Thyroxine Effects on Serum Insulin-like Growth Factor I Levels, Anthropometric Measures, and Body Composition in Patients After Thyroidectomy

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Abstract. Thyroxine is an important hormone related to growth. To study the effects of thyroxine on serum levels of insulin-like growth factor I (IGF-I), anthropometric measures, and body composition, we studied 28 patients who were receiving thyroxine therapy after thyroidectomy for well-differentiated thyroid cancer. Serum IGF-I levels decreased from 38.3 ± 19.0 ng/ml (mean ± SD) to 26.8 ± 12.8 ng/ml (p <0.001) after withdrawal of thyroxine and increased to 43.8 ± 20.2 ng/ml (p <0.001) after thyroxine was resumed. The serum levels of TSH, T3, and thyroxine changed accordingly after withdrawal and resumption of thyroxine therapy. Skinfold thickness increased from 21.8 ± 6.5 mm to 23.7 ± 6.4 mm (p <0.001) after withdrawal of thyroxine and decreased to 21.5 ± 6.9 mm after resumption of thyroxine. Similar changes occurred in the circumferences of the waist and hip (p <0.01), but no significant change occurred in arm muscle circumference (18.7 ± 2.3 cm vs 18.7 ± 2.3 cm vs 19.0 ± 2.4 cm). Body composition analysis by bioelectrical impedance showed no significant changes in the percentages of body fat and lean mass. In conclusion, withdrawal of thyroxine from patients with thyroid cancer was associated with an immediate decrease in serum IGF-I levels. However, lean mass did not respond to the changes in serum IGF-I levels.

Keywords: insulin-like growth factor I; body composition; thyroid; thyroxine

Introduction

In 1969, Hoffer et al [1] demonstrated a relationship between whole body impedance and total body water in normal subjects. The use of bioelectric impedance analysis technique to assess body composition has been validated [1-8]. Based on the differences of resistive effects in fat and fat-free mass, body fat and lean mass can be estimated.

Growth hormone (GH) is essential for somatic growth, and changes in body composition have been reported in patients with GH disorders [9,10]. GH affects somatic growth through the production of insulin-like growth factor I (IGF-I) in the liver. GH treatment normalizes the serum levels of IGF-I in prepubertal children, adults, and elderly persons with GH deficiency [11-13]. The increase in lean body mass and the decrease in total body fat after GH treatment are correlated with an increase in IGF-I [12]. The major effect on reducing body fat is a decrease in visceral fat [14].

Decreased serum levels of IGF-I in patients who are hypothyroid have been reported in only a few studies [15-17]. Moreover, the downstream effects of changes in serum levels of IGF-I on somatic growth in thyroid dysfunction is unclear.

We have studied the changes of serum IGF-I levels, anthropometric measures, and body composition of patients with acute hypothyroidism after thyroxine (T4) withdrawal. The relationships among anthropometric measures, body composition, and thyroid dysfunction have also been analyzed.
Materials and Methods

Subjects. The study group included 28 patients (5 men and 23 women, mean age 51 ± 13 yr, range 27-71 yr) who had been receiving thyroxine (T4) suppression therapy for 4.3 ± 2.1 yr (range 1-9 yr) after total thyroidectomy because of well-differentiated thyroid cancer. The mean T4 dose was 202 ± 44 mg/day (range 150-300 mg/day). The study subjects were outpatients at the National Chen Kung University Hospital, Taiwan. The research protocol was approved by the hospital’s Human Studies Committee and informed consent was obtained from each patient.

All blood specimens were drawn in the morning after overnight fast. After the initial sampling, T4 therapy was withdrawn until 1 mo later. After the second blood sample was obtained and a 1131-whole body scan was performed, T4 therapy was resumed. After T4 therapy had been reinstated for 2 mo, a third blood sample was obtained.

Biochemical and anthropometric measures, body composition measures, thyroid function tests, and serum IGF-I levels were performed at 3 visits: (a) before withdrawal of T4, (b) 1 mo post-withdrawal of T4, and (c) 2 mo after resumption of T4 administration.

Biochemical studies. The following biochemical studies and thyroid function tests were performed at the central laboratory of the National Cheng Kung University Hospital: serum albumin, urea nitrogen, creatinine, total cholesterol, and triglyceride (Spectrum analyzer, Abbott Diagnostics, Dallas, TX); triiodothyronine (T3) Coat-A-Count Total T3 (PDC, Los Angeles, CA) solid-phase radioimmunoassay (normal range 86-187 ng/dl; intra-assay CV, 5.5%; interassay CV, 7.6%); thyroxine (T4) Coat-A-Count Total T4 (PDC, Los Angeles, CA) solid-phase radioimmunoassay (normal range, 4.5-12.5 mg/dl; intra-assay CV, 3.1%; interassay CV, 8.2%); and serum thyroid-stimulating hormone (TSH) levels (SPAC-S TSH kit, IRMA method, Daiichi, Tokyo, Japan; normal range, 0.5-5.6 µU/ml; intra-assay CV, 2.1%; interassay CV, 2.5%). The normal ranges to be used in Taiwan were suggested by the respective vendors.

Anthropometry. Before and after withdrawal of T4 therapy, anthropometric factors, including body weight, body height, triceps skinfold thickness (TSF), and midarm circumference (MAC), were measured by the same research assistant. Body height was measured to the nearest centimeter, and body weight was measured with an accuracy of 0.1 kg. TSF and MAC were measured midway between the tip of the acromion and olecranon of the non-dominant arm. TSF was measured with a Lange skinfold caliper (Cambridge Scientific Industries, Cambridge, MA) with the arm pendant. Arm muscle circumference (AMC) was derived from the following formula [18]:

\[ AMC \text{(cm)} = MAC \text{(cm)} - TSF \text{(cm)} \times 3.14 \]

The waist-to-hip ratio was defined as the ratio between the circumference of the waist at the umbilicus and of the hips at the major trochanter.

Body composition analysis. Body composition was measured by bioelectric impedance with a BIA-106 machine (RJL System, Inc., Detroit, MI). Whole-body electrical impedance was determined by passing a small alternating current through the body and measuring the drop in voltage. A 4-electrode technique was used in the RJL System. The source electrodes were attached to the anterior surface of the foot at the distal end of the second metatarsal and the posterior surface of the hand at the distal end of the metacarpal bone. The hand-receiving electrode was placed between the distal prominences of the radius and ulna on the dorsal surface of the hand. The foot-receiving electrode was placed between the medial and lateral malleoli at the ankle and was contralateral to the hand electrodes. The RJL System delivered 800 µA at 50 KHz; this was passed between the 2 outer electrodes. The voltage drop between the 2 inner electrodes was measured with a high-input impedance amplifier. A complex impedance could measure both resistance and reactance. Body composition was estimated from these variables by a regression equation. The coefficient of variation for resistance was 2.6% in our laboratory [19]. The accuracy of the measurement of resistance, confirmed by using 250-, 400-, 500-, and 750-W precision resistors, was ± 2%. With a standard 500-W resistor, the daily measure-
ment of resistance ranged from 490 to 510 W. The bioelectric impedance measurements were made in triplicate, postabsorptively and postvoiding.

**IGF-I immunochemiluminometric assay.** IGF-I assays were performed in the peptide hormone laboratory of Mayo Medical Center. For the signal antibody, an affinity-purified IGF-I goat antibody (purchased from R&D Systems) was labeled with acridinium ester and prepared in-house. The signal antibody was diluted with assay buffer (0.04 M sodium phosphate, pH 7.4) to 1.2 x 10^6 RLU/200 µl and incubated with a 20-µl standard of IGF-I (0.666 to 21.3 ng/ml) or 20 µl of plasma extract and with monoclonal anti-IGF-I (Biodesign) (0.5 mg/50 µl). At the same time, a bead (Hoover 1/4 inch, grade 2 frosted) coated with sheep anti-mouse antibody (Biodesign, #W992728) was added and incubated together for 3 hr at room temperature. The beads were washed with phosphate saline buffer containing 0.1% Tween 20. The chemiluminescence was counted in a luminometer.

**Statistics.** Unless specified otherwise, the data were recorded as the mean and standard deviation. The Shapiro–Wilk W test was used to test the Normality. A repeated measures ANOVA of the serial data was used to analyze the results between clinical visits. P < 0.05 was considered statistically significant.

**Results**

The results of this study are summarized in Table 1. Serum IGF-I levels decreased significantly from 38.3 ± 19.0 ng/ml to 26.8 ± 12.8 ng/ml (p <0.001) after the withdrawal of T4 and then increased to 43.8 ± 20.2 ng/ml (p <0.001) after the resumption of T4 administration (Fig. 1).

After withdrawal of T4, TSF increased (p <0.001) and then decreased after resumption of T4. This same kind of change occurred for both waist and hip circumference (p <0.01). However, no significant change occurred in AMC, percentage of body fat, lean mass, or total body water with the withdrawal and resumption of T4 (Table 1).

### Table 1. Laboratory values, anthropometric indices, and body composition measurements of 28 patients with thyroid cancer after withdrawal and then resumption of thyroxine (T4) therapy.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before withdrawal of T4</th>
<th>One mo post-withdrawal of T4</th>
<th>Two mo after resumption of T4</th>
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</thead>
<tbody>
<tr>
<td><strong>Laboratory data</strong></td>
<td></td>
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<tr>
<td>Serum T4 (µM/dl)</td>
<td>11.8±2.4</td>
<td>1.4±0.7ᵃ</td>
<td>12.0±2.0</td>
</tr>
<tr>
<td>Serum T3 (µM/dl)</td>
<td>129.2±30.1</td>
<td>56.4±22.8ᵃ</td>
<td>129.2±24.8</td>
</tr>
<tr>
<td>Serum TSH (µU/ml)</td>
<td>0.06±0.06</td>
<td>102.3±64.1ᵃ</td>
<td>0.3±0.5</td>
</tr>
<tr>
<td>Serum IGF-I (ng/ml)</td>
<td>38.3±19.0</td>
<td>26.8±12.8ᵃ</td>
<td>43.8±20.2</td>
</tr>
<tr>
<td><strong>Anthropometric factors</strong></td>
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</tr>
<tr>
<td>Body weight (kg)</td>
<td>60.8±12.0</td>
<td>62.2±12.6ᵃ</td>
<td>61.5±12.1ᵇ</td>
</tr>
<tr>
<td>Body mass index (BMI) (kg/m²)</td>
<td>24.2±4.0</td>
<td>24.8±4.2ᵃ</td>
<td>24.5±4.1ᵇ</td>
</tr>
<tr>
<td>Pulse rate (beats/min)</td>
<td>78±8</td>
<td>73±6ᵃ</td>
<td>79±5</td>
</tr>
<tr>
<td>Triceps skinfold thickness (mm)</td>
<td>21.8±6.5</td>
<td>23.7±6.4ᵃ</td>
<td>21.5±6.9</td>
</tr>
<tr>
<td>Midarm circumference (cm)</td>
<td>25.5±3.0</td>
<td>26.1±3.1ᵃ</td>
<td>25.7±3.1</td>
</tr>
<tr>
<td>Arm muscle circumference (AMC) (cm)</td>
<td>18.7±2.3</td>
<td>18.7±2.3</td>
<td>19.0±2.4</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>83.2±9.6</td>
<td>85.4±10.4ᶜ</td>
<td>84.4±11.0</td>
</tr>
<tr>
<td>Hip circumference (cm)</td>
<td>94.3±7.2</td>
<td>95.4±7.3ᶜ</td>
<td>95.6±7.4</td>
</tr>
<tr>
<td>Waist/hip circumference ratio</td>
<td>0.88±0.08</td>
<td>0.90±0.07</td>
<td>0.88±0.07</td>
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<tr>
<td><strong>Body composition analysis</strong></td>
<td></td>
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<tr>
<td>Fat (%)</td>
<td>31.1±5.1</td>
<td>30.7±5.2</td>
<td>31.0±5.6</td>
</tr>
<tr>
<td>Lean mass (%)</td>
<td>68.9±5.1</td>
<td>69.2±5.2</td>
<td>69.0±5.6</td>
</tr>
<tr>
<td>Water (%)</td>
<td>51.3±4.6</td>
<td>51.5±5.0</td>
<td>51.1±4.8</td>
</tr>
</tbody>
</table>

BMI, body mass index (= body weight [kg] / body height² [m²]); AMC, arm muscle circumference (= MAC [cm] - TSF [cm] x 3.14); ⁿᵃ p <0.001; ⁿᵇ p <0.05; ⁿᶜ p <0.01.

Serum IGF-I, body composition, and thyroid function
Discussion

The results of this study demonstrated a 29% decrease of serum IGF-I levels after the withdrawal of T₄, confirming the findings of Angervo et al [15], who reported an 18% decrease after T₄ withdrawal. It has also been reported that serum IGF-I levels are increased significantly in hyperthyroid patients with Graves disease [20]. In other hypothyroid states, thyroid hormone replacement therapy significantly increases serum IGF-I levels [17]. However, T₄ treatment for euthyroid diseases has not been found to increase the circulating levels of IGF-I [21]. In summary, hypothyroidism is associated with decreased serum IGF-I levels, as shown in our study.

Because of decreased IGF-I levels, patients with GH deficiency have an increase of subcutaneous fat and a decrease of body muscle mass [9,10]. However, in our study, patients with an acute hypothyroid state and decreased serum IGF-I levels did not show a decrease in lean mass and muscle circumference. The explanation for this discrepancy may be the response of IGF-I receptors (IGF-IR) or the time needed for the response in somatic growth to develop (or both). In adult and perinatal animals, thyroid hormone exerts a negative effect on IGF-IR gene expression in the lungs and heart [22]. The increase in the number of IGF-IRs in the lungs and heart of the animals could represent a mechanism to ameliorate the negative effects of hypothyroidism on these organs. The counteracting of decreased serum IGF-I levels and the positive effect on IGF-IR in hypothyroidism may explain why, in our study, lean mass and arm muscle circumference were

![Fig. 1. Changes in serum IGF-1 of 28 patients with thyroid cancer after 1-month withdrawal (visit 2) and then after 2-month resumption of thyroxine (T₄) therapy (visit 3).](image-url)
unchanged in patients with acute onset of hypothyroidism. Another factor that presumably contributed to the lack of a somatic response in our study was the duration of acute hypothyroidism, which may not have been long enough for the decrease of serum IGF-I levels to produce a clinical effect.

Hypothyroidism can cause fluid retention through a decrease in glomerular filtration or disordered vasopressin modulation [23,24]. Pronounced diuresis has been observed soon after the initiation of T4 replacement therapy [24]. In the present study, the acute onset of hypothyroidism led to an increase of serum TSF and total body water. Perhaps the retained fluid may have accumulated partly in subcutaneous tissue and partly in lean mass.

Body composition analysis by bioelectrical impedance may be limited by the overhydration that occurs during T4 withdrawal. Although lean mass and body fat both serve as biologic conductors, most of the current passes through the lean mass because of the much higher resistivity of fat tissue. If hydration is assumed to be normal by the analyzer, the lean mass might be overestimated by the bioelectrical impedance method [25]. With this method, no changes of body composition were noted following the changes in IGF-I levels.

In conclusion, the withdrawal of T4 administration in patients with thyroid cancer after thyroidectomy was associated with a decrease in serum IGF-I levels and subsequently an increase upon the resumption of thyroxine therapy. However, neither AMC nor lean body mass changed in response to the decrease of serum IGF-I levels, perhaps because the duration of hypothyroidism was too short and because fluid retention may have interfered with the bioelectrical impedance method.

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References


