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fT3:fT4 ratio in Graves' disease — correlation with TRAb level, goiter size and age of onset

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Abstract: Introduction: Graves' Disease (GD) is an autoimmune hyperthyroidism occurring mostly in young women. The main pathogenic role of the disease is attributed to TSH receptor antibodies (TRAb), which stimulate the thyroid gland to increase production of the most active thyroid hormone-triiodothyronine (T3). High level of TRAb and a large goiter size are commonly known as poor prognostic factors for the disease and are used to predict relapse.
The aim: The purpose of our study was to check the correlation between fT3:fT4 ratio with TRAb concentration, total volume of thyroid and age of GD onset.
Materials and Methods: 114 patients with onset or relapse of GD were analyzed. Those after thyroidectomy or radioiodine therapy were not taken into analysis. The data was retrospectively retrieved from the hospital's records consisting of patients' sex, age, level of TRAb, fT3, fT4 and thyroid volume on ultrasonography. The association between fT3:fT4 and TRAb concentration, thyroid volume and age was evaluated using Pearson correlation coefficient.
Results: The group was predominated by women (19.3% men, 80.7% women). The average age was 47.0. The analysis revealed positive correlation between: 1) fT3:fT4 ratio and total volume of thyroid (correlation ratio: 0.37; $p < 0.05$) 2) fT3:fT4 ratio and level of TRAb (correlation ratio: 0.26; $p < 0.05$) 3) negative correlation between fT3:fT4 ratio and patient's age (correlation ratio: –0.14; $p = 0.144$.Conclusions: Positive correlations between fT3:fT4 ratio and TRAb level and total volume of thyroid (poor predictors of GD) may confirm that high level of fT3 can also be a prognostic factor for GD severity.

Key words: Grave's disease, fT3:fT4 ratio, TRAb.

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Introduction

Graves' disease (GD) is a common autoimmune disorder in endocrinologist practice, that is a cause of 60–80% cases of thyrotoxicosis [1]. The disease is about 6 to 8 times more frequent in females than males [2]. It affects 2% of women and 0.2% of men [3]. The main pathogenetic elements of GD are thyrotropin receptor antibodies (TRAbs), which stimulate the growth and the function of the thyroid follicular cells, that initiates an excessive production of thyroid hormones and goiter formation [4]. Risk factors of GD include genetic susceptibility and environmental triggers, such as smoking, viral/bacterial infection and chemicals [4]. The purpose of GD treatment is to decrease thyroid hormones synthesis through antithyroid drugs (ATDT), or to decrease thyroid tissue through radioactive iodine treatment (131-I) or surgical ablation [5].The ratio of total triiodothyronine (T3) to total thyroxine (T4) is a helpful index for the differentiation between GD and subacute thyroiditis [6]. However fT3 and fT4 are more widely used in clinical practice, because they are less dependent on thyroid hormone-binding proteins [6]. Due to numerous relapses and treatment failures, many researchers look for a better predictor of positive therapy outcome [1]. Known independent pretreatment predictors of GD therapy failure are higher TRAbs level and a larger goiter size at onset [4]. Furthermore patients less than 40 years old at onset have larger goiters and higher mean fT4 and fT3 concentration [7].

The aim of our study was to check the correlation in Graves' disease between free triiodothyronine to free thyroxine ratio (fT3:fT4) with TRAB concentration, total volume of thyroid and age of GD onset.

Materials and Methods

The study represents a retrospective analysis of 114 patients with a first episode or relapse of GD , who were admitted to the Department of Endocrinology at the University Hospital in Cracow. The group was predominated by women (92 vs. 22). Patients who were treated with thyroidectomy or radioiodine were excluded from the study. The sources of the data were medical history (sex, age, type of hyperthyroidism), physical examination (volume and dimensions of the thyroid measured in USG) and laboratory tests (concentrations of: fT3, fT4 and TRAb). The fT3:fT4 ratio was counted by dividing fT3 concentration by fT4 concentration.

A hormonal assessment of serum fT4 (reference range: 12.0–22.0 pmol/L) and fT3 (reference range: 3.1–6.8 pmol/L) was performed using electrochemiluminescent method and cobas pro 8000 analyzer (Roche Diagnostics, Basel, Switzerland). The concentration of anti TSH receptor (TRAb) antibodies (reference: <1U/L) was assessed by the radioimmunological method using highly sensitive Thermo Scientific

BRAHMS TRAK human RIA assay, (BRAHMS Diagnostic GmbH, Germany). All patients were tested using the same methods.

Shapiro-Wilk test, Spearman rank correlation and U Mann-Whitney test were used for statistical analysis of the results. The Shapiro-Wilk test was used to check if the data was consistent with a normally distributed population. The Spearman rank correlation was used to estimate correlation between several parameters. The U Mann-Whitney test was used to compare patients with first episode of GD and relapse of GD. The probability <0.05 was considered statistically significant. Statistical analyses were performed using Statistica version 13 for Windows (Statsoft Polska). Our study is an analysis of retrospective data of hospitalized patients. Each patient signed consent for performing all tests, which is included in patients documentation.

Results

The distribution of the analyzed population was not normal.

The group of patients consisted of 30 patients with a first episode of GD and 84 patients with relapse of the disease. The group was predominated by women (80.7%).

The baseline characteristics of the patients with Graves' disease are presented in the Table 1. The median age of patients in the group with relapse was higher than in the group with first episode: 49.0 vs 39.5 years. The comparison of patients with first episode and the relapse of GD shows higher fT3 (15.73 pmol/L vs 16.71 pmol/L), fT4 (40.01 pmol/L vs 42.88 pmol/L) and higher TRAb (15.31 U/L vs 19.61 U/L) as well as a larger goiter in patients with relapse.

In the group of patients with relapse, in 16 patients with recurrence of hyperthyroidism, it was not possible to clearly determine which recurrence it was. All of them were treated with anti-thyroid drugs for over 6 months. In the group of patients with relapses after ATDT withdrawal, the time from discontinuation of medication to the onset of relapse varied from 1 to 300 months. More detailed data were possible to be obtained in 68 of patients. Analysis of this group is presented in the Table 2.

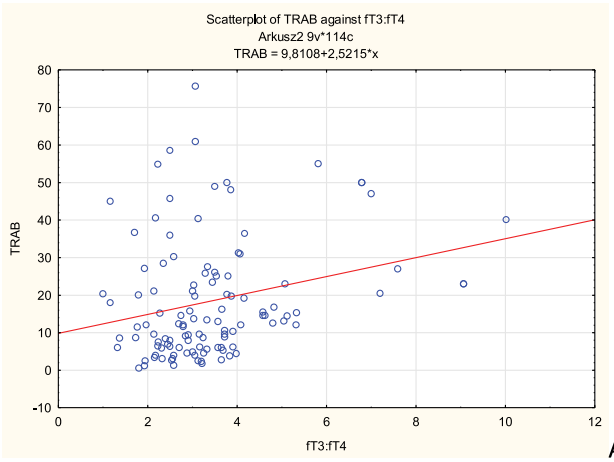
A positive correlations between fT3:fT4 ratio and TRAb concentration presents Fig. 1A-C. This correlation was found in the whole group, in the group with the first episode of GD as well as in the recurrent group. The strongest association was observed in the group with the first episode of GD ($R = 0.46$). All of these correlations were statistically significant (Table 3).

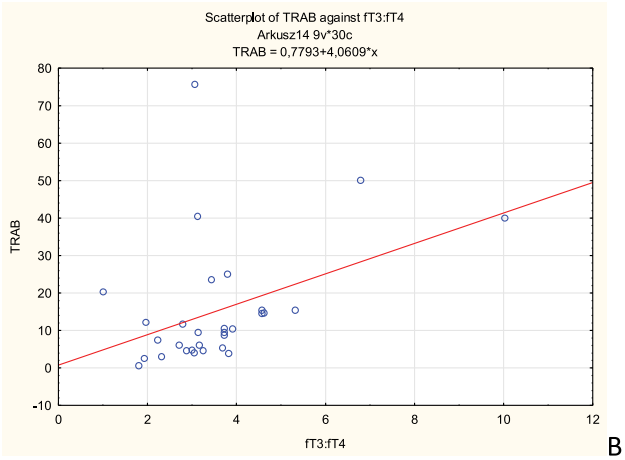
Table 1. Characteristic of patients with Grave's disease.

	Graves' disease Total group (N = 114)	Graves' disease First episode (N = 30)	Graves' disease Relapse (N = 84)
Age (years) Median, Min; Max	47.0 (18; 88)	39.5 (18; 79)	49.0 (18; 88)
Male N (%)	22 (19.3)	3 (10)	19 (22.6)
Female N (%)	92 (80.7)	27 (90)	65 (77.4)
Thyroid volume (mL) Mean ± SD	31.62 ± 24.27	29.68 ± 23.21	32.32 ± 24.60
Thyroid function tests			
fT3 (pmol/L) Mean ± SD	16.45 ± 10.26	15.73 ± 7.73	16.71 ± 11.00
fT4 (pmol/L) Mean ± SD	42.12 ± 24.71	40.01 ± 20.02	42.88 ± 26.13
TRAb (U/L) Mean ± SD	18.48 ± 15.80	15.31 ±16.25	19.61 ± 15.48
fT3:fT4 Mean ± SD	0.41 ± 0.19	0.43 ± 0.20	0.41 ± 0.19

Table 2. Analysis of subgroups of patients with relapse of Graves' disease.

	Patients with relapse during ATDT	Patients with relapse after ATDT withdrawal
Number of patients	31 (women: 19)	37 (women: 33)
Number of relapses	One relapse: 31	One relapse: 32 Two relapses: 4 Three relapses: 1
Time to relapse after starting ATDT (months)	Max: 36; Min: 1	x
Time to relapse after starting ATDT in women group (months)	Max: 24; Min: 1	x
Time to relapse after starting ATDT in men group (months)	Max: 36; Min: 1	x
Time to relapse after ATDT withdrawal (months)	x	Max: 300; Min: 1
Time to relapse after ATDT withdrawal in women group (months)	x	Max: 300; Min: 1
Time to relapse after ATD withdrawal in men group (months)	x	Max: 8; Min: 1





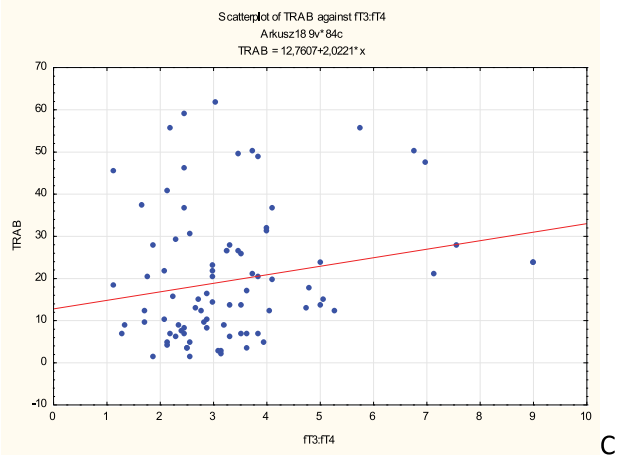


Fig. 1. Positive correlation between fT3:fT4 ratio and TRAb concentration. A — the whole group, B — the first episode group, C — the recurrence group.

Table 3. fT3:fT4 and TRAb correlation.

	Number of compared pairs	fT3:fT4 (×10) and TRAb	
		R Spearman	p
Whole group	114	0.264780	0.004414
The first episode	30	0.461984	0.010164
Recurrence	84	0.220875	0.043484

A positive correlation between fT3:fT4 ratio and total thyroid volume (Fig. 2A–C, Table 4) was observed. The strongest association was observed in the group with the recurrent GD (R = 0.46). The correlations in the whole group and in the recurrent group were statistically significant, whereas in the group with the first episode of GD was not statistically significant (Table 4).

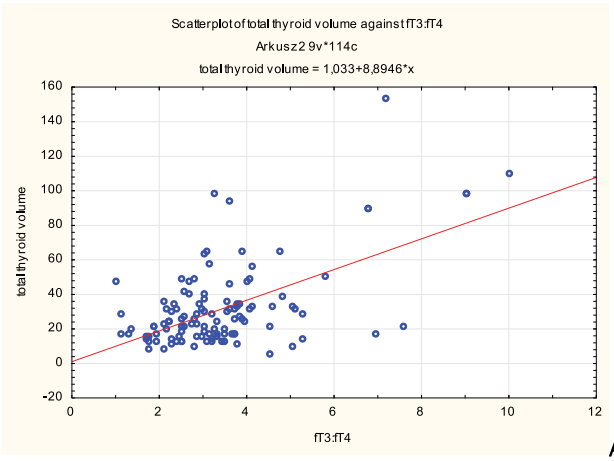
Moreover a negative association between fT3:fT4 ratio and age of GD onset was found in the whole group, in the first episode of GD as well as in the recurrent group (Fig. 3A–C). Nor of the correlations were statistically significant (Table 5).

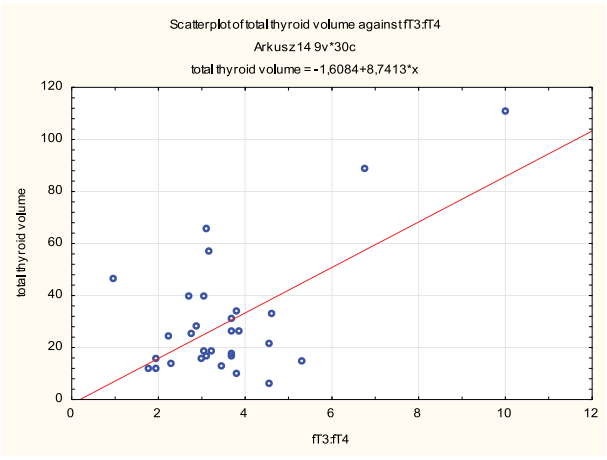
Table 4. fT3:fT4 and thyroid volume correlation.

	Number of compared pairs	fT3:fT4 (×10) and thyroid volume	
		R Spearman	p
Whole group	114	0.37231	0.00004
The first episode	30	0.162716	0.390281
Recurrence	84	0.463941	0.000009

Table 5. fT3:fT4 and age of onset GD correlation.

	Number of compared pairs	fT3:fT4 (×10) and age of onset	
		R Spearman	p
Whole group	114	–0.137665	0.144118
The first episode	30	–0.052368	0.783447
Recurrence	84	–0.139892	0.204381





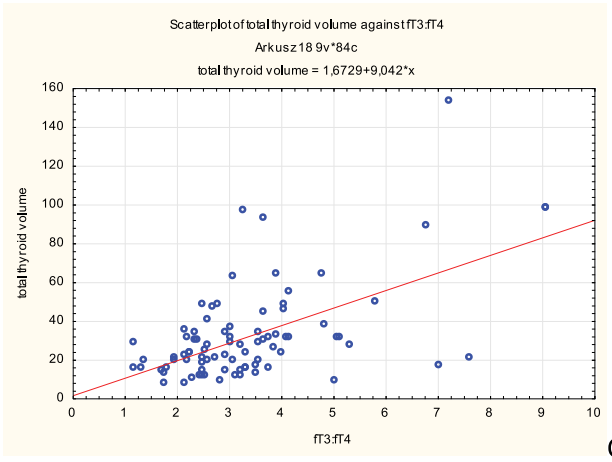
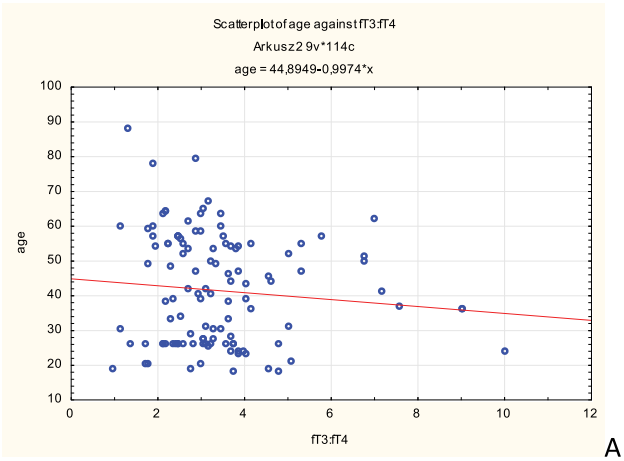
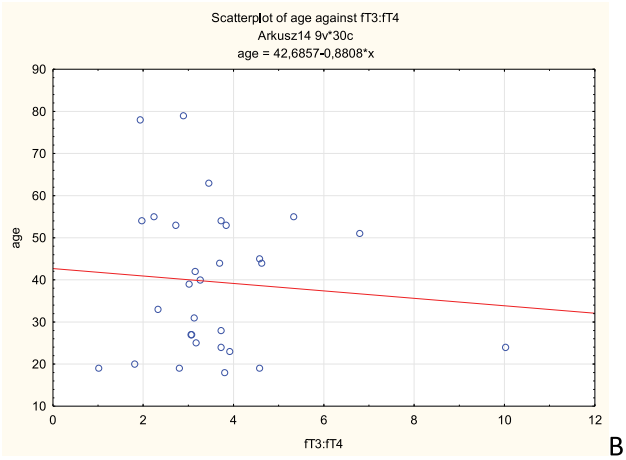


Fig. 2. Positive correlation between fT3:fT4 ratio and thyroid volume. A — the whole group, B — the first episode group, C — the recurrence group.





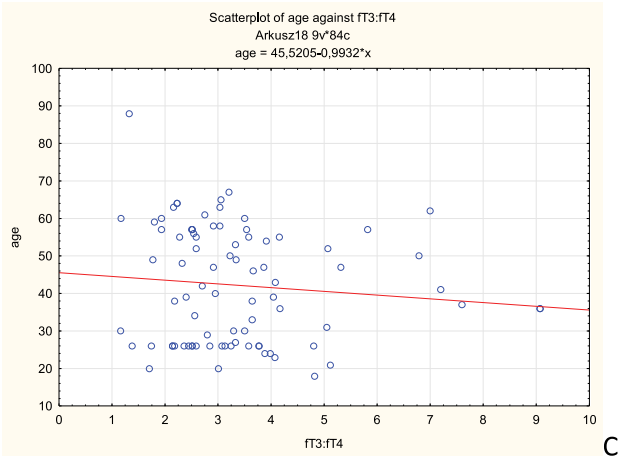


Fig. 3. Negative correlation between fT3:fT4 ratio and age of GD onset. A — the whole group, B — the first episode group, C — the recurrence group.

Discussion

There is no unequivocal treatment strategy for Graves' Disease. The first line therapy in The United States of America is radioiodine therapy after initial pharmacological management of acute phase of hyperthyroidism [8]. On the other hand — in Europe and Japan, long-term Antithyroid Drug Treatment (ATDT), lasting 12–18 months plays a main role [8]. The average rate of relapse after ATDT is 30–60% within 1–5years of discontinuation [4, 9]. The vast majority of recurrences occur in the first year after treatment [10]. This high rate of failure during treatment of GD indicates the need of accurate analysis of particular parameters among patients with different course of GD. It would create an opportunity to divide patients into several categories and choose the best strategy for treatment. Currently in Europe, all patients with GD are treated following the same algorithm regardless of the "resistance" to the conventional therapy [8]. This means that even those who show unresponsiveness to the pharmacological treatment, are exposed to long-term ATDT. This connects with higher risk of side effects, as well as elevating the costs of ineffective treatment. It evolves the need for clarifications of precise predictors of poor outcome during ATDT. Then those patients could be managed by radical methods (radioiodine therapy/surgery) after initial short time pharmacological treatment and they could be cured definitely just during the first episode of GD.

There are lots of studies analyzing different predictors, but there is no unequivocal consensus indicating precisely the values of particular parameters. In our work we confirm positive correlation between fT3:fT4 ratio and TRAb concentration (Fig. 1), positive correlation between fT3:fT4 ratio and goiter size (Fig. 2), as well as a negative correlation between fT3:fT4 ratio and age of onset (but not statistically significant) (Fig. 3). The hypothesis that higher fT3:fT4 ratio, TRAb level, goiter size and lower age of GD onset are predictors of worse response to ATDT remain coherent with many other studies. In our work we checked correlation between particular parameters in relation with fT3:fT4 ratio, because fT3 level reflects severity of hyperthyroidism.

TRAbs pose a major pathogenetic role in GD. They stimulate the thyroid gland, which contributes to elevation of triiodothyronine (T3) and thyroxine (T4) level as well as thyroid gland enlargement [4]. Moreover, TRAbs promote peripheral conversion of T4 to the ten times more active T3 [10]. These facts indicate that level of TRAb may correlate positively with the severity of the disease. Several works show that level of TRAb measured at the onset of GD or at the end of treatment remain a predictor of poor outcome of GD [4, 9, 11–14]. Dalia Dauksiene *et al.* claim that TRAb higher than 30.2 U/L at the onset of the disorder and higher than 12.97 U/L after ATDT withdrawal suggest insensitivity to pharmacological treatment [5].

The goiter size as a further predictor of poor response to ATDT is mentioned in several articles [1, 4, 5, 9, 15, 16]. Some of them point precise thyroid volume of more

than 40 mL [3], the others suggest grade II and III (according to the WHO classification) as an indicator of severe GD [1, 4]. Bjorn *et al.* claim that thyroidal hypoechogenicity on ultrasonography after ATDT discontinuation means active GD, contrasting with the ultrasonographic images at the onset of GD, which cannot be interpreted as a poor predictor [4, 9, 16, 17]. Vitti *et al.* revealed that thyroid hypoechogenicity on ultrasonography is closely associated with TRAb and TSH level [16].

Despite this higher fT3:fT4 ratio at the onset of GD is pointed out as a bad predictor of GD [1, 10], as there are not any accurate values above which unresponsiveness to pharmacological treatment can be confirmed. We found articles measuring this rate in regard to distinguishing different kinds of hyperthyroidism [6, 18] — but there are also some discrepancies, because the units of hormone levels are different in different studies, and the disambiguation is necessary.

Some authors suggest that continued TSH suppression after ATDT cessation predicts failure of pharmacological management. Prolonged TSH inhibition may indicate subclinical hyperthyroidism [5, 19].

Smoking [9, 20] and onset at a younger age also are pointed out in several articles as poor response to ATDT [7, 9]. Aizawa *et al.* mention that TRAb level and the severity of GD diminish with age [21].

The next question is: could modification of pharmacological approach influences the rate of relapses? The literature confirm that levothyroxine (LT4) added to ATDT (block and replacement) as well as LT4 supplementation after ATDT shows no differences in the results of treatment [4, 9, 22]. The philosophy of these approaches was explained by the thesis that exogenous suppression of TSH by synthetic thyroxine may put the thyroid gland in a resting state, reducing the risk of relapse due to stimulation by TSH. Despite this logical explanation, several works didn't prove the superiority of adding LT4 to the conventional pharmacological treatment of GD. Also a time of ATDT longer than 18 months doesn't contribute to better outcomes of treatment [1, 4].

Conclusions

Graves' Disease is associated with a high rate of relapses. The standard of management in Europe is the same for all patients, regardless of the existence of several factors considered as indicators for poor response to pharmacological therapy.

GD patients have a positive correlation between fT3:fT4 ratio and TRAB concentration, fT3:fT4 ratio and thyroid volume at the moment of thyrotoxicosis.

The fT3:fT4 ratio may be a predictor of an increased risk of relapse GD and may identify patients in whom early radical therapy would be beneficial to avoid bothersome relapses.

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Disclosure

The author declares that (s)he has no relevant or material financial interests that relate to the research described in this paper.

Conflict of interest

None declared.

Abbreviations

ATDT — antithyroid drug treatment
GD — Graves' Disease
LT4 — levothyroxine
T3 — triiodothyronine
fT3 — free triiodothyronine
T4 — thyroxine
fT4 — free thyroxine
TRAb — TSH receptor antibodies

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