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Early changes of thyroid hormone concentrations after ^{131}I therapy in Graves' patients pretreated or not with methimazole

Frühe Schilddrüsenhormon-Konzentrationsänderungen nach ^{131}I-Therapie bei Basedow-Patienten mit und ohne Methimazol-Vorbehandlung

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Keywords
Graves' hyperthyroidism, ^{131}I therapy, methimazole

Summary
Aim: Despite extensive use of ^{131}I therapy for Graves' hyperthyroidism the treatment regimen with ^{131}I and antithyroid drugs remain under discussion. In our prospective clinical study we followed acute thyroid hormone changes after ^{131}I in patients not pretreated with methimazole (MMI) and in patients with different MMI pretreatment regimens. **Patients, methods:** 187 patients were treated with fixed activity of 550 or 740 MBq of ^{131}I. First group (71 patients) received ^{131}I alone. In the second group (57 patients) MMI was stopped seven days before ^{131}I. The third group (59 patients) received MMI until ^{131}I application. Initial free triiodothyronin and free thyroxin were measured in the second group 7 and 2 days before ^{131}I therapy and in all three groups on the day of ^{131}I application as well as 2, 5, 12, and 30 days afterwards. Absorbed dose was measured in each patient. **Results:** In the non-pretreated group ^{131}I application was followed by a significant decrease of fT_4 in 5 days and of fT_3 in 2 days, higher reduction was detected in patients with higher baseline values. In MMI pretreated patients significant but clinically irrelevant increase of both thyroid hormones was detected with maximum value 7 days after discontinuation in the second group and 5 days after discontinuation in the third group. Additionally, in patients of the third group absorbed dose of ^{131}I was significantly lower relative to other two groups. We found no correlation between absorbed dose of ^{131}I and thyroid hormone changes. **Conclusion:** Our study demonstrates that ^{131}I application alone does not result in exacerbation of hyperthyroidism and therefore it may be considered as safe. Additionally, MMI withdrawal causes significant but clinically irrelevant elevation of thyroid hormones.

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Schlüsselwörter
Basedow-Hyperthyreose, ^{131}I-Therapie, Methimazol

Zusammenfassung
Ziel: Trotz häufiger Anwendung der ^{131}I-Therapie bei Basedow-Hyperthyreose ist das Therapieschema mit ^{131}I und Thyreostatika nach wie vor umstritten. In unserer prospektiven klinischen Studie führten wir eine Verlaufskontrolle akuter Veränderungen der Schilddrüsenhormone nach ^{131}I-Therapie bei Patienten durch, die entweder nicht oder unterschiedlich mit Methimazol (MMI) vorbehandelt wurden. **Patienten, Methodik:** 187 Patienten wurden mit einer fixierten Aktivität von 550 oder 740 MBq von ^{131}I behandelt. Die erste Gruppe (71 Patienten) erhielt nur eine ^{131}I-Therapie. In der zweiten Gruppe (57 Patienten) wurde die MMI-Therapie sieben Tage vor der ^{131}I-Therapie gestoppt. Die dritte Gruppe (59 Patienten) erhielt MMI bis zur Anwendung von ^{131}I. Anfangs erfolgte eine Messung von freiem Trijodthyronin und freiem Thyroxin: in der zweiten Gruppe 7 und 2 Tage vor der ^{131}I-Therapie und in allen drei Gruppen am Tag der ^{131}I-Anwendung sowie 2, 5, 12 und 30 Tage danach. Die resorbierte Dosis wurde gemessen. **Ergebnisse:** In der nicht vorbehandelten Gruppe kam es nach der ^{131}I-Gabe zu signifikanter Reduktion von fT_4 innerhalb von 5 Tagen und von fT_3 innerhalb von 2 Tagen. Eine stärkere Reduktion war bei Patienten mit höheren Ausgangswerten nachweisbar. Bei MMI-Vorbehandelten wurde ein signifikanter, jedoch klinisch nicht relevanter Anstieg beider Schilddrüsenhormone festgestellt. Die Höchstwerte waren 7 Tage nach dem Therapieabbruch in der zweiten Gruppe und 5 Tage nach dem Therapieabbruch in der dritten Gruppe nachweisbar. Außerdem war die resorbierte Dosis von ^{131}I bei der dritten Gruppe signifikant niedriger im Vergleich zu den anderen beiden Gruppen. Wir fanden keine Korrelation zwischen der resorbierten ^{131}I-Dosis und den Veränderungen der Schilddrüsenhormonkonzentrationen. **Schlussfolgerung:** Unsere Studie belegt, dass die ^{131}I-Therapie allein zu keiner Verschlimmerung der Hyperthyreose führt und daher als sicher betrachtet werden kann. Zudem verursacht der MMI-Entzug einen signifikanten, jedoch klinisch nicht relevanten Anstieg der Schilddrüsenhormone.

For several decades Graves' hyperthyroidism has been treated with ^{131}I. Its effect on the follicular cell necrosis (11) may be accompanied by radiation thyroiditis with usually mild symptoms. Considering the acute thyroid hormone changes after ^{131}I application, the results are contradictory. Some authors found short-term increase of thyroid hormone concentrations (7, 21), whereas others observed no changes (20, 26) or even immediate decrease of thyroid hormone concentrations (1, 4, 5, 14). To prevent possible exacerbation of hyperthyroidism antithyroid drugs are frequently prescribed before ^{131}I treatment (9, 16, 22). However, antithyroid drugs might reduce the effectiveness of ^{131}I therapy (18, 19, 23, 28) and according to some authors they should be stopped a few days before ^{131}I application. Recently, Andrade et al. (1) and Burch et al. (4) observed significant increase of thyroid hormone concentrations following antithyroid drug discontinuation, while ^{131}I application itself was not followed by exacerbation of hyperthyroidism. Therefore, in spite of extensive clinical use of ^{131}I only a few data of the acute changes of thyroid hormones after ^{131}I application in patients pretreated or not pretreated with MMI are available.

The aim of our prospective clinical study was to determine whether ^{131}I application causes clinical or biochemical exacerbation of hyperthyroidism in Graves' patients. Additionally, we evaluated the effect of methimazole (MMI) pretreatment on the acute changes of thyroid hormone concentrations after ^{131}I therapy.

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Patients and methods

Patients

187 patients with Graves' disease, diagnosed on the basis of biochemical hyperthyroidism, presence of TSH receptor antibodies (TSAb), and diffuse goiter with hypoechogenic ultrasound (US) pattern were included in the study (10). Exclusion criteria were

- previous treatment with radioiodine or thyroidectomy,
- severe ophthalmopathy and
- severe heart disease (symptomatic coronary heart disease or heart failure class III or IV according to the New York Heart Association criteria).

The study was approved by the local ethical committee and all patients gave informed consent before ^{131}I therapy.

Methods

TSH, free thyroxin (fT_4) and free triiodothyronin (fT_3) were measured using direct chemoluminiscent immunoassay (Bayer Diagnostics, Tarrytown, New York, USA; reference values: 0.35-5.5 mU/l, 11.5-22.7 pmol/l, and 3.5-6.5 pmol/l, respectively). TSAb were measured by TRAK Assay, first generation (Brahms, Hennigsdorf, Berlin, Germany; values >13 U/l were considered positive). Goiter volume was estimated ultrasonographically according to the standard formula

$a \times b \times c \times \pi/6$

(a: length, b: depth, c: width of each lobe and isthmus in cm) (3). ^{131}I-uptake after 24 hours was evaluated, using tracer activity of 1.85 MBq. Absorbed dose of ^{131}I was measured for each patient using method of cumulated activity (17).

Treatment protocol

We observed three groups of Graves' patients treated with ^{131}I. Patients of the

- first group were treated for the first recurrence of Graves' hyperthyroidism only with ^{131}I (without MMI pretreatment).

Other Graves' patients were treated for hyperthyroidism with MMI and they were consecutively divided in the second and third group. In the

- second group MMI (10 mg/d) was stopped seven days before ^{131}I therapy and the
- third group received MMI (10 mg/d) till the ^{131}I application.

Most patients received the fixed activity of 550 MBq, while others received 740 MBq of ^{131}I according to the goiter volume and the presence of Graves' ophthalmopathy. Initial fT_3 and fT_4 levels were measured in the second group 7 and 2 days before ^{131}I therapy and in all three groups on the day of ^{131}I application and 2, 5, 12, as well as 30 days after. On each occasion patients were clinically examined. Their symptoms of nervousness, heat intolerance, palpitations, hyperdefecation and neck tenderness were evaluated on a scale ranging from 0 to 3 (0: none, 1: mild, 2: moderate, 3: severe). All patients in the first group were treated with β adrenergic blockers (propranolol 40-120 mg/d). Patients in the second and the third group were treated with MMI for 2-12 months (median value, 4 months and 5 months, respectively) before ^{131}I.

Statistical analysis

Initial clinical and laboratory characteristics of the three groups were compared using χ^2 test for qualitative variables or using Student's *t* test for quantitative variables. The changes of clinical parameters, serum concentrations of fT_3 and fT_4 before and after ^{131}I therapy were analyzed using Student's *t* test. The symptoms after ^{131}I therapy were analyzed using χ^2 test. With Spearman's rank correlation procedure we assessed the relationship between fT_3 and fT_4 changes and following parameters: clinical signs and symptoms, absorbed dose of ^{131}I and thyroid volume. $P < 0.05$ was considered significant.

Results

As summarized in Table 1 groups of patients did not differ according to age, gender distribution, number of smokers,

	group 1	group 2	group 3
no. of patients	71	57	59
gender (women/men)	62/9	48/9	53/6
age, year (min - max)	45.6 ± 13.6 (17-80)	41.9 ± 12.3 (20-64)	46.5 ± 12.5 (22-75)
% of smokers	32.2	29.8	27.1
fT_4 before ^{131}I (pmol/l) mean ± SD	39.6 ± 19.0 *	16.6 ± 7.4	20.3 ± 13.2
fT_3 before ^{131}I (pmol/l) mean ± SD	13.3 ± 6.6 *	6.1 ± 2.7	7.5 ± 5.3
TSAb (U/l) median (min - max)	11 (1-289)	9 (1-162)	13 (1-178)
goiter volume (ml) mean ± SD	30.9 ± 15.3	33.6 ± 16.8	33.5 ± 17.5
^{131}I uptake (%) after 24 h	72 ± 18	76 ± 15	52 ± 20*
received activity of ^{131}I (MBq), mean ± SD	580.3 ± 60.6	571.9 ± 55.4	582.9 ± 70.9
AD of ^{131}I (Gy) mean ± SD	158.5 ± 104.3	168.8 ± 103.6	115.6 ± 92.9 **

Tab. 1
Patients data
(SD: standard deviation; AD: absorbed dose; *p <0.0001; **p <0.01)
group 1: without pretreatment
group 2: methimazole (MMI) stopped 7 days before ^{131}I application
group 3: MMI till the day of ^{131}I application

goiter volume and TSAb. FT_4 and fT_3 levels were significantly higher in non-pretreated patients. The number of patients with euthyroidism, subclinical hyperthyroidism (decreased TSH, fT_4 and fT_3 within the refernce ranges) and overt hyperthyroidism (decreased TSH elevated fT_4 and fT_3) in each group is presented in Table 2. Interestingly, TSAb value positively correlated with fT_3 concentrations before ^{131}I application in all three groups (non-pretreated group: R = 0.35, p <0.005; group with MMI stopped 7 days before ^{131}I: R = 0.67, p <0.0001; group treated with MMI till ^{131}I: R = 0.36, p <0.01).

Absorbed dose of ^{131}I was significantly lower in the third group receiving methimazole till the ^{131}I application, compared with the second group with MMI stopped 7 days before ^{131}I (p <0.01). ^{131}I-uptake after 24 hours was significantly lower in the third group receiving MMI till ^{131}I compared with the other two groups (p <0.0001) (Tab. 1). No significant changes of subjective symptoms were observed in all three groups. 4 patients (mean age, 63 years) had atrial fibrillation (1 patient in the first group, 2 patients in the second group and 1 patient in the third group), which persisted during 1 month of observation.

fT_4

As shown in Figure 1a the first non-pretreated group experienced a significant decrease of fT_4 level as soon as 5 days after ^{131}I application (39.6 ± 19.0 pmol/l at ^{131}I versus 34.2 ± 16.9 pmol/l 5 days after, p <0.001) with the lowest value 12 days after ^{131}I (29.2 ± 15.5 pmol/l). In the second group, receiving MMI till 7 days before ^{131}I, 5 days after stopping MMI fT_4 was significantly higher than the initial value (22.0 ± 14.0 pmol/l versus 16.6 ± 7.4 pmol/l, p <0.001) and further increased till ^{131}I (7 days after stopping MMI, 23.1 ± 14.5 pmol/l). Maximum value was reached 2 days after ^{131}I (9 days after stopping MMI, 26.6 ± 22.9 pmol/l). This value was significantly higher compared with the initial level and the level at ^{131}I application (p <0.0005 and p <0.05, respectively). 30 days after ^{131}I therapy values were still significantly higher than at the time of stopping MMI (23.4 ± 17.5 pmol/l versus 16.6 ± 7.4 pmol/l, p <0.01).

Tab. 2 Number of patients with euthyroidism, subclinical or overt hyperthyroidism before ^{131}I therapy
group 1: without pretreatment; group 2: methimazole (MMI) stopped 7 days before ^{131}I application; group 3: MMI till the day of ^{131}I application

	group 1	group 2	group 3
euthyroidism	0	15	18
subclinical hyperthyroidism	8	15	17
overt hyperthyroidism	63	27	24

In the third group receiving MMI till ^{131}I a significant increase of fT_4 was observed 2 days after ^{131}I application and MMI withdrawal compared to the initial value (22.8 ± 15.2 pmol/l versus 20.3 ± 13.2 pmol/l, p <0.0005). Maximum increase was detected 5 days after ^{131}I (26.6 ± 19.8 pmol/l, p <0.0001), afterwards a gradual decrease of fT_4 was observed.

fT_3

Changes of fT_3 are shown in Figure 1b. In the first non-pretreated group significant decrease of fT_3 was observed as soon as 2 days after ^{131}I therapy (11.3 ± 4.8 pmol/l versus 13.3 ± 6.6 pmol/l, p <0.001) with the lowest value 30 days after ^{131}I (8.2 ± 3.6 pmol/l). An increase of fT_3 value for

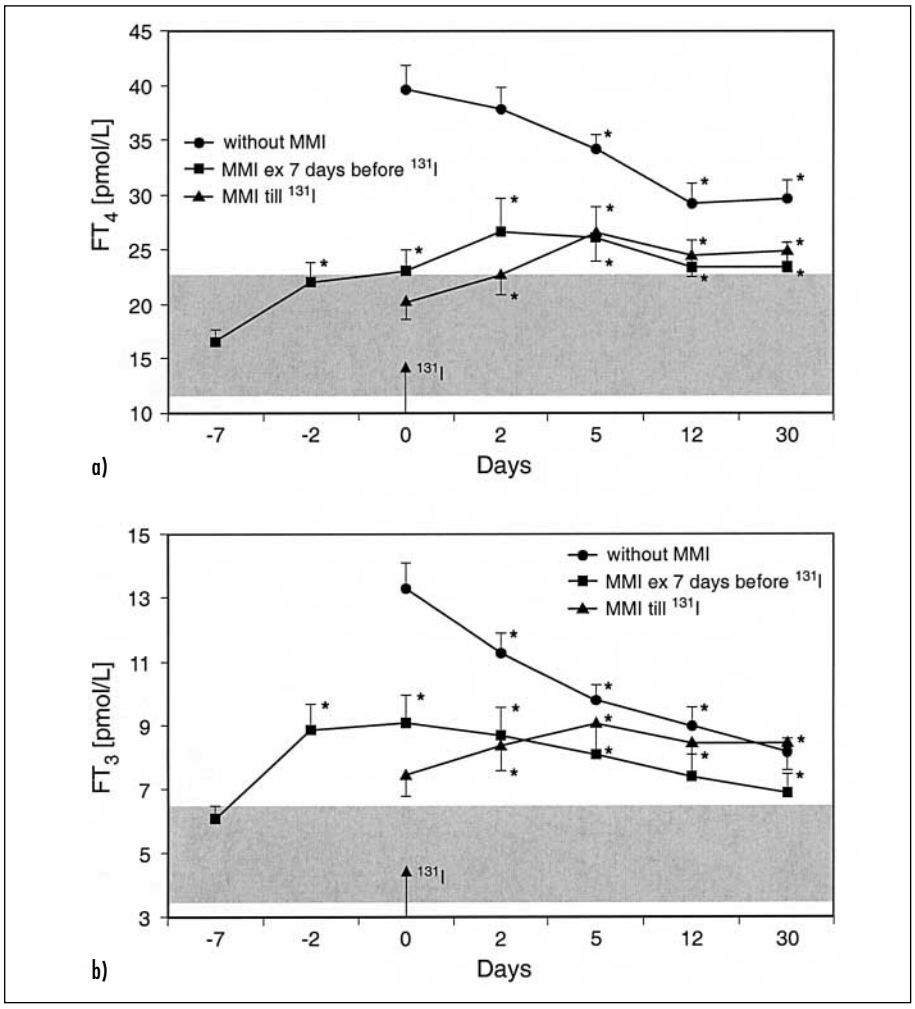

Fig. 1 Changes of fT_4 (a) and fT_3 (b) concentrations after MMI withdrawal and ^{131}I therapy: mean values and standard error (SE); reference range depicted in grey; *p <0.01 (compared with initial value)

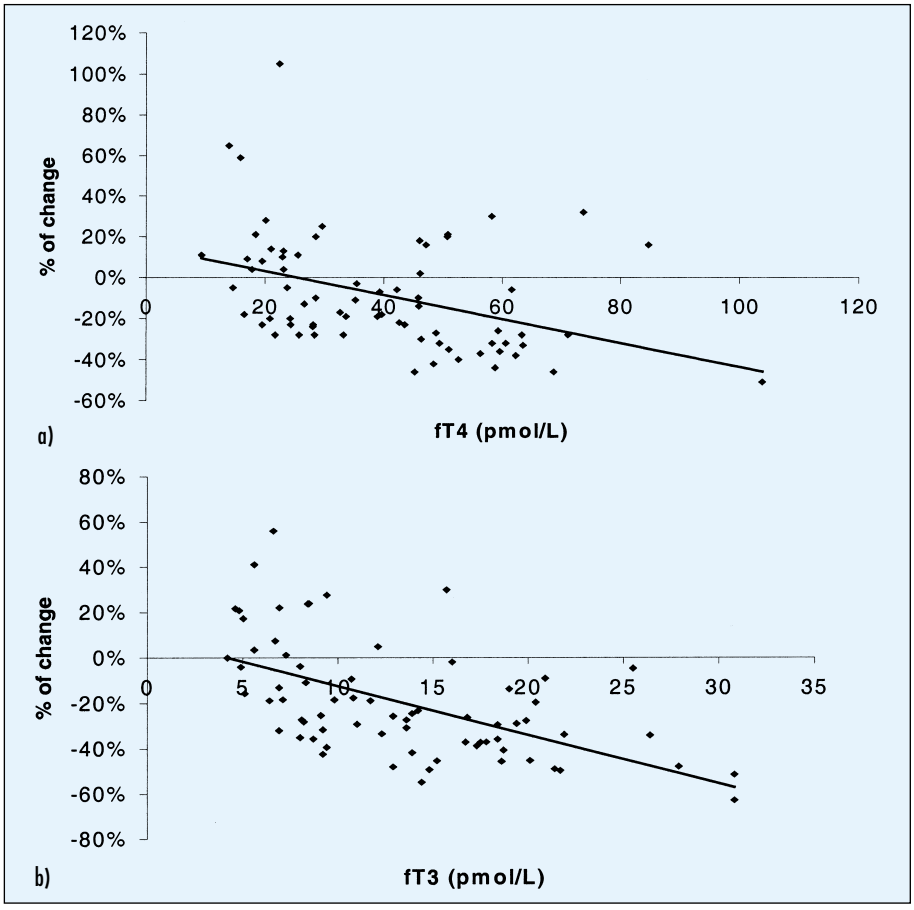

Fig. 2 Correlation between fT_4 (a) and fT_3 (b) before ^{131}I application and % of change in non-pretreated group after 5 days

Tab. 3 Correlation between thyroid hormone changes and ^{131}I uptake after 24 hours, absorbed dose of ^{131}I and goiter volume
a) in the second group (methimazole stopped 7 days before ^{131}I)
b) in the third group (methimazole stopped at ^{131}I application)

a)

time after ^{131}I	2 days		5 days		12 days	
	ΔfT_4	ΔfT_3	ΔfT_4	ΔfT_3	ΔfT_4	ΔfT_3
^{131}I uptake after 24 h	**R = 0.35 p <0.01**	**R = 0.41 p <0.005**	**R = 0.34 p <0.05**	**R = 0.36 p <0.01**	R = 0.26 p = NS	R = 0.22 p = NS
absorbed dose of ^{131}I	R = -0.20 p = NS	R = -0.18 p = NS	R = -0.24 p = NS	R = -0.21 p = NS	R = -0.21 p = NS	R = -0.15 p = NS
goiter volume	**R = 0.57 p <0.0001**	**R = 0.48 p <0.0005**	**R = 0.55 p <0.0001**	**R = 0.47 p <0.0005**	**R = 0.48 p <0.0005**	**R = 0.41 p <0.005**

b)

time after ^{131}I	2 days		5 days		12 days	
	ΔfT_4	ΔfT_3	ΔfT_4	ΔfT_3	ΔfT_4	ΔfT_3
^{131}I uptake after 24h	R = 0.25 p = NS	**R = 0.43 p <0.001**	R = 0.16 p = 0.234	R = 0.09 p = NS	R = 0.14 p = NS	R = 0.06 p = NS
absorbed dose of ^{131}I	R = -0.03 p = NS	R = -0.14 p = NS	R = -0.12 p = NS	R = -0.13 p = NS	R = -0.17 p = NS	R = -0.22 p = NS
goiter volume	**R = 0.33 p <0.05**	**R = 0.52 p <0.0001**	**R = 0.37 p <0.005**	R = 0.12 p = NS	R = 0.16 p = NS	R = 0.15 p = NS

more than 10% with no clinical worsening was observed in 9 patients, 5 of them had normal or slightly elevated baseline values.

In the second group, receiving MMI till 7 days before ^{131}I, 5 days after stopping MMI fT_3 significantly increased compared to the baseline value (8.9 ± 5.9 pmol/l versus 6.1 ± 2.7 pmol/l, p <0.001). Maximum value was detected 7 days after stopping MMI (9.1 ± 6.9 pmol/l, p <0.001). In the third group receiving MMI till ^{131}I significant increase was observed 2 days after ^{131}I therapy and stopping MMI (8.4 ± 5.8 pmol/l versus 7.5 ± 5.3 pmol/l, p <0.001) with the highest value after 5 days (9.1 ± 6.5 pmol/l, p <0.001).

Correlation between thyroid hormone changes and other parameters

In non-pretreated group a significantly higher reduction of thyroid hormones after ^{131}I application was observed in patients with higher baseline values (Fig. 2). On the contrary, the increase of thyroid hormones for more than 10% from baseline value occurred in 5 patients with subclinical hyperthyroidism and in only 4 patients with overt hyperthyroidism. No correlation was found between thyroid hormone changes and other parameters, including absorbed dose of ^{131}I and thyroid volume. In the second group, receiving MMI till 7 days before ^{131}I, both goiter volume and ^{131}I uptake after 24 hours correlated with increase of both thyroid hormones, while no correlation with absorbed dose of ^{131}I was found (Tab. 3a). Compared to the second group, in the third group receiving MMI till ^{131}I similar correlations were observed only 2 days after ^{131}I (Tab. 3b).

Discussion

Our study of 71 Graves' patients not pretreated with MMI provides evidence that ^{131}I application itself does not cause aggravation of clinical or biochemical hyperthyroidism. Moreover, ^{131}I therapy was followed by a significant decrease of

fT_3 as soon as after two days and of fT_4 after five days; afterwards both thyroid hormones gradually decreased during one-month period. This observation is in accordance with Andrade et al. (1) and Burch et al. (4) who found significant decrease of both thyroid hormones five days after ^{131}I in 28 and 21 Graves' patients not pretreated with MMI. Similarly, Kreisig et al. (14) reported significant decrease of total T_3 in 396 unselected hyperthyroid patients pretreated or not pretreated with MMI. Other authors (20, 26) detected no short-term change of thyroid hormone levels.

In contrast, Koornstra et al. (13) found asymptomatic increase in thyroid hormone levels in 29% of 21 Graves' patients treated only with ^{131}I. In equal group of 36 patients Stensvold et al. (24) reported increase in 36% four weeks after ^{131}I therapy. Results of a few earlier studies of unselected study population were similar. Creutzig et al. (7) reported an increase of serum T_3 concentrations 1 day after ^{131}I application in 46 not pretreated hyperthyroid patients with diffuse goiter. Similar was the observation of Shafer et al. (21) in 13 unselected patients.

Since worsening of hyperthyroidism had been frequently cited as an early complication of ^{131}I therapy, McDermott et al. (15) reviewed the literature regarding thyroid storm after ^{131}I therapy. In 2975 ^{131}I treated patients, half of them pretreated with antithyroid drugs, 0.34% experienced thyroid storm and 0,88% exacerbation of hyperthyroidism. Accordingly, the major proposed mechanism was the release of stored thyroid hormones after thyroid cell necrosis.

Regarding our and similar studies (1, 4), clinically important release of thyroid hormones after ^{131}I therapy did not occur in the majority of patients, especially in those with higher baseline thyroid hormone levels. Possible explanations are small amount of stored hormones in highly stimulated gland, cessation of new hormone synthesis and loss of intact follicular cells needed for adequate proteolysis of thyroglobulin (8). Shorter biological half-life in hypermetabolic state may contribute to our interesting observation that the decline of both thyroid hormone levels was greater in patients with higher pretreatment values. Faster decrease of fT_3 compared to fT_4 may be caused by similar mechanism together with inhibitory effect of β-blocking agents on fT_4 to fT_3 conversion.

Our study of 116 patients pretreated with MMI shows MMI discontinuation to be followed by a significant increase of both thyroid hormones regardless the time of stopping treatment before ^{131}I application. Similar results were obtained by some other authors (1, 2, 4, 5) and even thyrotoxic storm has been reported lately (12). According to Bogazzi et al. (2) this effect might be prevented with lithium. Recently, in vitro study has shown that MMI increases TPO mRNA and cellular TPO activity (25). Therefore, a transient increase of thyroid hormone synthesis that follows MMI discontinuation in Graves' patients might be related to relatively high intracellular TPO activity, especially if hyperthyroidism is still present at the time of stopping MMI.

Nevertheless, antithyroid drugs are frequently recommended before ^{131}I therapy of Graves' disease (9, 16, 22). They might reduce the risk of worsening thyrotoxicosis after ^{131}I application by reducing the amount of previously formed thyroid hormones. They act as inhibitors of thyroid hormone synthesis by inhibiting the TPO-catalyzed iodination of Tg (6, 27). According to several studies, antithyroid drug treatment at the time of ^{131}I diminishes the success of ^{131}I therapy and therefore authors recommend discontinuation before ^{131}I (18, 19, 23, 28). As shown in our and other studies patients who received MMI till ^{131}I application had significantly lower absorbed dose of ^{131}I, which is one of the major factors influencing the success of ^{131}I therapy. However, an optimal regimen of MMI treatment before ^{131}I remains unsolved.

Conclusion

Our study of Graves' patients revealed that ^{131}I alone does not result in worsening of hyperthyroidism in majority of patients; the decrease of both thyroid hormones is even higher in more hyperthyroid patients. It turned out that MMI discontinuation results in an aggravation of hyperthyroidism, regardless of the time of stopping before ^{131}I. However, absolute maximum values of thyroid hormones after stopping MMI are still far below the values in non-pretreated patients. It is our opinion, that treatment with ^{131}I alone is safe and therefore recommended in most patients with hyperthyroidism. However, we believe that severely hyperthyroid patients should be pretreated with MMI until the euthyroid state is reached. After a few days of MMI discontinuation ^{131}I application will be safe and effective.

References

1. Andrade VA, Gross JL, Maia AL. Effect of methimazole pretreatment on serum thyroid hormone levels after radioactive treatment in Graves' hyperthyroidism. J Clin Endocrinol Metab 1999; 84: 4012-6.
2. Bogazzi F, Bartalena L, Campomori A et al. Treatment with lithium prevents serum thyroid hormone increase after thionamide withdrawal and radioiodine therapy in patients with Graves' disease. J Clin Endocrinol Metab 2002; 87: 4490-5.
3. Brunn J, Block U, Ruf G et al. Volumetrie der Schilddrüsenlappen Mittels Real-time-Sonographie: Dtsch Med Wschr 1981; 106: 1338-40.
4. Burch HB, Solomon BL, Cooper DS et al. The effect of antithyroid drug pre-treatment on acute changes in thyroid hormone levels after ^{131}I ablation for Graves' disease. J Clin Endocrinol Metab 2001; 86: 3016-21.
5. Burch HB, Solomon BL, Wartofsky L et al. Discontinuing antithyroid drug therapy before ablation with radioiodine in Graves' disease. Ann Inter Med 1994; 121: 553-9.
6. Cooper DS. Antithyroid drugs for the treatment of hyperthyroidism caused by Graves' disease. Endocrinol Metab Clin North Am 1998; 27: 225-47.
7. Creutzig H, Kallfelz J, Haindl J et al. Thyroid storm and iodine-131 treatment. Lancet 1976; 2: 145-6.
8. Date J, Blichert-Toft M, Feldt-Rasmussen U et al. Lacking evidence for release of thyroid hormones from circulating thyroglobulin during subtotal thyroidectomy. Acta Endocrinol 1988; 117: 219-24.
9. Dietlein M, Dressler J, Joseph K et al. Guideline for radioiodine therapy (RIT) in benign thyroid diseases (version 2). Nuklearmedizin 2002; 41: N72-3 .
10. Dietlein M, Dressler J, Grünwald F et al. Guideline for in vivo- and in vitro procedures for thyroid diseases (version 2). Nuklearmedizin 2003, 42: 109-15.

11. Dobyns BM, Vickery AL, Maloof F et al. Functional and histologic effects of therapeutic doses of radioactive iodine on the thyroid of man. J Clin Endocrinol Metab 1953; 13: 548-67.
12. Kadmon PM, Noto RB, Boney CM et al. Thyroid storm in a child following radioactive iodine (RAI) therapy: a consequence of RAI versus withdrawal of antithyroid medication. J Clin Endocrinol Metab 2001; 86: 1865-7.
13. Koornstra JJ, Kerstens MN, Hoving J et al. Clinical and biochemical changes following 131I therapy for hyperthyroidism in patients not pretreated with antithyroid drugs. Neth J Med 1999; 55: 215-21.
14. Kresig T, Abenhard W, Mann K et al. Frühveränderungen der Schilddrüsenhormone nach Radiojodtherapie der Hyperthyreose unter Berücksichtigung von Ätiologie und begleitender Medikation. Klin Wochensch 1989; 67: 386-92.
15. McDermott MT, Kidd GS, Dodson LE et al. Radioiodine induced thyroid storm-case report and literature review. Am J Med 1983; 75: 353-9.
16. Meier DA, Brill DR, Becker DV et al. Procedure guideline for therapy of thyroid disease with iodine-131. J Nucl Med 2002; 43: 856-61.
17. Pirnat E, Fidler V, Zaletel K et al. Early change of thyroid hormone concentration after I treatment in patients with solitary toxic adenoma. Nuklearmedizin 2002; 4: 178-83.
18. Reynolds LR, Kotchen TA. Antithyroid drugs and radioactive iodine fifteen years' experience with Graves' disease. Arch Intern Med 1979, 139: 651-3.
19. Sabri O, Zimny M, Schulz G et al. Success rate of radioiodine therapy in Graves' disease: the influence of thyrostatic medication. J Clin Endocrinol Metab 1999, 84: 1229-33.
20. Schimmel M, Utiger RD. Acute effect of inorganic iodine after ^{131}I therapy for hyperthyroidism. Clin Endocrinol 1977; 6: 329-32.
21. Shafer RB, Nuttal FQ. Acute changes in thyroid function in patients treated with radioactive iodine. Lancet 1975; 6: 635-7.
22. Solomon B, Glinoer D, Lagasse R et al. Current trends in the management of Graves' disease. J Clin Endocrinol Metab 1990; 70: 1518-24.
23. Sridama V, McCormick M, Kaplan LE et al. Long-term follow-up study of compensated low-dose ^{131}I therapy for Graves' disease. N Engl J Med 1984; 311: 426-32.
24. Stensvold AD, Jorde R, Sundsfjord J. Late and transient increase in free T4 after radioiodine treatment for Graves' disease. J Endocrinol Invest 1997; 20: 580-4.
25. Sugawara M, Sugawara Y, Wen K. Methimazole and propylthiouracil increase cellular thyroid peroxidase activity and thyroid peroxidase mRNA in cultured porcine thyroid follicles. Thyroid 1999; 9: 513-8.
26. Tamaga EJ, Levine GA, Hershman JM. Thyroid hormone concentrations after radioiodine therapy for hyperthyroidism. J Nucl Med 1979; 20: 387-91.
27. Taurog AM. Thyroid hormone synthesis – Hormone synthesis: thyroid iodine metabolism. In: Braverman LE, Utiger RD (eds). Werner and Ingbar's the Thyroid. 8th ed. Philadelphia : Lippincott-Raven 2000; 61-85.
28. Tuttle RM, Patience T, Budd S. Treatment with propylthiouracil before radioactive iodine therapy is associated with a higher treatment failure rate than therapy with radioactive iodine alone in Graves' disease. Thyroid 1995; 5: 243-7.

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