence of thyrotoxicosis and all became hypothyroid. Ten patients received radioiodine; six became hypothyroid, 1 remained hyperthyroid and started taking antithyroid drug again; 1 achieved remission and 2 unknown progresses due to lost up follow up.

Conclusion: This study demonstrated that using anti-thyroid drugs with the hope that the patients will enter a remission over time is generally accepted first-line approach in Turkish children and adolescents with GD, however, this approach achieved low remission rate which was consistent with previous studies

What is already known on this topic?

- Graves' disease is the most common cause of the thyrotoxicosis in children and adolescents as in adults. Management of thyrotoxicosis in children and adolescents is controversial and often unsatisfactory.
- There is no data on clinical features and treatment outcomes of Turkish children and adolescents with thyrotoxicosis.

What this study adds?

- Using anti-thyroid drugs with the hope that the patients will enter a remission over time is generally accepted first-line approach in Turkey, however, this approach achieved low remission rate which was consistent with previous studies
- Surgery has been preferred more than radioactive iodine ablation for poor disease control and adverse events associated with antithyroid drugs in Turkish children and adolescents with Graves' disease.

Introductions

Thyrotoxicosis is characterized by excess circulating thyroid hormones, irrespective of the source (1). Juvenile thyrotoxicosis can have various clinical manifestations. It may affect growth and development of children and may cause pronounced neuropsychological manifestations (2). Graves' disease (GD) is the most common cause for thyrotoxicosis in childhood (2). Incidence of GD increases with age accordingly it is less common in children than in adults. However, increasing incidence rate of GD in children have been reported by several studies (3-6).

Although a few treatment guidelines have been published, its management is controversial and often unsatisfactory (7-9). Treatment options for thyrotoxicosis in children include antithyroid drugs (ATDs), radioactive iodine therapy (RI), and surgical interventions. Most

patients diagnosed with thyrotoxicosis are initially treated with ATDs as there is a chance of remission with ATDs therapy although optimal treatment duration is controversial. Patients with thyrotoxicosis who do not respond to medical therapy or who have adverse reactions to ATDs must choose a second line treatment such as RI or thyroid surgery. However, all of treatment options have unique advantages and disadvantages (10) There are novel approaches like using rituximab, TSHR-specific peptides or monoclonal blocking TSHR antibodies that aim to ameliorate the immune dysfunction seen in GD. Very few studies continue in this respect and some completed studies have shown conflicting results (11-13).

Remission is reported approximately in one third of children with GD and subsequently relapse occurs in half of patients after achieved remission (7, 14-21). Remission rates are lower and relapse rates are higher in children than in adults (22). However, the definitions of remission and relapse are differs between studies.

In this study, we aimed to determine demographic and biochemical features of children and adolescents with thyrotoxicosis, preference of physicians for treatment juvenile thyrotoxicosis and outcome of management of patients.

Patients and methods

In December 2017, an invitation was sent to all pediatric endocrinologists across the Turkey by an email to review their patients with elevated free T4 (above upper limit of reference range of commercial kits of laboratory) under age of 18 years between 2007 and 2017. By case notes, clinical and biochemical features, treatments' preferences and outcome in relations to treatment were documented. Thyrotoxicosis was defined as elevated fT4 and/or fT3 (above upper limit of reference range of commercial kits of laboratory) with suppressed TSH levels (below lower limit of reference range of commercial kits of laboratory).

Clinical features of patients studied included gender, age, clinical symptoms, anthropometric measurements [weight, height and body mass index (BMI); the weight in kilograms divided by the square of the height in meters]. Standard deviation scores (SDS) of weight, height and BMI of patients were calculated by using reference values in Turkish children (23).

Biochemical parameters studied included serum alanine transaminase (AST); aspartate transaminase (AST); thyroid-stimulating hormone (TSH); free thyroxine (fT4); free tri-iodothronine (fT3); thyroid peroxidase antibodies (anti-TPO); thyroglobulin antibodies (anti-Tg) and TSH receptor antibodies (TRAb). Commercial kits had been used to assay these hormones and antibodies. Because different commercial kits had been used to assay TRAb among clinics and sometimes in same in clinic, TRAb/upper limit for TRAb ratio (TRAb ratio) was used for analysis and TRAb ratio above 1 was accepted as elevated TRAb.

Graves' disease was defined as thyrotoxicosis with either elevated TRAb or clinical signs suggestive of GD, for example thyroid ophthalmopathy or diffuse uptake of radioisotope in thyroid scan or persistent thyrotoxicosis more than 2 years during follow-up without any other cause. Declaration of physicians has been taken into account for presence of ophthalmopathy.

Thyrotoxic phase of chronic lymphocytic thyroiditis (Hashitoxicosis) was defined as thyrotoxicosis with the presence of at least one of the anti-TPO antibodies or anti-Tg antibodies (based on reference range of commercial kits) in patients without any other cause.

Preferred approach of ATD treatment (block-and-replace or dose reduction), type of ATD (methimazole or propylthiouracil), duration, side effects and date/age of stopping treatment, RAI treatment or surgery and relapse were also recorded. Remission was defined as biochemical euthyroidism at the time of collecting data after cessation of ATD for at least 3 months.

Patients were classified based on their final diagnosis and expressed in percentages. Patients with Graves' disease or Hashitoxicosis have been analyzed in more details. Insufficient data, repetition of same patient, diagnosis of subclinical hyperthyroidism (low serum TSH, but

normal free T4 and free T3 concentration) and gestational thyrotoxicosis were considered as exclusion criteria.

Continuous variables were described as median and ranges or mean ± standard deviation, and intergroup comparison was performed using Mann-Whitney U tests or Student's t test. χ^2 test was used for categorical variables. Multiple regression analysis was used to analyze to examine whether age, sex, weight SDS, Height SDS, BMI SDS, free T4, free T3, TRAb / TRAb upper limit ratio at diagnosis, and duration of ATD had independent association with occurring relapse in the patients' group which ATD therapy was stopped for possible remission . $P < 0.05$ was considered to be statistical significant, and all analyses were performed using IBM SPSS Statistical software (Version 22, SPSS Inc., Chicago, IL, USA).

Results

Case sheets of 514 patients were received and 11 patients were excluded because of insufficient data (n: 2), repetition (n: 4), diagnosis of subclinical hyperthyroidism (n: 4), gestational thyrotoxicosis (n: 1). Between 2007 and 2017, medical records of eligible 503 children from 22 institutions in 12 different cities were reviewed. Of the 503 patients who entered study, 375 (74.6%) patients had been diagnosed with Graves' disease and 75 (14.9%) patients had hashitoxicosis. Diagnosis in the remaining patients were thyroid hormone receptor-beta mutation 22 (4.4%), subacute thyroiditis 4 (0.8%), toxic nodular goiter 4 (0.8%), neonatal Graves' disease 3 (0.6%), papiller thyroid carcinoma 2 (0.4%) and 18 patients (3.6%) could not be diagnosed specifically. Diagnosis of patients with GD was mostly based on positive for TRAb (81.6%) or elevated radioactive iodine (or ^{99m}Tc) uptake or observed ophthalmopathy (9.6%). Only 32 patients (8.8%) who were negative for TRAb or had no TRAb measurement had diagnosed with GD based on clinically during follow up.

The most common reported presenting complaints among patients with GD or hashitoxicosis were tachycardia and/or palpitation, weight loss and excessive sweating. Distribution and frequencies of complaints at admission were similar between groups except that goiter and ocular symptoms are more frequent in patients with GD (Table 1).

Clinical features of patients with GD and hashitoxicosis have been elaborated in Table 2. There was no significant difference between the two groups with regards to gender distribution, age at diagnosis, weight SDS, height SDS and BMI SDS. Patients with GD had higher median fT4 and fT3 levels. The mean starting dose of ATDs was higher and duration of ATD therapy was longer in patients with GD ($p < 0.05$). With respect of medical treatment options, the vast majority of patients treated with methimazole as ATD and dose reduction regimen. The mean starting dose ATDs was significantly higher in Graves' disease group than hashitoxicosis group (Table2).

Outcome of patients with GD is shown in Figure 1.

Five of 375 patients with GD did not receive ATDs. These patients were managed only with beta blockers. Approximately 62% (231/370) of patients received ATDs initially were remained on ATD at the time of last contact for data collection. The median duration of ATD therapy in these patients was 16.1 (range 0.3-99.6) months. Anti-thyroid drugs were stopped in approximately one-third of patients (112/370) for possible remission. In 58 patients, trial of cessation of ATD performed in first 3 years of treatment, 46 patients (79.3%) remained in remission. In 54 patients, requirement of ATD had persisted, and trial of cessation of ATD performed beyond 3 years of treatment, 19 patients (35.2%) remained in remission. Forty-seven of 112 patients who relapsed after stopping ATD therapy for possible remission; 34 remained on ATD, 6 underwent total thyroidectomy and all became hypothyroid, 7 received radioiodine and 4 of them became hypothyroid and 2 of them remain hyperthyroid. One of two who remained hyperthyroid remained on ATD and the other received a second dose radioiodine and thereafter became hypothyroid (Figure 1). The median interval between with ATD treatment cessation and relapse of hyperthyroidism was 6.0 months (range 0.7-60.8

months) The cumulative remission rate was 17.6% in 370 patients with GD who received ATDs for initial treatment, and were treated for a median of 22.8 months (range 0.3 – 127 months). Clinical and biochemical features of patients with Graves' disease who stopped anti-thyroid drug treatment for remission or relapsed afterwards have been elaborated in Table 2. We observed that patients who did not achieve remission had lower body mass index (BMI) standard deviation score (SDS) at diagnosis, higher initial free T4 and free T3 levels and longer duration of ATD therapy (Table 3). However, these variables were not identified as independent predictors of relapse by regression analysis (Table 4). We also observed 4 patients who had high AST and/or ALT level did not remained euthyroid and relapsed after discontinuation of ATD.

Twenty-seven patients with GD received second-line treatment (surgery or radioactive iodine ablation); for poor disease control and adverse events associated with ATD while patients on using the ATDs (Figure 1). Total thyroidectomy was performed in 17 patients with no recurrence and all became hypothyroid without severe complication in these patients. Ten patients received radioiodine; six became hypothyroid, 1 remained hyperthyroid and started taking ATD again, 1 achieved remission and 2 unknown progresses due to lost up follow up. There is no significant difference in age of patients at second-line treatment time between patients received radioiodine [16.1±2.8 years (range 10.8-19.4)] and patients underwent surgery [15.2±2.4 years (range 9.3-19.6)].

Six of 75 patients with hashitoxicosis did not receive ATD and were managed with only beta blockers. Anti-thyroid drugs were stopped after mean 9.3±6.3 months (range 0.7-22.5) in 32 patients with hashitoxicosis for possible remission and all of them achieved remission. The remained 37 patients have continued to use ATD at their last visits with 8.0±6.9 months (range 0.3-34.0) mean duration of ATD.

Discussion

This is one of the largest reports till date on childhood and juvenile thyrotoxicosis in the literature.

Graves' disease is the most common cause of the thyrotoxicosis in children and adolescents; accounting for more than 95% of cases (2). However the occurrence of GD was much lower in our series, accounting for approximately three quarter of all cases. The second frequent cause of juvenile thyrotoxicosis is hashitoxicosis and its prevalence was reported as 0.5% to 22% in different studies (9). Like as results reported in a recent study from Scotland and 19.6% of patients with thyrotoxicosis classified as hashitoxicosis in that cohort (20). The distinction of GD and hashitoxicosis may be difficult as seen in this study, the most common reported presenting complaints among patients with GD and hashitoxicosis are similar. Additionally most patients with hashitoxicosis probably have not been diagnosed specially because of its relatively short thyrotoxic course. The hallmark of GD is the presence of TRAb while patients with hashitoxicosis will typically have anti-TPO and/or anti-Tg. (24, 25) Being most of patients with GD were tested for presence of TRAb is the one of strong feature of this study. On the other hand thyroid–stimulating hormone receptor antibodies may also be present in sera of patients with hashitoxicosis and some experts consider GD and hashitoxicosis to be the some disorder at different end of a continuum (26).

Graves' ophthalmopathy is an inflammatory disease of the eye and orbital tissues, and its prevalence has been previously reported to range from 17.1-67.6% of children and adolescents with GD in different studies (21, 27). Relatively high prevalence (86.8%) of eye signs in children with GD was reported in a recent study (20). This data may be consequence of inclusion of mild signs such as lid lad too rather than assessing true proptosis. In the present study, ophthalmopathy was reported approximately in one third patients with GD and this finding is in concordance with previous studies. Despite of the lack of standard protocol

for definition Graves' ophthalmopathy in our study, we suppose that reported cases presumably are children with moderate or severe ophthalmopathy.

Treatment options for GD in children include anti-thyroid drugs, radioactive iodine therapy and surgical thyroidectomy, and each of these treatment approaches is associated with specific risks (2) Anti-thyroid drugs are generally accepted option by physicians for initial treatment of GD the children and adolescents in most countries. In this study, almost all patients with GD received ATD, preferably methimazole, except a few patients had been treated with beta-blockers. Propylthiouracil is no recommended for use in children because of its potential severe hepatotoxicity (28). The clinic practice has been concordant with this recommendation in our country; there is no patient who received propylthiouracil as initial treatment in last five years in this patient group. Despite of various definitions of remission and a wide variety ATD treatment durations, ranged from 2 to several years, reported remission rates after ATD withdrawal varied from 11% to 49% (7, 19, 21, 22, 29). In the present study, remission was achieved in 58.0% of patients who their anti-thyroid drugs treatments were ceased for possible remission. This relative high remission rate should be interpreted with caution due to the retrospective nature of this study and that there was no standard protocol, which applied to all the patients in this study. The cumulative remission rate was 17.6% when we estimated remission rate in all patients who received ATDs for initial treatment, which is consistent with the results of previous studies.

In several studies, some prognostic factors were identified to be associated with lower remission chance in children and adolescents with GD (22, 30). These studies have reported that ethnicity, age, pubertal status, BMI (SDS), goiter volume, initial severity (higher FT4 and TRAb levels) and with other autoimmune conditions are prognostic factors (14-16, 31). However, a number of other studies including the present one have found no clinical variable that is constantly associated with a definite outcome (6, 7, 17, 32). The major limitation of these studies is almost all of them including the current one are retrospective studies. The only prospective study which was conducted by Kaguelidou et al. demonstrated that the risk of relapse was higher in very young patients and patients of non-Caucasian origin and high levels of serum TRAb and free T4 levels (16). In our study, higher remission rate in patients who received ATD's less than 3 years group indicates that patients who will achieve remission may be predicted based on follow up of thyroid function tests and requirement of lower doses of ATDs. Thus, earlier trial of cessation of ATDs can be performed.

If remission is not achieved or relapse occurs or severe side-effect occurs during ATDs therapy, radioiodine ablation and surgical thyroidectomy are available treatments for second line approach in patients with GD. Thyroidectomy is an effective treatment for GD (8). In this study we determined this method had been used slightly more than radioiodine ablation to treat patients. Various studies reported that hypothyroidism occurs near all children who undergo total thyroidectomy (20, 21, 33, 34). Our observations were concordant with these studies.

^{131}I therapy had been generally contraindicated in children, however according to the guidelines ^{131}I therapy can be performed with caution (8, 9). Because of its ease of administration there is a trend towards permanent therapy with radioactive iodine ablation (10). Remission rates vary due to variability in the dose of ^{131}I used for treatment. Despite a lot of patients being successfully treated with ^{131}I therapy, approximately in one third of patients remission is not achieved or relapse occurs (30). According to our data in 11 of 17 children who were treated with ^{131}I therapy achieved biochemical remission of hyperthyroidism. Fears about radioiodine ablation, compounded by the lack of access to radioactive iodine therapy may contribute to the relative low rate of using ^{131}I therapy in children with GD.

Our study has potential limitations and strengths. The major limitation of this study is its retrospective nature and the lack of globally accepted standard protocol for management of thyrotoxicosis in children and adolescents. In addition, adverse events associated with ATD treatment, thyroidectomy or radioactive iodine ablation were not included in the survey of this study. The deficiency of detailed information about the side effects hampered interpreting the adverse events and treatment preferences. The strengths of this study are inclusion of data from multiple centers throughout Turkey and relatively large sample size when compared with previous studies.

In conclusion, generally clinical manifestations and laboratory findings of patients with GD and hashitoxicosis do not differ from each other. Positive for TRAb, elevated radioactive iodine (or ^{99m}Tc) uptake and ophthalmopathy are the key features for diagnosis of GD. Despite there is no optimal accepted treatment for Graves' disease, we have observed initial treatment with ATDs and using total thyroidectomy and ^{131}I therapy as a second line treatment for permanent therapy is generally accepted approach for treatment of patients with GD.

Authors' contributions:

IE: Main author of the manuscript

EB, MY, MA, EKÖ, ZA, SB, HÖ, YK, DÖ, EÜ, AÖ, OE, AÇ, MT, AY, AKU, MB, BÖ, OA, ÇB, SK, RY, EHA, ES: Collected the data and reviewed and revised the manuscript

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Compliance with Ethical Statements

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Figure 1. Outcome in 375 children and adolecents with Graves' disease seen in Turkey between 2007-2017

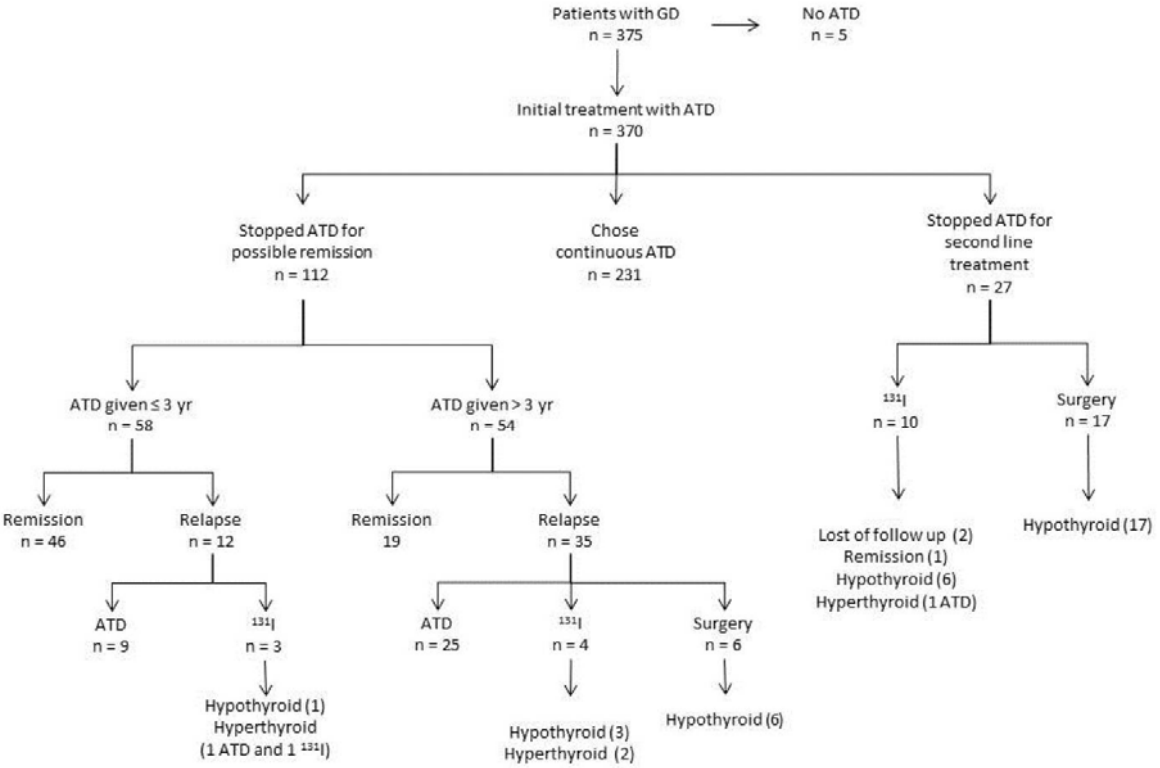

Table 1. The most common reported presenting complaints among patients with Graves' disease and hashitoxicosis.

Complaints	Graves' disease n: 375	Hashitoxicosis n: 75
Tachycardia and/or palpitation	169 (45.1%)	29 (38.7%)
Weight loss or no weight gain	106 (28.3%)	15 (20.0%)
Excessive sweating	105 (28.0%)	18 (24.0%)
Swelling in the neck (Goiter)	74 (19.7%)	9 (12.0%)
Hand tremor	65 (17.3%)	16 (21.0%)
Irritability or nervousness	64 (17.1%)	15 (20.0%)
Ocular symptoms	38 (10.1%)	1 (1.0%)
Weakness	36 (9.6%)	9 (12.0%)
Hair loss	19 (5.1%)	4 (5.3%)
Intolerance to heat	18 (4.8%)	4 (5.3%)
Sleep problems	15 (4.0%)	2 (2.7%)
Restlessness	10 (2.7%)	-
Headache	4 (1.1%)	2 (2.7%)
Decreased school performance	4 (1.1%)	-
Family history of Graves' disease	3 (0.8%)	-
Incidental	12 (3.2%)	14 (18.7%)

Table 2. Clinical and biochemical features of patients with GD and hashitoxicosis.

	Graves' disease	Hashitoxicosis	P value
Number	375	75	
Gender(F/M)	284/91	64/11	0.072
Age at diagnosis, mean ± SD, median (range)	12.6±3.6 13.4 (1.2-17.9)	13.3±3.6 13.6 (4.0-17.9)	0.130
Weight SDS, mean ± SD	-0.29±1.37	-0.16±1.26	0.447
Height SDS, mean ± SD	0.07±1.24	-0.18±1.30	0.117
BMI SDS, mean ± SD	-0.44±1.34	-0.11±1.36	0.055
Ophthalmopathy (%)	117 (%31.2)	n/a	
Positive for TRAb (%)	306 (81.6)	n/a	
TRAb / TRAb upper limit ratio, median (range)	4.1 (0.06 - > 40.00)	n/a	
Free T4 (ng/dL), median (range)	3.65 (1.69 - >7.70)	2.50 (1.69 - >7.70)	
Free T3 (ng/dL), median (range)	13.60 (1.40 - >30.00)	8.07 (1.14 - >30.00)	
Positive for anti-TPO and/or anti-Tg (%)	309 (%82.4)	n/a	
High AST and/or ALT level, number (%)	27 (%7.2)	4 (%5.3)	
Using scintigraphy for diagnosis (%)	87 (%23.2)	8 (%10.6)	
Dose reduction / Block and replace	290/88	65/5	<0.001
Preferred antithyroid drug, MMI/PTU	330/40	63/6	0.003
Starting dose of MMI (mg/kg/day), mean ± SD (range)	0.46±0.22 (0.07-1.51)	0.39±0.20 (0.08-1.05)	0.017
Starting dose of PTU (mg/kg/day), mean ± SD (range)	4.92±1.80 (1.79-10.13)	2.83±0.73 (1.90-3.45)	<0.001
Duration of ATD therapy (months), mean ± SD, median (range)	27.5±22.8 22.8 (0.3-127.0)	9.0±7.5 7.7 (0.3 – 34.0)	<0.001

Table 3. Clinical and biochemical features of patients with Graves' disease who stopped anti-thyroid drug treatment for possible remission relating to achieved remission or relapsed afterwards

	Remission	Relapse	P value
Number	65	47	
Gender (F/M)	50/15	37/10	0.821
Age at diagnosis, mean ± SD, median (range)	12.2±3.6 12.9 (1.4-17.8)	12.4±3.2 13.3 (3.1-17.1)	0.664
Weight SDS, mean ± SD	-0.09±1.47	-0.50±1.22	0.111
Height SDS, mean ± SD	-0.13±1.32	-0.09±1.07	0.340
BMI SDS, mean ± SD	-0.07±1.35	-0.66±1.11	0.013
Ophthalmopathy, (%)	16 (24.6%)	12 (25.5%)	0.912
TRAb / TRAb upper limit ratio, median (range)	2.67 (0.16 – 35.00)	3.84 (0.26 - > 40.00)	
Free T4 (ng/dL), median (range)	3.39 (1.70 - >7.70)	4.50 (1.70 ->7.70)	
Free T3 (ng/dL), median (range)	10.20 (2.90 - >30.00)	14.74 (1.40 - >30.00)	
Positive for anti-TPO and/or anti-Tg, (%)	56 (86.2%)	43 (91.5%)	0.384
High AST and/or ALT level, n (%)	0 (0.0%)	4 (8.5%)	0.029
Dose reduction / Block and replace	45/20	33/14	0.911
Duration of ATD therapy (months), mean ± SD, median (range)	29.8±18.4 25.5 (3.1-77.7)	51.8±26.3 49.8 (10,4-127.0)	<0.001

Table 4. Multiple regression analysis in the patients' group which ATD therapy was stopped for possible remission, with occurring relapse as the dependent variable.

Independent variable	Beta	P
Age at diagnosis	0.057	0.629
Gender	0.021	0.823
Weight SDS	0.686	0.356
Height SDS	-0.162	0.630
BMI SDS	-0.866	0.162
Free T4	-0.006	0.972
Free T3	0.031	0.867
TRAb / TRAb upper limit ratio	0.148	0.234
Duration of ATD	-0.009	0.929