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Original

The value of estimating serum apoptotic marker concentrations in the monitoring and prognosis of ^{131}I – therapy in Graves' disease. Preliminary report

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Abstract

BACKGROUND: The effect of radioiodine (^{131}I) in Graves' disease (GD) is probably due to the direct physical destruction of thyrocytes by beta radiation, and by the indirect action through stimulation of apoptosis in these cells. The aim of our study was to investigate the changes in serum concentrations of sFas and sFasL as stimulators of apoptosis, and Bcl-2 as an inhibitor of apoptosis in patients with GD following ^{131}I administration.
MATERIAL AND METHODS: The study was performed on 30 patients with GD (29 female and 1 male aged 25–45). All patients were euthyroid (biochemical and clinical) prior to radioiodine therapy. The target absorbed dose ranged between 90 and 160 Gy. We assessed markers of apoptosis and hormone concentrations (fT3, fT4 and TSH) in the following manner: before ^{131}I administration, then two weeks, one month, two, three, four, and five months after ^{131}I administration.
RESULTS: After four months, the concentrations of sFas and sFasL rose by 50% and decreased during the next month. Pretherapeutic concentrations of Bcl-2 were elevated, and peaked two weeks after ingestion, showing a gradual decrease with time. We found a significant increase in serum TSH, and a decrease of fT3 and fT4 concentrations by the end of the third month of radioiodine therapy.
CONCLUSIONS: Decreases in serum levels of sFas and sFasL and increases of Bcl-2 are regarded as characteristic for GD patients before radioiodine therapy. Radioiodine therapy reverses the ratio of estimated markers after four months. The concentrations of hormones reflect actual thyroid function, whereas concentrations of markers of apoptosis may suggest morphological changes.
Key words: Graves' disease, ^{131}I therapy, apoptosis

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Introduction

The hyperthyroidism of Graves' disease can be treated using three methods: by using antithyroid drugs which block production of thyroid hormones, radioiodine (^{131}I), which destroys active thyroid tissue, and surgery based on total or subtotal resection of the gland. Radioiodine therapy is the treatment of choice in the USA. Treatment with antithyroid drugs is popular in Japan, Europe, and Poland. When thyrostatics are less effective or poorly tolerated, over half of patients are treated with radioiodine [1, 2]. In a few cases, there are indications for surgery.

The ideal aim of using radioiodine is to achieve a euthyroid state, although many specialists believe that radioiodine therapy often causes hypothyroidism, and that this is a preferred outcome because hyperthyroidism is eliminated, whilst pharmacological therapy of hypothyroidism is relatively easy. Our department accepts cases with advanced cardiovascular symptoms and opthalmopathy for considerable or total destruction of thyroid tissue [3].

The determination of dosage of ^{131}I is difficult despite using Marinelli's formula, which takes into account isotope uptake and retention in the gland [4]. The cause of this difficulty is the inability to measure the radiosensitivity of the thyroid in a given patient. Using our own experience, and that of a few generations of thyroidologists, it would appear that differences in radiosensitivity are considerable.

The healing effect of ^{131}I arises probably as a result of the direct physical destruction of thyroctes by beta radiation, and by the indirect action through stimulation of apoptosis in these cells [5, 6].

In untreated Graves' disease, there is a constant stimulation of thyroid stimulating hormone (TSH) receptors by serum autoantibodies, which inhibits apoptosis [7, 8]. The beta and gamma radiation of ^{131}I which enters cells probably neutralizes their hormone stimulation and enhances auto destructive processes.

Cysteine proteases known as caspases play a main role in the process of apoptosis [9]. These enzymes are stored in cells in the form of inactive precursors. By the action of ionising radiation, these precursors undergo oligomerisation, and then autoproteolysis, whereby these precursors are rendered active. The activation of proteases may occur by an extracellular route by the family of membrane receptors known as "death receptors" (e.g. Fas/ /CD95 and it's corresponding ligand FasL; CD95L) [10]. The union of these subunits induces the activation of the caspase cascade. Many observations suggest that FasL binds to Fas, which belongs to the tumour necrosis factor (TNF) super-family of receptors, and produces a complex which is one of the strongest stimulators of apoptosis. In some cell lines, the expression of pro and anti-apoptotic proteins belonging to the Bcl-2 family may modulate the caspase cascade.

An increased intracellular concentration of Bcl-2 inhibits the processes leading to programmed cell death [11]. The Bcl-2 family of proteins participate in the regulation of intracellular (mitochondrial) processes of apoptosis.

The literature available on the subject does not mention the behaviour of apoptotic markers in the sera of patients with Graves' disease following radioiodine therapy. By proposing that the degree of apoptosis in thyroid glands following ^{131}I administration can be a measure of the extent of destruction of thyrocytes, the concentration of apoptotic markers may be useful in the prognosis and monitoring of patients. This is why we chose to assess the serum concentrations of soluble pro-apoptotic factors such as sFas and sFasL, and the anti-apoptotic protein Bcl-2 in Graves' disease patients treated with ^{131}I.

Materials and methods

The study was performed on 30 patients with Graves' disease (29 female, 1 male, aged 25–45 years), referred to our department for radioiodine therapy. Before treatment, all patients underwent clinical examinations; namely a physical examination, history, determination of free triiodothyronine (fT3), free thyroxine (fT4), TSH, ultrasound examination (US), ^{131}I scintigraphy and uptake (24 and 48 hour). Patients diagnosed with Graves' disease were unsuccessfully previously treated with antithyroid drugs 1–2 years, or did not consent to surgery. Ocular examination of 10 patients with moderate Graves' opthalmopathy eliminated the presence of active opthalmopathy. The concentrations of the hormones fT3 and fT4 in sera were assessed by radioimmunoassay, whilst TSH was detected by immunoradiometric assay (Polatom, Świerk). These concentrations were within normal values in all patients (i.e. fT3 = 3.1–6.5 pmol/L, fT4 = 9.3–23.2 pmol/L, TSH = 0.5–5.0 mU/L). We discontinued antithyroid drugs (methimazole, carbimazole) in all patients for at least four days prior to treatment. We estimated the effective half-life of radioiodine (Teff) by plotting the 24- and 48-hour uptakes on a semi-logarithmic chart. The administered radioactivity — A (in megabequerels — MBq) was calculated using the formula of Marinelli [4].

$$A\,(MBq) = \frac{Gy\ selected \times estimated\ gland\ weight\ (g) \times 24.946}{(\%)\ uptake\ at\ 24\ h\ (T_{24}) \times T_{1/2}eff\ (days)}$$

^{131}I ($Na^{131}I$) was given in gelatine capsules (Polatom, Świerk). The therapeutic activity ranged from 240–600 MBq.

The administrated dose ranged from 90 to 160 Gy. The thyroid mass before radioiodine therapy, based on scintigraphy and ultrasonography (US) worked out to be 35–60 g. Serum concentrations of pro and anti-apoptotic markers (sFas, sFasL, and Bcl-2) were assessed, along with the hormones fT3, fT4 and TSH before therapy, and following therapy (two weeks, one month, 2, 3, 4, 5 months). Apoptotic markers were assessed using ELISA immunoenzymatic sets (Bender, Austria). The control group consisted of 10 healthy volunteers from our department of a corresponding age. We performed statistical analysis using Student's *t*-test. We considered differences of P of value less than 0.05 to be significant.

The medical ethics committee of the Medical University of Białystok approved the protocol of the study, and we obtained written informed consent from all participants.

Results

The results presented in Figure 1 show a slight increase in the concentration of sFas in the sera of patients two weeks after ^{131}I administration, and then a successive decline in concentration by the first, second, and third months. We found considerably decreased concentrations in patients compared to controls. By the fourth month, we observed an almost double fold increase in the concentration of sFas, compared to those of the previous month. These concentrations were at this point greater than those of healthy subjects. By the fifth month, the concentrations of the markers decreased to control values.

The concentrations of sFasL, presented in Figure 2, show an increase in serum concentration at two weeks, and one month following ^{131}I administration, when compared to pretherapeutic concentrations. The results obtained before therapy, then two weeks and three months following ^{131}I ingestion show a significant decrease of marker concentrations lower than those observed in controls. The greatest concentrations of sFasL appeared during

Study groups / Time of study	Control group (n = 10)	Graves' disease (n = 30)
	pg/ml	pg/ml
Before ingestion	3.28 ± 0.02	2.27 ± 0.45
X ± SD		p < 0.0001
2 weeks after		2.73 ± 0.55
X ± SD		p < 0.01
1 month after		2.60 ± 0.52
X ± SD		p < 0.001
2 months after		2.40 ± 0.48
X ± SD		p < 0.0001
3 months after		1.90 ± 0.38
X ± SD		p < 0.0001
4 months after		3.83 ± 0.75
X ± SD		p < 0.05
5 months after		3.3 ± 0.61
X ± SD		NS

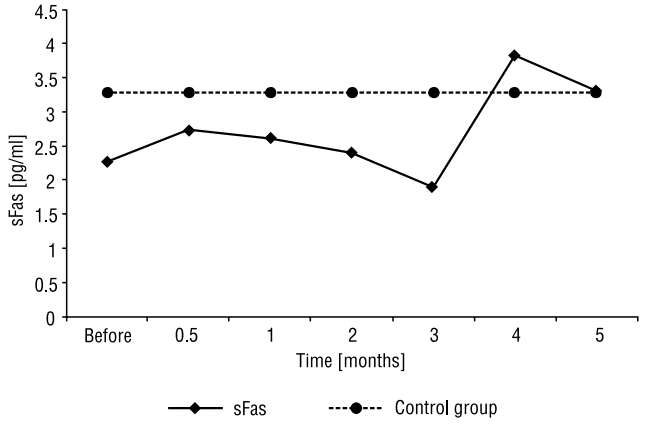

Figure 1. Mean concentrations of sFas in sera of patients with Graves' disease: in controls, before, two weeks, one, two, three, four and fifth months after ^{131}I ingestion; NS — no statistical significance.

Study groups / Time of study	Control group (n = 10)	Graves' disease (n = 30)
	ng/ml	ng/ml
Before ingestion	0.65 ± 0.07	0.59 ± 0.07
X± SD		p < 0.02
2 weeks after		0.60 ± 0.06
X± SD		p < 0.05
1 month after		0.64 ± 0.07
X± SD		NS
2 months after		0.62 ± 0.07
X± SD		NS
3 months after		0.60 ± 0.07
X± SD		p < 0.05
4 months after		0.68 ± 0.08
X± SD		NS
5 months after		0.6 ± 0.07
X± SD		p < 0.05

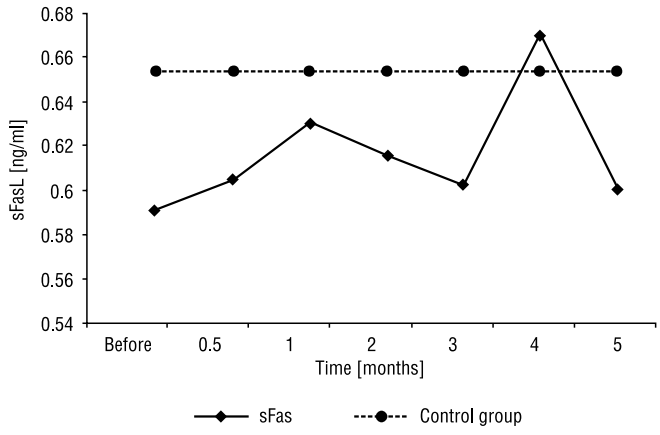

Figure 2. Mean serum concentrations of sFasL in patients with Graves' disease: in controls, before, two weeks, one, two, three, four and fifth months after ^{131}I ingestion; NS — no statistical significance.

the fourth month following ^{131}I administration, and were greater than those of the control group. The fifth month following ^{131}I administration showed a decline in sFasL to a value lower than that observed in controls.

The results presented in Figure 3 show an increase in the concentrations of Bcl-2 at 2 weeks, 1 month and 5 months after ^{131}I administration, in comparison to controls and pretherapeutic values. The highest concentrations of Bcl-2 appeared during the 2 weeks and fifth month following ^{131}I administration, and we observed the lowest concentrations three months following ^{131}I. Patients with Graves' disease had significantly higher concentrations of Bcl-2 during the whole observation period than did controls.

We observed a similar (Figure 4) increase in the concentration of fT4 at two weeks and four months after ^{131}I administration, and then a significant decrease by the third month, when compared to fT4 values, in comparison to pretherapeutic values. The concentrations of fT3 were lowest during the fourth month and highest during the second month following radioiodine ingestion. TSH concentrations in Graves' disease patients were significantly greater during the second and third months, in comparison to pretherapeutic values.

Our results correlated with a decrease in goitre size, weight gain, and a decrease in symptoms. Out of the group of 30 patients with Graves' disease, 8 patients (around 30%) required oral

Study groups	Control group (n = 10)	Graves' disease (n = 30)
Time of study	U/ml	U/ml
Before ingestion	1.31 ± 0.26	12.66 ± 0.97
X ± SD		p < 0.0001
2 weeks after		21.80 ± 2.32
X ± SD		p < 0.0001
1 month after		15.8 ± 1.35
X ± SD		p < 0.0001
2 months after		10.42 ± 2.08
X ± SD		p < 0.0001
3 months after		3.2 ± 0.64
X ± SD		p < 0.0001
4 months after		5.65 ± 0.78
X ± SD		p < 0.0001
5 months after		13.80 ± 1.87
X ± SD		p < 0.0001

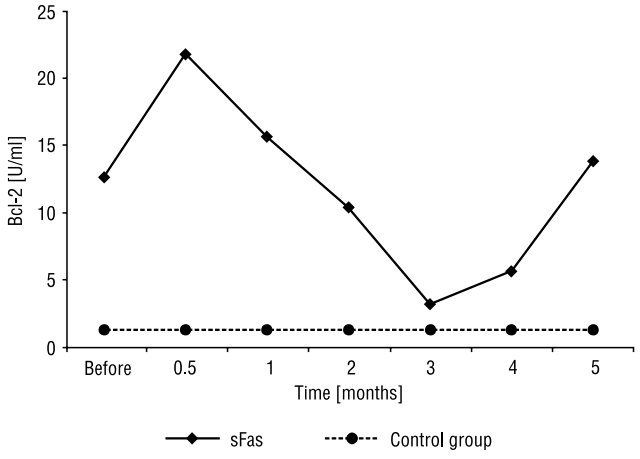

Figure 3. Mean serum concentrations of Bcl-2 in patients with Graves' disease: in controls, before, two weeks, one, two, three, four and fifth months after ^{131}I ingestion.

Study groups	Graves' disease (n = 30)		
Time of study	TSH [mU/L] Norm range (0.5–5)	FT3 [pmol/L] Norm range (3.1–6.5)	FT4 [pmol/L] Norm range (9.3–23.2)
Before ingestion X± SD	0.74 ± 0.09	4.50 ± 0.6	19.01 ± 2.25
2 weeks after X± SD	0.56 ± 0.04	5.0 ± 0.45	24.33 ± 2.18
1 month after X± SD	1.14 ± 0.12	5.8 ± 0.5	22.0 ± 2.12
2 months after X± SD	8.89 ± 1.21	5.94 ± 0.42	21.30 ± 2.16
3 months after X± SD	14.23 ± 2.24	3.65 ± 0.26	16.22 ± 1.18
4 months after X± SD	3.18 ± 0.23	2.05 ± 0.46	23.30 ± 2.16
5 months after X± SD	0.52 ± 0.12	3.0 ± 0.46	20.1 ± 1.15

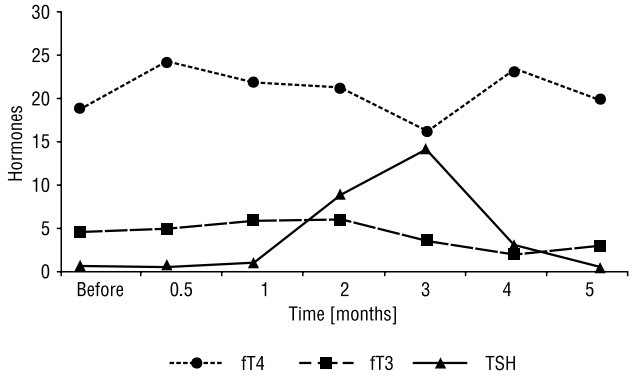

Figure 4. Mean serum concentrations of fT3, fT4 and TSH in patients with Graves' disease: before, two weeks, one, two, three, four and fifth months after ^{131}I ingestion.

hormone supplementation for hypothyroidism, 18 became euthyroid, and 4 were qualified for a second dose of radioiodine due to relapse of hyperthyroidism (Table 1).

Discussion

Graves' disease is an autoimmunological disease, dependant on the presence of serum antibodies to TSH receptors (TSI, thyroid stimulating immunoglobulins). Thyroid stimulating immunoglobulins stimulate thyrocytes and prevents their entry into the mechanism of apoptosis [7, 8].

The best moment to administer ^{131}I in patients with Graves' disease is when they are euthyroid (clinical and biochemical). The remission achieved during earlier treatment with antithyroid drugs protects patients from entering temporary thyrotoxicosis.

The literature on the topic indicates that the concentrations of Fas and FasL may correlate with the clinical course of Graves' disease; remaining elevated during the period of hyperthyroid-

Table 1. Results of ^{131}I treatment of patients with Graves' disease

Study groups	Graves' disease (GB) n = 30				
Time of study	Number of patients with hypothyroidism		Number of patients with euthyroidism	Number of patients with hyperthyroidism	
	Without substitution	With substitution		Without antithyroid drugs	With antithyroid drugs
Before ingestion n = 30	–	–	30	–	–
2 weeks after n = 30	–	–	17	13	
1 month after n = 30	–	–	23	–	7
2 months after n = 30	2	2	22	–	4
3 months after n = 30	1	6	21	–	2
4 months after n = 30	–	8	18	–	4
5 months after n = 30	–	8	18	–	4 Second dose of ^{131}I

ism, and decreasing during the period of remission [12]. Our own observations seem to confirm this hypothesis.

The pretherapeutic concentrations sFas and sFasL were significantly lower in comparison to those of the control group. On the one hand, it needs to be stressed that increased concentrations of the soluble ligand Fas may be a reaction to the increased biosynthesis of this receptor, and the readiness to enter the extracellular pathway of apoptosis. On the other hand, the binding of sFasL can prevent the initiation of apoptosis [13–15].

Histochemical findings suggest an increased biosynthesis of Bcl-2 by thyrocytes in Graves' disease patients during hyperthyroidism. The initiation of apoptosis usually arises after a decrease of this protein in thyrocytes and infiltrating lymphocytes [16]. What our study confirms is an elevated serum concentration of Bcl-2 before ^{131}I administration when compared to concentrations in healthy volunteers. This seems to support the idea of an increased expression of this protein during the course of Graves' disease.

In the early phase following administration of ^{131}I, necrotic death of thyrocytes considerably outweighs apoptosis. This corresponds to the effect of the intracellular presence of beta emitting radioiodine. An inflammatory reaction of varying intensity is observed in tissues during this period. At two weeks following ^{131}I ingestion, we observed a significant increase in the concentrations of sFas, sFasL, Bcl-2 and fT4 in sera, when compared to pretherapeutic concentrations.

One month following ^{131}I administration saw a further rise in sFasL and TSH, and a decrease in the concentrations of sFas, Bcl-2 and fT4, compared to the values obtained two weeks earlier. These results seem to suggest a fading out of necrosis. This observed increase in the concentration of soluble Fas ligand may be regarded as an indicator of increased apoptotic processes [17].

We noticed a significantly greater increase in TSH concentrations two months after ^{131}I administration, in comparison to controls. Four patients showed clinical and biochemical features of hypothyroidism. All patients showed a decrease in thyroid volume. These changes were accompanied by a decrease in the concentrations of sFas, sFasL, Bcl-2, fT3 and fT4. These results appear to suggest a mechanism of protection against excessive thyrocyte loss. The examinations of the following months confirmed this hypothesis, namely by a further rise in serum TSH, accompanied by a significant rise in Bcl-2. Furthermore, this was associated with a decrease in fT4, sFas, and sFasL concentrations.

The fourth month following ^{131}I ingestion showed a significant increase in the concentration of sFas, sFasL and Bcl-2, compared to the third month. The concentration of fT4 increased, and TSH decreased, returning to pretherapeutic values. Of interest is the fact that the mean concentrations of sFas and sFasL rose to a concentration exceeding that of controls (for the first time following ^{131}I administration), whilst Bcl-2 was greater in controls.

We observed a decrease in the concentrations of sFas and sFasL, with an accompanying rise in Bcl-2 at five months following ^{131}I ingestion compared to the results of the previous month. This observation may suggest an increased anti-apoptotic process.

Our last examinations showed that 18 patients became euthyroid, 8 required hormonal substitution, and 4 required repeated administration of ^{131}I. The average decrease in goitre volume was around 45%. The concentrations of Bcl-2 increased, whilst sFas and sFasL decreased in recurrences of hyperthyroidism. We observed an inverse relationship of these markers in the case of hypothyroidism.

The results we achieved regarding the effectiveness of treating Graves' disease patients using radioiodine are similar to those described in European literature [1, 17, 18]. The interpretation of the change in serum concentrations of apoptotic markers is difficult with respect to an absence of data on the subject, namely the

effect of radioiodine on apoptosis in Graves' disease. The literature available on the topic suggests that the process of apoptosis is an underlying feature of autoimmunological thyroid disease [19, 20]. The interaction of Fas/FasL appears to be the main factor initiating apoptosis in most thyroid disease states [21, 22].

The common opinion is that apoptosis is a result of the simultaneous stimulation of not one, but many death receptors, and the disturbance of the balance between pro and anti-apoptotic factors [19, 23].

Of considerable interest is the opinion that apoptosis may be an indicator of tissue radiosensitivity, and that Bcl-2 is excessively expressed by radioresistant cells [24, 25].

Maybe our data allow the administered activity of radioiodine to be tailored to tissue radiosensitivity, with a subsequent decrease in the number of patients who become hypothyroid following the radioiodine therapy of Graves' disease [26].

Conclusions

1. A significant decrease in the peripheral blood concentrations of sFas and sFasL (stimulators of apoptosis) and a significant increase in Bcl-2 concentration (an inhibitor of apoptosis), are regarded as characteristic for Graves' disease patients before radioiodine treatment.
2. Radioiodine therapy reverses the ratio of estimated markers after four month of therapy. Furthermore, after five months of treatment, in euthyroid patients, the average concentrations of Bcl-2 are increased, and sFas and sFasL are decreased to pretherapeutic concentrations.
3. The concentrations of thyroid hormones and TSH reflect actual thyroid function, whereas concentrations of apoptotic markers may suggest morphological changes that precede changes in thyroid gland function.

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