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Circulating adiponectin concentrations were related to free thyroxine levels in thyroid cancer patients after thyroid hormone withdrawal

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Abstract

Because it is unclear whether adipose-derived hormones are related to thyroid hormone metabolism, this study evaluated the relationship between adiponectin concentrations and changes in the thyroid hormones in athyreotic patients after thyroid hormone withdrawal. Twenty-eight athyreotic thyroid cancer patients (4 male and 24 female; mean age, 52.2 ± 11.3 years) were analyzed on the final day of levothyroxine treatment and 1 day before serum thyroglobulin and radioiodine scanning examinations after an average of 4 weeks of thyroid hormone withdrawal. Evaluations included analysis of thyroid function test, serum adiponectin, body composition by bioimpedance analysis, and insulin sensitivity index as determined by the homeostasis model assessment of insulin resistance (HOMA-IR). Discontinuation of thyroid hormone treatment resulted in a significant change in thyroid-stimulating hormone (82.1 ± 9.8 vs 1.0 ± 0.4 mL/L, $P < .05$), free thyroxine (FT4) (5.7 ± 0.4 vs 18.7 ± 2.3 pmol/L, $P < .05$), and free triiodothyronine levels (1.8 ± 0.2 vs 3.4 ± 0.2 pmol/L, $P < .05$) as compared with the prewithdrawal values, whereas circulating adiponectin levels (5.7 ± 0.6 vs 5.4 ± 0.6 mg/L), body fat mass (20.3 ± 1.2 vs 19.4 ± 1.2 kg), and insulin sensitivity index (1.8 ± 0.2 vs 2.2 ± 0.3) remained unaltered. A positive correlation between adiponectin and FT4 ($r = 0.61$, $P < .01$) independent of age, sex, fat body mass, HOMA-IR, and other potential covariates known to affect thyroid hormone metabolism, such as renal and liver functions, was observed after thyroid hormone withdrawal. In addition, baseline circulating adiponectin levels were correlated with a diminished postwithdrawal reduction of FT4 concentrations after adjusting for baseline FT4 levels and changes in body mass index, fat body mass, and HOMA-IR ($r = 0.71$, $P < .01$). In conclusion, adiponectin concentrations were associated with FT4 levels in the athyreotic patients after thyroid hormone withdrawal. The relevant roles of adiponectin in the regulation of thyroid hormone metabolism require further investigation.

1. Introduction

Thyroid hormones play an important role in regulating energy homeostasis [1]. They can stimulate expression of uncoupling proteins in the mitochondria of fat and skeletal muscle cells, modulate adrenergic receptor numbers by enhancing responsiveness of catecholamines, and regulate metabolic rate and body weight [2-4]. Overt thyroid dysfunction is well known to affect body weight [5]. Moreover, in euthyroid individuals, the population studies have demonstrated a negative correlation between body mass index (BMI) or waist circumference and serum free thyroxine (FT4) levels as well as a positive association between BMI and serum thyroid-stimulating hormone (TSH) [6,7]. It is proposed that even small differences in thyroid function may affect body weight, fat distribution, and the occurrence of obesity. However, whether obesity per se also influences thyroid function remains unclear.

Adiponectin is an adipose tissue–derived protein with multiple functions [8]. In addition to increasing insulin sensitivity, clinical and experimental data have demonstrated that adiponectin also regulates body weight and metabolic rate by increasing fatty acid oxidation and thermogenesis [9-11]. Circulating adiponectin concentrations are reduced in obese humans and negatively correlated with total body fat and waist-to-hip ratio [12]. Because adiponectin and thyroid hormone mediate similar physiologic actions between

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adiponectin and thyroid hormones, it seems reasonable to speculate that adiponectin may interact with the thyroid axis. Blood adiponectin concentrations are positively associated with circulating thyroxine (T4) in the euthyroid healthy subjects as well as patients with chronic renal failure [13,14], and a negative relationship between TSH and adiponectin is observed in severely obese women [15]. Because obese euthyroid individuals have lower FT4 and higher TSH levels, indicating reduced thyroid hormone synthesis initially with normal pituitary feedback, we hypothesized that the adipose tissue–derived hormones, such as adiponectin, might influence the metabolism of thyroid hormones. Thus, this prospective study investigated the relationship between blood adiponectin and the thyroid hormone concentrations in a group of athyreotic thyroid cancer patients before and after thyroid hormone withdrawal.

2. Subjects and methods

2.1. Study participants

Twenty-eight patients (4 male and 24 female; mean age, 52.2 ± 11.3 years) with histologically proven papillary or follicular thyroid cancer intended for routine follow-up of serum thyroglobulin and radioiodine scanning after thyroid hormone withdrawal were recruited at the Taichung Veteran's General Hospital, Taiwan. All the patients had received total or near-total thyroidectomy and postoperative radioactive iodine ablation therapy, and were administrated regular levothyroxine therapy. At baseline, all participants had no apparent active disease or residual thyroid remnants as determined by analysis of serum thyroglobulin, whole-body radioiodine scintigraphy, or other imaging examinations. The goal of the thyroid hormone therapy was to achieve low normal circulating TSH level in consideration of the patients' disease-free and low-risk status [16]. In addition, participants did not receive estrogen/progesterone, oral contraceptives, or other medications known to affect thyroid hormone binding or metabolism before initiation of the study. Furthermore, patients with other malignancies or chronic medical disorders, such as cardiac, pulmonary, renal, and hepatic disease or diabetes mellitus, were excluded from this study. This study was approved by the Hospital Ethics Committee, and all patients provided their informed consent.

2.2. Study protocols

All the thyroid cancer patients were evaluated pre– and post–thyroid hormone withdrawal that consisted of an average of 4 weeks rather than using the recombinant human thyrotropin injection because recombinant human thyrotropin injection is not routinely used for the evaluation of postoperative thyroid cancer patients in Taiwan. During a physical examination, body weight (in kilograms) and height (in meters) of subjects were recorded for computing BMI. In addition, the body compositions of all participants were assessed using a bioelectrical impedance analyzer (Model BIA-101; RJI Systems, Detroit, MI). Current injector electrodes with a radiofrequency current of 800 μA at 50 kHz were placed on the hands and feet with the patient lying in supine position. Lean mass and fat mass were calculated according to the formula provided by the software manufacturer; the coefficient of variation (CV) between measurements was less than 2%. A fasting venous blood sample was taken after these anthropometric measurements; serum and plasma were, respectively, collected and stored at −70°C until assay.

2.3. Laboratory analysis and immunoassays

Renal and liver function tests as well as blood lipid and glucose levels were measured by enzymatic methods using a chemistry analyzer (Hitachi 7600, Tokyo, Japan) at the central laboratory of the hospital. Plasma glucose levels were determined using the glucose oxidase procedure (Hitachi 7170). Serum thyroid hormones, including TSH, total T4, FT4, total triiodothyronine (T3), and free T3 (FT3), and insulin were assessed using a chemiluminescence assay (Immulite 2000; Diagnostic Products, Los Angeles, CA). The mean intraassay and interassay CVs were less than 10% for all these assays. Serum adiponectin concentration was measured using an enzyme-linked immunosorbent assay (Quantikine; R & D Systems, Minneapolis, MN) designed to measure total (low, middle, and high molecular weight) human adiponectin, with mean intraassay and interassay CVs less than 5% and 7%, respectively, and sensitivity of 0.246 μg/L. Serum leptin concentration was measured using an enzyme-linked immunosorbent assay (BioVendor Laboratories, Brno, Czech Republic) with mean intraassay and interassay CVs less than 4% and 6%, respectively, and sensitivity of 0.2 ng/mL. Insulin resistance (IR) was estimated using the homeostatic model assessment for IR (HOMA-IR index), calculated as plasma glucose level (in millimoles per liter) × serum insulin level (in microunits per liter)/22.5. Estimated creatinine clearance (in milliliters per minute) was calculated as [(140 − age) × body weight/(serum creatinine × 72)] × 0.85 (if female) [17].

2.4. Statistical analysis

All data were expressed as mean ± SEM. Student *t* test was used for between-group comparison. Spearman and Pearson correlation tests as well as partial correlation test were used to determine the relationship between principal variables and other continuous variables. Results were considered statistically significant if $P < .05$. All data were analyzed using SPSS V10.0 (SPSS, Chicago, IL) statistical software.

3. Results

As shown in Table 1, demographic data, thyroid hormone levels, and adiponectin concentrations before and after

Table 1
Demographic, body composition, biochemical, and hormonal data in thyroid cancer patients before and after levothyroxine withdrawal

	Before (n = 28)	After (n = 28)	*P* value
TSH (mU/L)	1.0 ± 0.4	82.1 ± 9.8	<.01
Total T4 (nmol/L)	54.4 ± 5.1	23.2 ± 2.6	<.01
FT4 (pmol/L)	18.7 ± 2.3	5.7 ± 0.4	<.01
Total T3 (nmol/L)	1.7 ± 0.1	0.7 ± 0.1	<.01
FT3 (pmol/L)	3.4 ± 0.2	1.8 ± 0.2	<.01
FT3/FT4 ratio	0.14 ± 0.03	0.30 ± 0.06	<.01
Adiponectin (mg/L)	5.4 ± 0.6	5.7 ± 0.6	NS
Leptin (ng/mL)	12.9 ± 2.2	8.6 ± 0.7	<.05
BMI (kg/m^2)	24.4 ± 0.7	24.6 ± 0.7	NS
Fat mass (kg)	19.4 ± 1.2	20.3 ± 1.2	NS
Lean mass (kg)	40.8 ± 1.2	41.2 ± 1.2	NS
Glucose (mmol/L)	6.0 ± 0.3	5.6 ± 0.3	.05
Insulin (pmol/L)	64.8 ± 6.5	60.2 ± 6.5	NS
HOMA-IR	2.2 ± 0.3	1.8 ± 0.2	.05
Cholesterol (mmol/L)	5.1 ± 0.2	6.8 ± 0.2	<.01
Triglyceride (mmol/L)	1.3 ± 0.1	1.9 ± 0.2	<.01
HDL-C (mmol/L)	1.4 ± 0.1	1.6 ± 0.1	<.01

NS indicates not significant.

stopping thyroid hormone were assessed. The thyroid hormone withdrawal resulted in increased serum TSH and reduced total T4, total T3, F4, and FT3 levels in all the participants. In addition, elevated blood lipid concentrations, including total cholesterol, total triglyceride, and high-density lipoprotein cholesterol (HDL-C), were observed. No significant changes in BMI, fat mass, serum adiponectin, glucose levels, and HOMA-IR were detected; however, the leptin levels were reduced after levothyroxine withdrawal. Postwithdrawal circulating adiponectin concentrations were positively correlated with FT4 ($r = 0.60$, $P < .01$) and FT3 ($r = 0.41$, $P < .05$), but not with HOMA-IR, BMI, lean mass, or fat mass (Table 2). In addition, a negative relationship between FT4 concentration and fat mass ($r = -0.384$, $P < .05$) was observed; but leptin levels were positively correlated with fat mass ($r = 0.43$, $P < .05$). After adjustment for age, sex, fat mass, HOMA-IR, FT3, and other potential covariates known to affect thyroid hormone metabolism, such as renal and liver functions, the correlation between adiponectin and FT4 concentrations remained significant

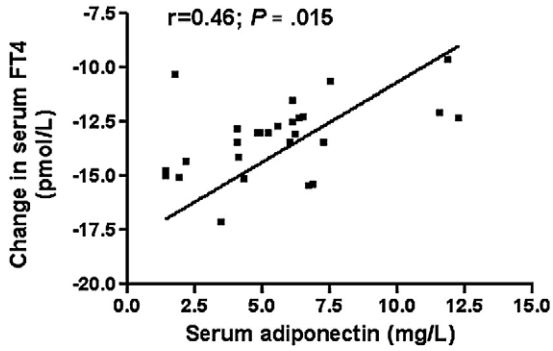

Fig. 1. The relationship between baseline adiponectin and the changes in FT4 levels before and after withdrawal of levothyroxine therapy.

($r = 0.61$, $P < .01$). Furthermore, baseline adiponectin levels were correlated with the subsequent changes in FT4 levels ($r = 0.46$, $P < .05$, Fig. 1). For example, a higher baseline adiponectin concentration was associated with a diminished reduction in FT4 level upon thyroid hormone withdrawal. However, baseline serum adiponectin and prewithdrawal FT4 levels were not correlated. After adjustment for baseline FT4 values and changes in BMI, fat body mass, and HOMA-IR, serum adiponectin concentrations at baseline remained correlated with changes in FT4 ($r = 0.71$, $P < .01$).

4. Discussion

In athyreotic thyroid cancer patients after withdrawal of thyroid hormone, a mean serum TSH concentration of 82.1 ± 9.8 mU/L was detected, which is greater than the generally recommended value of 30 mU/L [16]. In addition, FT4 concentration was reduced from 18.7 ± 2.3 to 5.7 ± 0.4 pmol/L and FT3 from 1.7 ± 0.1 to 0.7 ± 0.1 pmol/L upon discontinuation of thyroid hormone. These values were consistent with those described in previous studies of thyroid cancer patients; serum TSH concentration increased exponentially, whereas the T4 and T3 levels decreased less rapidly after short-term thyroid hormone withdrawal [18,19]. Furthermore, although T4 and T3 were reduced, the ratio of

Table 2
Bivariate correlation coefficients between adiponectin, thyroid hormones, and anthropometric variables in thyroid cancer patients after levothyroxine withdrawal

	Adiponectin	FT4	FT3	BMI	FM	HOMA-IR	Cholesterol	Triglyceride	HDL-C
FT4	0.60†								
FT3	0.41*	0.74†							
BMI	−0.03	−0.34	−0.36						
FM	−0.03	−0.38*	−0.36	0.86†					
HOMA-IR	−0.08	−0.27	−0.41*	0.42*	0.38*				
Cholesterol	−0.26	−0.28	−0.41*	0.20	0.01	0.08			
Triglyceride	−0.08	−0.21	−0.38	0.37*	0.36	0.51†	0.05		
HDL-C	−0.02	−0.04	0.14	0.40*	−0.47*	−0.47*	0.33	−0.57†	
Leptin	0.16	0.27	−0.02	0.38*	0.43*	0.11	−0.22	0.25	−0.39*

FM indicates fat mass.
* $P < .05$.
† $P < .01$.

T3 to T4 was significantly increased after discontinuation of thyroid hormone, possibly representing a compensatory response during a hypothyroid state [20]. Finally, a trend toward lower blood glucose and HOMA-IR levels after thyroid hormone withdrawal was observed, which may be due to less nutrient requirements during a hypothyroid state, resulting in decreased lipolysis from adipose tissue and generation of hepatic glucose [21]. Consistent with previous studies, circulating adiponectin concentrations did not change significantly after thyroid hormone withdrawal–induced hypothyroidism [22-24]. Although adiponectin levels remained unchanged with respect to thyroid dysfunction, this study attempted to address another issue concerning the association between adiponectin and thyroid hormone metabolism in the hypothyroid patients. A previous study had demonstrated that obese patients required higher doses of thyroid hormone to attain similar reduction in TSH as compared with lean participants [25]. It was suggested that metabolic disposal of thyroid hormone was faster in the subjects with a higher BMI. In this study, hypothyroid patients who were prepared for the radioiodine examination by thyroid hormone withdrawal were assessed. The advantage of this design was that we could obtain the paired changes in serum adiponectin levels and thyroid function, as well as the other metabolic variables, before and after a short-term thyroid hormone withdrawal in a homogenous group of patients with respect to the etiology and duration of thyroid dysfunction without other major comorbidities. After thyroid hormone withdrawal, circulating adiponectin concentrations were significantly correlated with postwithdrawal circulating FT4 after adjustment for several potential confounding factors, including age, body composition, IR index, and renal and liver functions. In addition, baseline adiponectin levels were correlated with diminished reduction of postwithdrawal FT4 levels. However, a relationship between prewithdrawal FT4 and adiponectin concentrations was not observed; variable length and duration of levothyroxine use as well as other factors may confound the relationship between adiponectin and thyroid hormones.

Within the body, the serum half-life of T4 was approximately 7 days in the euthyroid state; and its clearance depended mainly on deiodination catalyzed by deiodinase and, to a lesser extent, on other pathways, such as sulfation and glucuronidation [26]. Yet, no studies have reported that adiponectin was directly involved in the regulation of thyroid hormone metabolism. A previous study had demonstrated an association between thyroid hormone levels and insulin sensitivity in euthyroid subjects [27]. Furthermore, it was shown in an in vivo animal model that a peroxisome proliferator–activated receptor agonist that increases insulin sensitivity can also inhibit type 3 deiodinase enzymatic activity, a major deactivating enzyme of T4 and T3 in the body [28]. Because adiponectin was strongly correlated with insulin sensitivity, the observed relationship between adiponectin and FT4 in the athyreotic patients after thyroid hormone withdrawal might be indirectly linked by the insulin pathway. However, the association between adiponectin levels and T4 levels was independent of IR, suggesting that other mechanisms might underlie the relationship. Thus, to fully determine the relevant roles of adiponectin in the regulation of thyroid hormone metabolism, further investigation is required.

Unchanged, reduced, and elevated leptin levels have been observed in hypothyroid patients [29]. In the present study, circulating leptin values were significantly reduced after levothyroxine discontinuation; and a positive relationship between fat body mass and serum leptin values remained [30]. Although leptin and T4 both regulate energy expenditure and thermogenesis [31], this study did not observe an association between serum leptin levels and changes in FT4 after thyroid hormone withdrawal.

There were some limitations in this study. Although it was performed prospectively, the causal relationship between adiponectin and T4 metabolism was not precisely defined. Most importantly, the association between adiponectin and T4 might only represent an adaptive mechanism to reverse the decrease in basal energy expenditure and energetic substrate requirement that occurs in overt hypothyroidism. In addition, during the thyroid hormone withdrawal, many physical parameters were affected, including metabolic rate, glucose and lipid metabolism, food intake, and body composition, all of which could potentially modulate the relationship between adiponectin and T4 [8]. Further studies are required to determine the physiologic meaning or clinical significance of our findings.

Despite these limitations, this study observed that serum adiponectin concentrations were related to FT4 levels in athyreotic patients after discontinuation of thyroid hormone, although no differences in the adiponectin values between pre– and post–thyroid hormone withdrawal were detected. Whether adiponectin contributed to the regulation of T4 metabolism requires further investigation.

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