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A Patient with Graves' Hyperthyroidism Associated with Non-Insulin Dependent Diabetes Mellitus Who Showed T4-Toxicosis

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A 41-year-old man was admitted to Tottori University Hospital because of a very poor control state of diabetes mellitus (DM). At admission, he showed T4-toxicosis [T4 13.4 μg/dL, free T4 (FT4) 3.0 ng/dL, T3 105 ng/dL, and free T3 (FT3) 2.7 pg/mL] with a high reverse T3 (rT3; 189 ng/dL) and a high thyroid $^{99m}TcO4^-$-uptake (8.0%), and did not show apparent physical findings suggestive of hyperthyroidism except for a diffuse goiter. After the initiation of diet and insulin therapy for DM, his serum FT3 level was gradually increased despite a slight decrease in his serum FT4 level, and reached a supra-normal level (5.4 pg/mL) on the 35th day after admission. In this interval, he became to show apparent physical findings suggestive of hyperthyroidism, such as tachycardia, moist skin, finger tremor and a decrease in diastolic blood pressure. Both serum FT4 and FT3 levels were in normal ranges 3 weeks after the initiation of methimazole therapy. Thus, the patient with Graves' hyperthyroidism associated with a very poor control state of DM may show T4-toxicosis, which is induced by the inhibition of extrathyroidal conversion of T4 to T3. Such a patient may not show apparent physical findings suggestive of hyperthyroidism owing to normal FT3 level and probably owing to the diminished T3-binding to the T3 receptor and/or post-T3 receptor responses.

Key words: diabetes mellitus; Graves' hyperthyroidism; T4-toxicosis

Some hyperthyroid patients associated with severe non-thyroidal illness (NTI) may show T4-toxicosis (Joasso, 1975; Engler et al., 1978; Caplan et al., 1980; Shigemasa et al., 1982) because the illness inhibits extrathyroidal conversion of T4 to T3. In diabetic patients, who are not in diabetic coma, inhibition of extrathyroidal T4 to T3 conversion has also been reported (Pittman et al., 1979; Kabadi, 1984). To our knowledge, however, there have been no reports of hyperthyroid patients associated with non-insulin dependent diabetes mellitus (NIDDM) who showed T4-toxicosis. On the other hand, the metabolic impact and adaptive significance of the low T3 state in patients with NTI is less well understood. It has been reported that rat hepatic (Surcs et al., 1978) and pituitary (St. Germain and Galton, 1985) nuclear T3-receptor numbers are reduced by NTI and starving. Furthermore, a divergence in post-receptor T3 responses occur in fasted rats (Oppenheimer and Schwartz, 1980), and T3 administration does not appear to alter the rate of weight loss in rats (Schwartz et al., 1980).

We reported herein a patient with Graves' hyperthyroidism associated with NIDDM who developed T4-toxicosis and did not show apparent physical findings suggestive of hyperthyroidism except for a diffuse goiter.

Abbreviations: DM, diabetes mellitus; FBS, fast blood sugar; FT3, free T3; FT4, free FT4; MMI, methimazole; NIDDM, non-insulin dependent diabetes mellitus; NTI, non-thyroidal illness; rT3, reverse T3; TBG, T4-binding globulin; TSH, thyroid-stimulating hormone

Patient report

A 41-year-old man was admitted to Tottori University Hospital because of general fatigue, thirst, and polydipsia for one month. He had lost progressively 13 kg over the previous one and a half months. He had noted already the excretion of urine sugar 4 years before. Thereafter, however, he did not visit any physician. He also had not ingested an excessive amount of seaweed and had not received treatment with iodide.

At admission, he was emaciated weighing 42.4 kg (at 170 cm). His blood pressure was 108/74 mmHg, pulse rate 66 beats/min and body temperature 36.2˚C. Moist skin and finger tremors were not found. The thyroid was diffusely enlarged (transverse width, 4.3 cm) with a smooth surface and soft consistency. Results of chest and abdomen examinations were unremarkable. Abnormal neurological findings, such as hyperactive deep tendon reflexes with a brisk relaxation phase and sensory disturbance, and abnormal findings of ocular fundi were not noted.

Laboratory values were as follows: fasting blood sugar, (FBS) 445 mg/dL; HbA1c, 12.5%; serum sodium, 136 mEq/L; potassium, 4.9 mEq/L; chloride, 95 mEq/L; blood urea nitrogen, 20 mg/dL; and creatinine, 0.6 mg/dL; total serum calcium, 9.6 mg/dL with albumin, 4.3 g/dL; alkaline phosphatase, 253 IU/L (normal, 111–295); total bilirubin, 0.5 mg/dL; glutamic oxaloacetic transaminase, 27 IU/L (normal, < 40); glutamic pyrubic transaminase, 27 IU/L (normal, < 47); lactic dehydrogenase, 159 IU/L (normal, 100–225) and total cholesterol, 186 mg/dL; hematocrit, 44.3% and Hb, 14.8 g/dL; C-reactive protein, < 0.06 mg/dL; arterial blood bicarbonate, 24 mmol/L (normal, 21–26); urine sugar, > 1.0 g/dL; ketonuria, (+); albuminuria, (–); and a daily excretion of urine sugar, 126.9 g; finally, urinary excretion of C-peptide was at 14.6 μg/day (normal, 43–146).

Methods

Serum T4, T3, rT3 and TBG concentrations were measured by RIA kits (Amerlex M-T4; Amersham International Ltd., Amersham, United Kingdom, T3-RIA·Beads and rT3 kit; Dainapot Radioisotope Laboratories, Tokyo, Japan, and Riagnost TBG; Hoechst Japan, Tokyo, respectively). The T3-uptake value was determined using macroaggregated albumin as inert binding material (Amersham International). The serum thyroid-stimulating hormone (TSH) level was measured using immunoradiometric assay (Riagnost hTSH, Hoechst Japan). Serum free T4 (FT4) and free T3 (FT3) concentrations were measured using Amerlex MAB

Table 1. Results of thyroid function tests at admission

Parameter	(unit)	Datum	Normal range
T4	(μg/dL)	13.4	4.5 – 12.0
T3	(ng/dL)	105	80 – 190
rT3	(ng/dL)	189	19.0 – 37.5
T3-uptake	(%)	43.3	24 – 35
FT4	(ng/dL)	3.0	0.95 – 1.84
FT3	(pg/mL)	2.7	2.2 – 4.6
TBG	(μg/mL)	17.6	12 – 30
TSH	(mU/L)	< 0.03	0.1 – 3.0
Anti-thyroglobulin antibody		< 80 ×	< 80 ×
Anti-microsomal antibody		8100 ×	< 100 ×
TSH-binding inhibitory immunoglobulin	(%)	14.6	< 14.8
Thyroid-stimulating antibody*	(%)	113	< 145
$^{99m}Tc4^{-}$-uptake	(%)	8.0	0.7 – 3.0

FT3, free T3; FT4, free T4; rT3, reverse T3; TBG, TS-binding globulin; TSH, thyroid-stimulating hormone.
*Measured using cultured porcine thyroid cells.

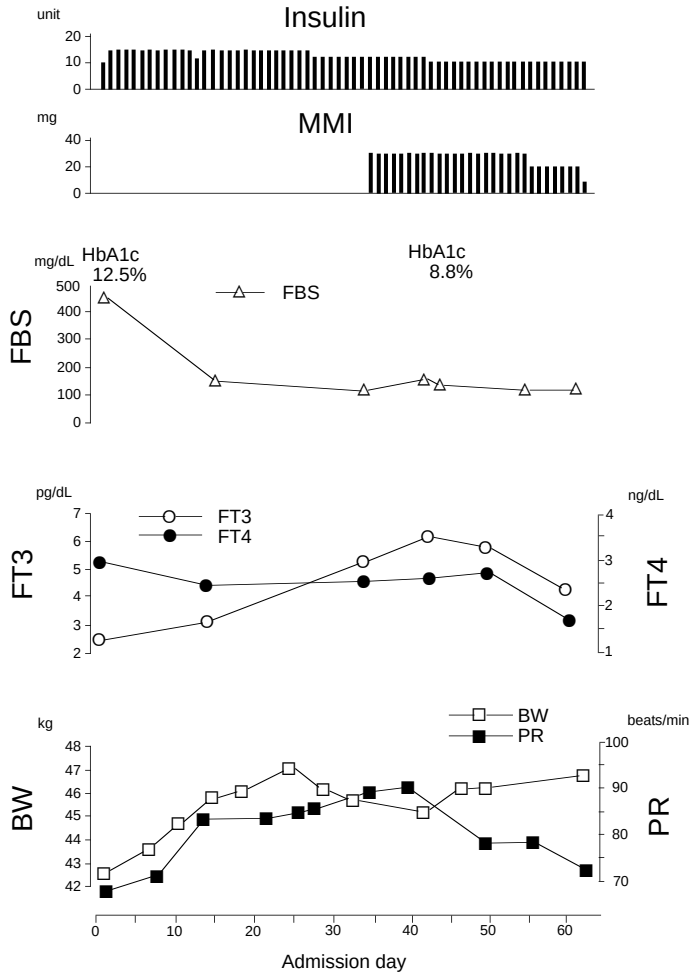

Fig. 1. The sequencial changes in clinical findings after the initiation of therapy for diabetes mellitus. BW, body weight; FBS, fasting blood sugar; FT3, free triiodothyronine; FT4, free thyroxine; MMI, methimazole; PR, pulse rate.

kits (Amersham International). Urinary excretion of C-peptide was measured by a RIA kit (C-Peptide Kit "Daiichi" III, Daiichi Radioisotope Laboratories, Ltd., Japan). Serum insulin concentration was measured by a RIA kit (Ab bead insulin "Eiken", Tokyo). HbA1c was measured by HPLC (Hi-AUTO A1c HA-8131, Kyoto-Daiichi Kagaku, Kyoto, Japan).

Thyroid function at admission

Results for the thyroid function tests at the initial examination were shown in Table 1. T4-toxicosis (T4 13.4 μg/dL, T3 105 ng/dL, T3-uptake 43.3%, FT4 3.0 ng/dL FT3 2.7 pg/mL) with high reverse T3 (rT3; 189 ng/dL) and high thyroid $^{99m}TcO4^{-}$-uptake (8.0%) was observed. Serum T4-binding globulin (TBG) concentration was normal (17.6 μg/mL).

Clinical course

We evaluated the sequential changes in clinical findings including serum FT4 and FT3 concentrations after the initiation of therapy for diabetes mellitus (DM). The sequential changes in serum FT4 and FT3 concentrations were evaluated in the same assay series.

Immediately after admission, diet (1920–2080 kcal/day) and insulin (Humalin N-40; 14–10 U/day) therapies were initiated. As shown in Fig. 1, according to the improvement of the control state of BS and the increase of body weight, the serum FT3 concentration gradually

increased in spite of a slight decrease in serum FT4 which reached a supra-normal level (5.4 pg/mL) on the 35th day after admission. At that time, serum T3, rT3, T4 and FT4 concentrations and the T3-uptake value were 198 ng/dL, 52 ng/dL, 12.8 μg/dL, 2.51 ng/dL and 39.1%, respectively. In this interval, the pulse rate at rest gradually increased and reached 90 beats/min on the 35th day after admission. Physical examination revealed finger tremor, moist skin, a decrease in diastolic blood pressure (blood pressure, 120–46 mmHg) and hyperactive deep tendon reflexes with a brisk relaxation phase. Therefore, methimazole (MMI: a 30 mg daily dose) therapy was initiated on the 35th day after admission. Thereafter, body weight that was gained decreased again. Thereafter, the pulse rate at rest gradually decreased and body weight gradually increased with the normalization of serum FT4 and FT3. The HbA1c level was 8.8% 44 days after admission.

Discussion

It has been generally known that the NTIs that vary widely from trauma, sepsis, malignancy, and metabolic disorders to febrile illness and undernutrition may show a low T3 state because the illness inhibits extrathyroidal tissue conversion of T4 to T3 (Nikoloff and LoPresti, 1991). Therefore, some hyperthyroid patients who are admitted due to Graves' disease or a toxic nodule and who concomitantly have severe NTIs may show T4-toxicosis (Joasso, 1975; Engler et al., 1978; Caplan et al., 1980; Shigemasa et al., 1982). The present case also shows T4-toxicosis before treatment for DM. It has been reported that T4-toxicosis may be found in patients with iodide induced thyrotoxicosis (Sobliho et al., 1977) and in elderly hyperthyroid patients (Caplan et al., 1978). Furthermore, the pattern of T4-toxicosis as a normal biochemical finding has been observed in elderly women (Britton et al., 1975) or in patients with acute or chronic NTIs (Braverman and Veganakis, 1979; Gavin et al., 1979). Our patient, however, had not ingested an excessive amount of seaweed nor received any treatment with iodide, and showed a high $^{99m}TcO4^{-}$-uptake with very low serum TSH level. Furthermore, the patient showed a marked elevation of serum rT3 level despite a normal serum T3 level at the initial examination. Usually in patients with NTI, serum rT3 levels have been generally known to increase reciprocally as serum T3 falls, because impaired rT3 clearance is ascribed secondary to a decrease in 5'-deiodination and not because of an increase in rT3 production (Fabel et al., 1981; LoPresti et al., 1991). Accordingly, T4-toxicosis in our case is strongly suggested to be induced by the increased inhibition of peripheral tissue 5'-deiodination owing to the association of a very poor control state of DM with Graves' hyperthyroidism. Indeed, the patient showed the common pattern of the elevations of both T4 and T3 with a reduction of rT3 after the initiation of diet and insulin therapy.

The changes in serum FT3 concentration in patients with T4-toxicosis due to hyperthyroidism associated with severe NTI have been less well understood. It has been reported that free T3 concentration is predicted to vary from a normal to supra-normal level. Indeed, serum FT3 in our case showed a normal value.

It has been suggested that inhibitors of thyroid hormone binding to T4-binding protein exist in the serum of patients with NTI (Chopra et al., 1979; Woeber and Maddux, 1981). A T4-binding inhibitor in the serum of NTI patients has been suspected to be a free fatty acid (Chopra et al., 1986; Haynes et al., 1989). It has been generally known that free fatty acids increase in the serum of DM patients with a very poor control state. Therefore, the serum FT4 level slightly decreased after the initiation of DM therapy. Nevertheless, the serum FT3 level was elevated gradually after the initiation of DM therapy. This might be due to recovery from the inhibition of T4 to T3 conversion in the extra-thyroidal tissues.

The metabolic impact and adaptive significance of the low T3 state associated with NTI is less well understood. In the present case, any apparent physical findings suggestive of hyperthyroidism were not observed at admission. This might be due to the normal FT3 level.

However, if the patient was not associated with hyperthyroidism, serum T3 and FT3 levels should be further decreased. It has been reported that the rat hepatic nuclear T3 receptor number is reduced by NTI and fasting (Surcs et al., 1978). Furthermore, there is evidence that T3 receptor capacity is decreased in DM (Das and Ganguly, 1981; Wartofsky et al., 1981). On the other hand, a divergence in post T3 receptor responses occur in fasted rats (Oppenheimer and Schwartz, 1980), and T3 administration does not appear to alter the rate of weight loss in rats (Schwartz et al., 1980). In the present case, the pulse rate at rest abruptly increased despite little increase in the serum FT3 level at 2 weeks after the initiation of DM therapy. This might be reflected in the diminished T3-binding to the T3 receptor or the post receptor response probably due to intra-cellular glucose deficiency.

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