Relationship between Serum Free Thyroid Hormone Concentrations and Target Organ Responsiveness in Thyroid Disease Patients before and after Treatment

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YOSHIDA, K., SAKURADA, T., KAISE, K., KAISE, N., NOMURA, T., ITAGAKI, Y., YAMAMOTO, M., SAITO, S. and YOSHINAGA, K. *Relationship between Serum Free Thyroid Hormone Concentrations and Target Organ Responsiveness in Thyroid Disease Patients before and after Treatment.* Tohoku J. Exp. Med., 1989, **159** (4), 323-331 — Relationship between serum free thyroid hormone concentrations and several markers of peripheral tissue response to thyroid status was studied in 24 patients with hyperthyroidism, 17 with euthyroidism with goiter and 10 with primary hypothyroidism before and after the initiation of standard forms of treatment. Before treatment, serum free T_4 correlated significantly, either positively or negatively, with the basal metabolic rate (BMR), duration of the achilles tendon reflex (ATR), resting pulse rate (RPR), serum total cholesterol (T-cholesterol), ratio of the pre-ejection period to the left ventricular ejection time (PEP/LVET), serum high density lipoprotein (HDL) and creatine phosphokinase (CPK) in the descending order. Serum free T_3 also correlated significantly all the these parameters. After treatment, changes in both serum free T_4 and free T_3 correlated well with those of the BMR and ATR in the patients with hyperthyroidism, and with those of the ATR, serum CPK and T-cholesterol in the patients with hypothyroidism. These results indicate that these peripheral parameters correlated well with serum free thyroid hormone concentrations in thyroid disease patients. Therefore, these parameters can be used to assess thyroid functions in patients with thyroid hormone resistance. ——— thyroid hormones; thyroid diseases; target organ

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function, major emphasis is generally placed on measurement of the concentration of circulating thyroid hormones. It is apparent, however, that the ultimate determinants of the thyroidal status of the patient are the biological effects of thyroid hormones (Bantle et al. 1980). In patients with thyroid hormone resistance there is a discrepancy between serum free thyroid hormone concentrations and peripheral thyroid hormone effects (Refetoff et al. 1967, 1983).

This study was undertaken to compare serum free thyroid hormone concentrations with several markers of peripheral tissue response to thyroid hormone in patients with hyperthyroidism, hypothyroidism and euthyroidism with goiter before and after the standard forms of treatment. As measures of peripheral thyroid hormone effects we used several commonly employed indices (Becker 1986), such as the basal metabolic rate (BMR), duration of the achilles tendon reflex (ATR), resting pulse rate (RPR), ratio of the pre-ejection period to the left ventricular ejection time (PEP/LVET), serum creatine phosphokinase (CPK), high density lipoprotein (HDL), and total cholesterol (T-cholesterol) concentrations.

SUBJECTS AND METHODS

Fifty-one patients referred to our clinic were studied. Twenty-four of them were hyperthyroid, as judged by both clinical and laboratory criteria. Seventeen of the hyperthyroid patients were female and 7 were male. The mean age of the hyperthyroid patients was 30. These patients took 10 mg of methylmercaptoimidazole (MMI) three times per day and BMR, RPR, and ATR were measured and blood samples for measurements of serum free T_4 , T_3 , CPK, HDL and T-cholesterol were obtained every two weeks for 12 weeks.

Seventeen of the patients, who had diffuse or nodular goiter, were euthyroid as judged by both clinical and laboratory criteria. They were diagnosed as having Hashimoto's thyroiditis or adenoma of the thyroid. Their serum TSH concentrations measured by highly sensitive immunoradiometric assay were within normal limits. Fifteen of them were female and 2 were male. The mean age was 45.

Ten of the patients had primary hypothyroidism, as judged by elevated serum TSH and low free T_4 levels, 3 of them had normal and 7 had low free T_3 levels. They were all female and their mean age was 50.

The euthyroid and hypothyroid patients were treated with L- T_4 . In most patients, the initial dose of L- T_4 was 25 $\mu\text{g}/\text{day}$. At approximately monthly intervals, the dose of L- T_4 was increased by 25 $\mu\text{g}/\text{day}$ to a maximum of 100 $\mu\text{g}/\text{day}$. Measurements of thyroid hormones and their effects were carried out monthly. Measurement of PEP/LVET was not done after the treatment.

Serum free T_4 and free T_3 concentrations were measured by radioimmunoassay using commercial kits (Amersham; Amersham Japan, Tokyo). The normal ranges were 0.62–2.30 ng/100 ml for free T_4 and 2.53–4.85 pg/ml for free T_3 , respectively. Serum TSH concentration was measured by a highly sensitive immunoradiometric assay kit (RIA-gnost hTSH, Hoechst Japan, Tokyo), and the normal range was 0.28–3.42 $\mu\text{U}/\text{ml}$. The M mode echocardiography was used to measure LVET and PEP (Lewis et al. 1979), and the normal range was 0.206–0.310. RPR was measured immediately before the BMR determination, and the normal range was 60–80 beat/min. All other laboratory tests were performed in the routine chemistry laboratories of the Tohoku University Hospital. Laboratory-derived reference ranges were used for BMR (–10% + 15%), ATR (205–260 msec), CPK (50–193 IU/liter for men and 46–135 IU/liter for women), HDL (38–81 mg/100 ml) and T-

cholesterol (128~225 mg/100 ml).

Statistical analyses were performed using the *t*-test for unpaired and paired comparison. Correlations between two different variables were calculated by linear regression analyses.

RESULTS

Before treatment

Pretreatment mean serum free T_4 , free T_3 , CPK, HDL, T-cholesterol concentrations and the BMR, ATR, PEP/LVET, RPR in the patients with hyperthyroidism, euthyroidism with goiter and hypothyroidism are shown in Table 1. The BMR, ATR and RPR were in the hyperthyroid range in most of the patients with hyperthyroidism, and the BMR and PEP/LVET were in the hypothyroid range in most of the hypothyroid patients with low serum free T_3 concentrations. All of the peripheral parameters tested were in the normal range in more than two out of three hypothyroid patients with normal serum free T_3 levels. Most of the peripheral parameters were in the normal range in the euthyroid patients with goiter. More than half of the peripheral parameters were in the hyperthyroid range in 21 out of 24 hyperthyroid patients, in the normal range in 16 out of 17 euthyroid patients with goiter, and in the hypothyroid range in 6 out of 7 hypothyroid patients with low free T_3 levels and in 0 out of 3 hypothyroid patients with normal free T_3 levels.

Correlations between serum free thyroid hormone concentrations and peripheral parameters are shown in Table 2. Serum free T_4 correlated significantly, either positively or negatively with the BMR, ATR, RPR, T-cholesterol, PEP/LVET, HDL and CPK in the descending order. Serum free T_3 also correlated significantly with all these parameters (Table 2).

After treatment

Changes in serum free T_4 and free T_3 concentrations and the peripheral parameters in the hyperthyroid patients after the treatment with MMI are shown in Fig. 1. After the treatment for 12 weeks, serum free T_4 and free T_3 decreased to 17 and 18% of the initial values, respectively. As serum free T_4 and free T_3 decreased, the BMR and RPR also decreased and the ATR, serum CPK, HDL and T-cholesterol tended to increase. Alterations in both serum free T_4 and free T_3 concentrations after the MMI treatment correlated significantly with the changes in all of the peripheral parameters tested, but better with the BMR and ATR than the other parameters (Table 3).

In euthyroid patients with goiter, serum free T_4 increased significantly after the treatment with 25 μ g of L- T_4 , but serum free T_3 increased and serum TSH decreased after 50 μ g of L- T_4 . However, all of the peripheral parameters did not change significantly even after 100 μ g/day of L- T_4 (data not shown).

Changes in serum free thyroid hormone concentrations and the peripheral parameters in the hypothyroid patients after the treatment with L- T_4 are shown

TABLE 1. *Serum free thyroid hormone concentrations and peripheral parameters in thyroid disease patients*

		Hyperthyroid	Euthyroid	Hypothyroid
FT ₄ (ng/100 ml)	Mean	7.60**	1.10	0.26**
FT ₃ (pg/ml)	Mean	38.9**	3.5	1.6**
BMR (%)	Mean	+44**	+7	-16**
	Number in hyper range	22	3	0
	Number in normal range	2	13	4 (3)
	Number in hypo range	0	1	6
ATR (msec)	Mean	185**	239	280*
	Number in hyper range	21	0	0
	Number in normal range	2	13	4 (2)
	Number in hypo range	0	2	6 (1)
PEP/LVET	Mean	0.245	0.272	0.356*
	Number in hyper range	3	0	0
	Number in normal range	8	8	1 (1)
	Number in hypo range	1	2	5
RPR (beat/min)	Mean	92**	65	62
	Number in hyper range	23	2	0
	Number in normal range	1	14	6 (3)
	Number in hypo range	0	1	4
CPK (IU/l)	Mean	46**	101	484
	Number in hyper range	13	0	0
	Number in normal range	10	14	5 (2)
	Number in hypo range	0	2	5 (1)
T-chole (mg/100 ml)	Mean	143**	212	240
	Number in hyper range	7	0	0
	Number in normal range	17	12	4 (2)
	Number in hypo range	0	5	6 (1)
HDL (mg/100 ml)	Mean	48	56	59
	Number in hyper range	7	0	0
	Number in normal range	16	15	7 (1)
	Number in hypo range	0	0	1

The number of hypothyroid patients with normal free T₃ levels is in parentheses.

* $p < 0.05$; ** $p < 0.01$ vs. euthyroid values.

in Fig. 2. As serum free T₄ and free T₃ increased, the BMR and RPR increased, while the ATR, serum CPK and T-cholesterol decreased, but HDL did not change significantly. Changes in both serum free T₄ and free T₃ concentrations correlated significantly with those of the ATR, serum CPK and T-cholesterol concentrations, but not with those of the RPR and serum HDL concentrations (Table 3).

TABLE 2. Correlation between serum free thyroid hormone concentrations and peripheral parameters

	FT ₃	BMR	ATR	PEP/LVET	RPR	CPK	HDL	T-chole
FT ₄	0.96**	0.89**	-0.83**	-0.62**	0.80**	-0.34*	-0.34*	-0.77**
FT ₃	—	0.88**	-0.81**	-0.55**	0.66**	-0.35*	-0.38*	-0.75**

* $p < 0.05$; ** $p < 0.01$. Fig. 1. Changes in serum free thyroid hormone concentrations and peripheral parameters in the patients with hyperthyroidism treated with daily dose of 30 mg of MMI. Values given are means $\pm$ S.D. B.T., before treatment.* $p < 0.05$; ** $p < 0.01$ vs. values before treatment.

TABLE 3. Correlation between changes in serum free thyroid hormone concentrations and those in peripheral parameters in patients with hyper- and hypo-thyroidism after treatment

		FT ₃	BMR	ATR	RPR	CPK	HDL	T-Chole
Hyperthyroid	FT ₄	0.97**	0.82**	-0.62**	0.41**	-0.31*	-0.52**	-0.54**
	FT ₃	—	0.77**	-0.66**	0.34*	-0.40*	-0.44**	-0.39*
Hypothyroid	FT ₄	0.70**	0.51**	-0.56**	0.22	-0.53**	-0.00	-0.62**
	FT ₃	—	0.32	-0.65**	0.06	-0.54**	-0.36	-0.58**

* $p < 0.05$; ** $p < 0.01$.

Fig. 2. Changes in serum free thyroid hormone concentrations and the peripheral parameters in the patients with hypothyroidism treated with increasing dose of L-T₄. Values given are means ± s.d.

* $p < 0.05$; ** $p < 0.01$ vs. values before treatment.

DISCUSSION

A small but significant number of patients have been described to have congenital or acquired refractoriness to thyroid hormone. Serum free T_4 and free T_3 levels in these patients are elevated despite the fact that they appear to be clinically euthyroid and often have an elevated serum TSH (Refetoff et al. 1967, 1983). Confirmation of their euthyroid status with peripheral parameters is important in the delineation of this syndrome. The BMR, ATR, circulatory function, serum cholesterol and some enzymes such as CPK are commonly used as measures of peripheral thyroid hormone effects (Becker 1986). The major difficulty with those parameters is that they are affected by factors other than thyroid hormones. However, when many of these parameters are measured in groups of patients with overt hyperthyroidism or hypothyroidism, unequivocal and statistically significant abnormalities are found (Gow et al. 1987).

In the present paper, relationship between serum free thyroid hormone concentrations and several markers of peripheral tissue response to thyroid hormones was studied in thyroid disease patients before and after the standard forms of treatment. And we found that serum free T_4 and free T_3 concentrations correlated significantly with all of the parameters tested. Among the peripheral parameters the BMR and ATR correlated especially well with serum free T_4 and free T_3 concentrations.

Measurements of the BMR, ATR and RPR were especially useful to discriminate hyperthyroidism from euthyroidism, and those of the BMR and PEP/LVET were useful to differentiate hypothyroidism from euthyroidism. Bantle et al. (1980) reported that there were the large changes in serum cholesterol and CPK concentrations, and ATR in the transition from hypothyroidism to the euthyroid state and the small changes in these parameters in the transition from euthyroid to hyperthyroidism. They concluded that elevated levels of serum cholesterol and CPK and prolonged ATR are more useful in supporting the diagnosis of hypothyroidism than are reduced values in the diagnosis of hyperthyroidism. In our series, however, ATR were in the hyperthyroid range in 21 out of 23 patients with hyperthyroidism and in the hypothyroid range in 5 out of 7 hypothyroid patients with low free T_3 levels. Therefore, we think that ATR is useful to differentiate not only hypothyroidism from euthyroid state, but also euthyroidism from hyperthyroidism.

After the treatment, alterations in serum free T_4 and free T_3 concentrations correlated especially well with those of the BMR and ATR in patients with hyperthyroidism, and with those of the ATR, serum CPK and T-cholesterol concentrations in patients with hypothyroidism. We have recently reported (Yoshida et al. 1989, 1990) that red blood cell (RBC) zinc (Zn) in patients with hyperthyroidism was decreased and after treatment with antithyroid drugs the normalization of RBC Zn lagged about 2 months behind the normalization of

plasma thyroid hormones. Furthermore, the RBC Zn levels significantly correlated with the plasma T_4 levels obtained 0, 4, 8 and 12 weeks prior to the RBC sampling, and the highest correlation was observed between the RBC Zn levels and plasma T_4 levels measured 8 weeks previously (Yoshida et al. 1989). Therefore, it is likely that RBC Zn levels in hyperthyroid patients reflect integrated plasma thyroid hormone levels over the previous few months, not just at the time of measurement. In the present study, however, all of the parameters tested reflected thyroid hormone levels at the time of measurement.

In patients with subclinical hypothyroidism (normal serum free T_4 levels, but elevated serum TSH levels), Cooper et al. (1984) reported that no significant changes occurred in the mean systolic time interval, BMR and serum cholesterol levels as a result of T_4 treatment (50 μg daily), and Bell et al. (1985) reported that T_4 treatment (75–125 μg daily) did not cause significant changes in sleeping heart rate, nerve conduction velocities and serum lipids. In our euthyroid patients with goiter, whose serum TSH level was normal before treatment, serum free T_4 and free T_3 increased, and serum TSH decreased after the treatment with L- T_4 , but the peripheral parameters did not change at all. These results may be because the doses of L- T_4 (50–125 μg daily) were not sufficient to induce alterations in the peripheral parameters in euthyroid patients.

Our results indicate that these peripheral parameters correlated significantly with serum free thyroid hormone concentrations and some of them were useful to discriminate hyperthyroidism and hypothyroidism from euthyroidism, indicating that these parameters can be useful to assess thyroid functions in patients with thyroid hormone resistance.

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