PRELIMINARY REPORT

Triiodothyronine Supplementation for Hypothalamic Obesity

J.K. Fernandes, M.J. Klein, Joann L. Ater, John F. Kuttesch, and Rena Vassilopoulou-Sellin

Patients with suprasellar lesions develop profound hypothalamic obesity and listlessness with no effective treatment. We added triiodothyronine (T_3) supplementation in 3 such patients and present their response. All had previous nutritional counseling without benefit. All were treated for diabetes insipidus (DI) and hypopituitarism; serum free thyroxine (T_4) level was normal. A 24-year-old woman (pineal tumor and astrocytoma) had weight gain (4.7 kg/yr for 3 years), cold intolerance, fatigue, dry skin, and constipation; after T_3, she lost 14 kg over 27 months and reported overall improvement. Her bone mineral density also improved. A 10.6-year-old boy (optic glioma) was gaining 6 kg/yr for 4 years; after T_3 supplement, he lost 4.3 kg over 11 months. A 12-year-old girl (mixed germ cell tumor) had weight gain (8.3 kg/yr for 3 years) and listlessness; after T_3, she lost 8.1 kg over 16 months and had improved alertness. All patients were asymptomatic despite supraphysiologic T_3 levels. We suggest that T_3 may serve as a simple and effective supplement, which can promote weight loss and improve the well being of these patients with hypothalamic obesity.

UNTIL RECENTLY, OBESITY has been viewed as the result of a primary eating disorder. Recent advances in our understanding of body weight regulation have begun to change our view of this problem. Obesity is now considered as a final phenotype that can result from a variety of underlying alterations in metabolism.[1] One uncommon intractable obesity syndrome occurs after cranial insult and is termed hypothalamic obesity.[2-4] This condition is often associated with other hypothalamic and pituitary disturbances, such as growth and thyroid hormone deficiencies, which may exacerbate the obesity. However, obesity is resistant to standard hormonal replacement therapy and causes significant morbidity for the patients. There has been no effective treatment for hypothalamic obesity. In this report, we describe our experience in 3 patients with hypothalamic obesity who responded to triiodothyronine (T_3) supplementation.

PATIENTS AND METHODS

The patients had been treated for suprasellar lesions during childhood and were followed at the Child and Adolescent Center of the University of Texas M.D. Anderson Cancer Center. They had received surgery, radiation therapy, chemotherapy, or a combination of these for the primary tumor according to standards of care at the time of treatment. All patients had diabetes insipidus (DI) and panhypopitutrism and were receiving age-and gender-appropriate hormone replacement plus desmopressin (DDAVP). More importantly, serum free thyroxine (T_4) levels were normal before initiation of a T_3 supplement (Liothyronine, Cytomel, SK Beecham Pharmaceuticals, Philadelphia. PA). Unrelenting weight gain and listlessness were common complaints among the patients. All patients received dietary counseling during the 12- to 24-month observation period before initiation of T_3 supplementation, but attempts to restrict calorie intake and promote exercise were unsuccessful in reducing the patients' weight. Patient characteristics are summarized in Table 1.

Patient 1 is a 24-year-old woman with a history of pineal germ-cell tumor and anaplastic astrocytoma at 7 years of age. She developed DI and panhypopituitarism after surgery, chemotherapy, and radiation therapy. In addition to a steady weight gain of 4.7 kg/yr for the past 3 consecutive years, she complained of cold intolerance, fatigue, dry skin, constipation, and lethargy; she was 147.3 cm tall and weighed 60.8 kg. Her serum free T_4 was 1.7 ng/dL (normal range, 0.9 to 1.8). Serum T_3 level was 95 ng/dL (normal range, 60 to 181). Because her symptoms had elements reminiscent of hypothyroidism, she was empirically started on T_3 at 10 μg twice per day, which was later increased to 25 μg twice per day. Five months later, she had lost 15.2 kg; after 27 months she had a sustained weight loss of 14 kg. Her serum total T_3 level was 490 ng/dL (normal range, 60 to 181), but she had no symptoms or signs of thyrotoxicosis. Because hyperthyroidism has been associated with bone loss, we were concerned about this patient and also monitored her bone mineral density (BMD). Despite being on estrogen replacement, her BMD was very low before T_3 was started (T-score of -3.02 at the lumbar spine and –3.27 at the total hips). Six months after initiation of T_3, her BMD showed a +18.9% improvement at the lumbar spine and a +12.1% improvement at the total hips. At 27 months, BMD showed an overall improvement of +27.3% at the lumbar spine and an overall improvement of +23% at the total hips (Table 2). She continues to report substantial subjective improvement of overall energy and performance, with no symptoms or signs of hyperthyroidism.

Patient 2 is a 10½-year-old boy with a history of optic chiasmal glioma at 3 years of age. After surgery, chemotherapy, and radiation therapy, he developed DI and panhypopituitarism and was treated with DDAVP, T_4, and cortisone. After 2½ years he was also given growth hormone. Despite adequate hormone replacement, the patient had suboptimal linear growth (4.7 cm/yr), polyphagia, and weight gain (6 kg/yr, annualized for 4 years). His serum T_3 was 126 ng/dL (60 to 181). Before starting T_3 supplementation, he weighed 48.6 kg and was 137.9 cm tall (body mass index [BMI], 25.7). T_3 supplementation was started at 10 μg twice per day and increased to 20 μg 3 times per day. After 11 months, he had a sustained weight loss of 4.3 kg and had gained 8.6 cm in height; during his most recent clinic evaluation, he weighed 44.3 kg, and he was 146.5 cm tall. The patient and his family reported a decrease in food intake and an improvement in school performance. His serum T_3 levels were high at 397 ng/dL (normal, 60 to 181 ng/dL), with no symptoms or signs of hyperthyroidism.

From the Department of Endocrinology and the Division of Pediatrics, University of Texas M.D. Anderson Cancer Center, Houston, TX.
Submitted April 11, 2002; accepted June 16, 2002.
Address reprint requests to Rena Vassilopoulou-Sellin, MD, 1515 Holcombe Blvd, Box 435, Houston, TX 77030-4009.

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Table 1. Patient Characteristics

Diagnosis	Age at Diagnosis	Treatment	Endocrinopathy	Medications	BMI Before T_3	Free T_4 Before T_3
Pineal germ cell tumor and anaplasic astrocytoma	7 yr	Rad Chemo Surg	DI hypopituitarism	DDAVP Synthroid Cortef Prempro	28.2	1.7
Optic chiasmal glioma	3 yr	Rad Surg Chemo	DI hypopituitarism	GH DDAVP Synthroid Cortef	25.7	0.9
Suprasellar mixed germ-cell tumor	7 yr	Rad Chemo Surg	DI hypopituitarism	DDAVP Synthroid Cortef	25.2	1.1

Abbreviations: Rad, radiotherapy; chemo, chemotherapy; surg, surgery; DI, diabetes insipidus; GH, growth hormone; free T_4 normal range = 0.9 to 1.8 ng/d.

Patient 3 was a 12-year-old girl with a history of suprasellar mixed germ-cell tumor at 7 years of age. She also received surgery, chemotherapy, and radiation therapy and developed DI and panhypopituitarism. She did not receive growth hormone for oncologic considerations. The patient and her family reported that she had an excessive appetite, short attention span, and excessive daytime somnolence. She had gained 8.3 kg/yr annualized over 3 years. Before starting T_3 supplementation therapy, she weighed 48.3 kg and was 137.5 cm tall (BMI, 25.2). T_3 was started at 10 μg 3 times per day. After 16 months, she had a sustained weight loss of 4.3 kg. Her T_3 levels ranged between 242 and 279 ng/dL without any symptoms or signs of hyperthyroidism. Her family and school teachers reported that she had more energy and improved performance.

DISCUSSION

Hypothalamic obesity with increased appetite and unrelenting weight gain after cranial insult is a rare, but well documented, and frustrating clinical problem.[5] The present report describes the benefit of T_3 supplementation in 3 such patients.

Previous attempts at controlling hypothalamic obesity through behavioral interventions or pharmacologic manipulations of appetite have largely failed to produce sustained weight loss.[6] All of our patients also underwent nutritional counseling on numerous occasions without durable weight benefit. In rodents, experimental damage to ventromedial hypothalamus causes hyperphagia, obesity, hyperinsulinism, and insulin resistance.[6,7] Interestingly, weight gain continues in rodents with ventromedial hypothalamic damage despite caloric restriction.[8] Lusting et al[9] postulated that insulin hypersecretion accentuates weight gain and used a somatostatin analog (octreotide) to treat patients with cranial insults and hypothalamic obesity. At baseline, the patients demonstrated elevated leptin levels and insulin hypersecretion in response to oral glucose. After treatment, they reported stabilization of weight, and 5 of the 8 patients had marked weight loss.

Table 2. BMD of Patient 1

	Baseline		+6 Months		+27 Months	
	g/cm^2	T-Score	g/cm^2	T-Score	g/cm^2	T-Score
L spine	0.715	−3.0	0.850	−1.8	0.910	−1.2
R total hip	0.522	−3.4	0.584	−2.9	0.636	−2.5
R femur neck	0.443	−3.6	0.477	−3.3	0.522	−3.0
L total hip	0.564	−3.1	0.633	−2.5	0.700	−2.0
L femur neck	0.489	−3.2	0.540	−2.8	0.622	−2.0

Based on the first patient's symptom complex, which contained elements reminiscent of thyroid deficiency, we empirically added a T_3 supplement with very encouraging results. The other 2 children were later treated based on the first experience, also empirically. All patients developed supraphysiologic serum T_3 levels without symptoms and signs of hyperthyroidism. Their weight loss has been sustained without increase in appetite.

In addition to the desired weight benefit, we also noted some unexpected though welcome skeletal effects. Patient 2 appeared to have improvement in growth velocity (from 4.7 cm/y the year before T_3, to 6.7 cm/y during the following year). In addition, patient 1 had temporally associated improvement of BMD. Hyperthyroxinemia has been implicated in the development of osteoporosis. Patients with hyperthyroidism have increases in both osteoblastic and osteoclastic activities with predominance of bone resorption, resulting in decrease in a BMD.[10,11] We therefore monitored BMD in the first patient who already had osteopenia before adding T_3. Paradoxically (and fortunately), not only did T_3 not induce bone loss, but it appeared temporally associated with a robust increase in BMD (+23% to +27% over a 27-month period).

Our observation, if confirmed by appropriate prospective studies, suggests that T_3 supplementation may prove to be a simple, safe, and effective intervention that can help control weight gain and improve listlessness that so seriously impairs the quality of life of patients with hypothalamic obesity. The mechanism of T_3 action in this setting may relate to altered hypothalamic homeostasis, but remains unclear and requires further investigation. We would like to emphasize that this approach is suggested only for patients with documented hypothalamic pituitary damage.

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