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Changes in Adipocyte Hormones Leptin, Resistin, and Adiponectin in Thyroid Dysfunction

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Abstract Thyroid hormones as well as the recently discovered secretory products of adipose tissue adiponectin and resistin take part in energy metabolism. To study the changes in the adipocyte hormones with changes in the thyroid functional status, we measured adiponectin, resistin, and leptin in 69 subjects with Graves' disease before and 32 patients at follow up after treatment for hyperthyroidism at hypothyroid state. Concentrations of serum adiponectin and resistin were higher in hyperthyroid state than in hypothyroid state (adiponectin: 5.73 ± 1.1 vs. 3.0 ± 0.5 ng/ml, $P = 0.03$) (resistin: 6.378 ± 0.6 vs. 5.81 ± 0.57 ng/ml, $P < 0.0001$). Resistin levels correlate positively with free t4($r = 0.37$, $P < 0.01$), free t3 levels($r = 0.33$, $P < 0.01$) and negatively with TSH($r = -0.22$, $P < 0.05$). Adiponectin levels correlate with free t4($r = 0.33$, $P < 0.01$) and free t3 ($r = 0.44$, $P < 0.01$). Though the adiponectin levels did not correlate with leptin or resistin levels, strong positive correlation of both resistin and adiponectin with thyroid hormones is noted. Serum levels of leptin did not change with change in the thyroid functional status (leptin: 53.38 ± 2.47 vs. 55.10 ± 2.58 NS). Leptin levels did not correlate with resistin and adiponectin. We conclude that thyroid function has effect on adipocyte hormones adiponectin and resistin but not leptin. J. Cell. Biochem. 93: 491–496, 2004.

Key words: adiponectin; resistin; leptin; Graves' disease; hyperthyroidism; hypothyroidism

Patients with thyroid disease usually exhibit changes in the body weight, appetite, and thermogenesis. Alterations of lipolysis in adipose tissue result secondary to changes in thyroid functional status. Hypothyroid patients gain weight with decreased thermogenesis and decreased metabolic rate, where as hyperthyroidism is associated with loss of weight despite increased appetite owing to increased metabolic rate and increased gut motility [Walton et al., 1965; Iossa et al., 1992; Liverini et al., 1992; Duntas, 2002]. Reduction in serum lipid levels as well as lipid storage is typical of hyperthyroid state and increase in serum lipids with hypothyroidism [Weetman, 2000; Duntas, 2002].

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Until recently adipocytes were considered as reservoir of energy that play a passive role in energy metabolism. The discovery of the obese gene and leptin [Zhang et al., 1994], its secretory product, firmly established the endocrine role of the adipocytes. Among a variety of secretory products of adipocytes, adiponectin, resistin, and leptin seem to have a role in energy metabolism. Of these, adiponectin draws more attention as an insulin sensitizer. Adiponectin, expressed only in adipocytes seems to increase tissue sensitivity to insulin [Combs et al., 2001; Yamauchi et al., 2001; Berg et al., 2002]. Plasma adiponectin levels seem to decrease with obesity and are positively associated with whole-body insulin sensitivity in animal models of obesity and lipoatrophy [Yamauchi et al., 2001]. Hypoadiponectinemia may contribute to insulin resistance and accelerated atherogenesis associated with obesity. Resistin, another recently discovered adipocyte-secreted polypeptide, is expressed in human adipose tissue [McTernan et al., 2002b]. In animal studies, adiponectin and resistin are down-regulated in obese rats and adiponectin expression is

restored to normal levels where as resistin mRNA further decreased after weight loss [Steppan and Lazar, 2002].

Leptin is a hormone produced exclusively by adipocytes with levels proportional to fat mass. During periods of weight loss, plasma leptin levels decline. A fall in leptin acts through the hypothalamus to increase appetite, decrease energy expenditure, and modify neuroendocrine function in a direction that favors survival. Deficiency of leptin gene expression leads to hyperphagia and obesity. Leptin decreases appetite and enhances thermogenesis [Korbonits, 1998]. Yoshida et al. [1997] have shown in vitro that thyroid hormones regulate the expression of leptin mRNA and secretion of leptin by adipocytes. Most studies of hyperthyroid patients before and after treatment have shown similar leptin levels to those of controls matched for sex, age, and BMI [Corbetta et al., 1997; Sreenan et al., 1997; Leonhardt et al., 1998]. However, Zimmermann-Belsing et al. [1998] noted that the serum leptin concentrations increased during the initial 12 months of antithyroid drug therapy. Others noted that the leptin levels are not changed in the hyperthyroid state but decreased in the hypothyroid state [Valcavi et al., 1997]. The values in hypothyroidism have been reported as unchanged [Corbetta et al., 1997; Sreenan et al., 1997; Pinkney et al., 1998] or even decreased [Valcavi et al., 1997; Yoshida et al., 1997]. To date there is only one study with resistin and adiponectin in relation to thyroid function [Iglesias et al., 2003].

The object of our study is to evaluate the alterations in the adipocytes hormones in relation to thyroid functional status. As thyroid hormones, adiponectin, resistin as well as leptin are involved in the energy metabolism and weight changes, we measured resistin, leptin, and adiponectin levels in subjects with Graves' disease at hyperthyroid state as well as at hypothyroid state at follow up after radioiodine therapy.

SUBJECTS AND METHODS

Subjects

The study subjects include 69 subjects with Graves' disease seen at LSU Health sciences center and Overton brooks VA medical center for hyperthyroidism. Graves' disease was diagnosed by the abnormal thyroid function tests in patients with symptoms suggesting hyperthyroidism and homogenous uptake on thyroid scans with I^{123}radioiodine scan. Clinical characteristics of the study subjects are shown in Table I. Patients with Graves' disease were treated with radioactive iodine or antithyroid drugs and followed in the endocrinology clinic. All the subjects studied were followed during outpatient visits to the endocrinology clinic. The exclusion criteria included pregnancy, those on steroids and those with co-morbid conditions and critically ill. A detailed clinical history was obtained and complete physical examination performed. Informed consent was obtained from the subjects and our institutional Review Board approved the protocol. Of this group, 32 subjects were followed after radioiodine therapy when they are hypothyroid clinically and confirmed by thyroid function tests. This group served as hypothyroid group.

Blood Sampling

Baseline samples for thyroid function tests and adipocyte hormones namely resistin, adiponectin, and leptin were drawn in the morning from patients with active Graves' disease at the time of diagnosis. Samples for adipocyte hormones were stored at $-20^{\circ}C$ until subsequent assay. At follow up after therapy for Graves' disease, repeat samples for adipocyte hormones were drawn for 32 patients when they are clinically and or chemically hypothyroid.

TABLE I. Clinical and Biochemical Characteristics of the Patients

	Subjects with hyperthyroidism (n = 69)	Subjects with hypothyroidism (n = 32)
Age (years)	42.68 ± 1.5	40 ± 2.2
Sex (male/female)	15/54	5/27
BMI (kg/m^2)	25.7 ± 1.5	27.5 ± 1.0
Smoking (Yes/No)	12/57	6/26
Systolic blood pressure	132 ± 26	136 ± 25
Diastolic blood pressure	76 ± 10	81 ± 14

BMI, body mass index; HOMA-R, homeostatic model assessment.

Hormone Assays

Samples of venous blood obtained were centrifuged immediately and the serum was stored at −20 or −80°C until assayed.

Thyroid function tests were measured by immunoassay. Adiponectin levels were measured by the enzyme-linked immunosorbent assay (ELISA) using the human adiponectin ELISA kit (B-Bridge International, Inc., Sunnyvale, CA). The intra- and interassay CVs for adiponectin is 3.2 and 5.2%, respectively. The sensitivity of the assay was 23.4 pg/ml. The human leptin levels were measured using the enzymatic immunoassay (EIA) kit from Phoenix Pharmaceuticals, Inc., Belmont, CA. Serum resistin concentration was measured by using a sandwich enzyme-linked immunosorbent assay (ELISA; Phoenix Pharmaceuticals, Inc.). The intra- and interassay CVs were 3.4 and 6.3%, respectively. The sensitivity of the assay was 0.2 ng/ml.

Statistical Analysis

Data are reported as mean value ± standard error (SE). Mean values were compared using standard Student's *t*-tests.

The hormone levels measured in the beginning at hyperthyroid state and at the end at hypothyroid state were compared by ANOVA. Statistical analyses were carried out with Microsoft Excel data analysis for Windows using simple correlation, *t*-test for paired data. A P value ≤ 0.05 was considered significant in all comparisons.

RESULTS

The clinical characteristics of the study population are summarized in Table I. The results of thyroid function tests at both hyperthyroid state and hypothyroid state are shown in Table II. As the same subjects are followed at different thyroid functional status, there was no need for matching for age, sex and race. Both adiponectin and resistin levels decreased significantly at hypothyroid state compared to hyperthyroid state (adiponectin 5.73 ± 1.11 vs. 3.0 ± 0.5 ng/ml, $P < 0.03$) (resistin 6.37 ± 0.09 vs. 5.81 ± 0.13 ng/ml, $P < 0.0001$). As seen in Table III, leptin levels did not change with the thyroid function status and did not correlate with resistin and adiponectin (Table IV).

Resistin as well as adiponectin levels correlated positively with both free t4 (adiponectin $r = 0.33, P < 0.01$; resistin $r = 0.37, P < 0.01$) and free t3 (adiponectin $r = 0.44$, $P < 0.01$; resistin $r = 0.3$, $P < 0.01$). Resistin levels correlated negatively with TSH where as adiponectin levels did not. At hyperthyroid state, resistin levels correlated positively with free t4 ($r = 0.24$, $P < 0.005$) but not with free t3 (NS) or TSH. At hypothyroid state resistin levels correlated positively with free t4 ($r = 0.36$, $P < 0.05$) as well as with free t3 ($r = 0.39$, $P < 0.02$) but not with TSH.

Since we had fasting glucose levels for 35 of 69 subjects, we measured insulin and calculated insulin resistance index by HOMA-R. Our group of hyperthyroid patients showed data for insulin resistance, such as elevated levels of insulin with increased values of the HOMA-R index. Insulin resistance index by HOMA-R did not correlate with adiponectin or resistin but correlated with free t4 ($r = 0.38, P < 0.02$) and t3 ($r = 0.34$, $P < 0.05$) during hyperthyroid state (Table IV).

TABLE II. Serum Concentrations of Thyroid Stimulating Hormone (TSH), Free Tetra Iodothyronin (FT4), and Free Triiodothyronine (FT3) in the Group of 69 Hyperthyroid Patients Before and After Normalization of Thyroid Function With Appropriate Therapy and in the Group of 32 Hypothyroid Subjects*

	Subjects with hyperthyroidism (n = 69)	Subjects with hypothyroidism (n = 32)
TSH (mU/L)	0.087 ± 0.05	20.35 ± 4.2
FT4 (pmol/L)	2.72 ± 0.18	0.68 ± 0.06
FT3 (nmol/L)	10.56 ± 0.94	1.49 ± 0.13

Data are mean ± SEM.
*$P < 0.05$ hyperthyroid versus hypothyroid group; $P < 0.0001$ hypothyroid versus hyperthyroid subjects.

TABLE III. Levels of Leptin, Adiponectin, and Resistin in Relation to Hyperthyroid and Hypothyroid States

	Subjects with hyperthyroidism (n = 69)	Subjects with hypothyroidism (n = 32)
Leptin (μg)	53.38 ± 2.4	55.10 ± 2.57***
Adiponectin (mg)	5.73 ± 1.1	3.0 ± 0.5**
Resistin (μg)	6.37 ± 0.09	5.81 ± 0.12*

Data are mean ± SE.
*$P < 0.0003$ hypothyroid versus hyperthyroid patients.
**$P = 0.03$ hypothyroid versus hyperthyroid patients.
***P not significant hypothyroid versus hyperthyroid patients.

TABLE IV. Relationship Between Thyroid Function Tests and Adipocyte Hormones and Insulin Resistance Calculated by HOMA-R (Homeostatic Model Assessment)

	TSH	Free T4	T3	HOMA-R
Adiponectin	−0.10***	0.33*	0.44*	0.04***
Resistin	−0.22**	0.37*	0.30*	0.16***
Leptin	0.02***	0.02***	−0.19***	0.05***
HOMA-R	−0.19***	0.38**	0.34**	

Pearson's correlation coefficients with level of significance.
*$P < 0.01$.
**$P < 0.05$.
***P not significant.

DISCUSSION

The present study is designed to study the adipocyte hormones namely leptin, resistin, and adiponectin levels in relation to thyroid functional status. Our results clearly show that the thyroid hormones play a major role in the adiponectin and resistin levels but not leptin. Significant findings in our study are (a) resistin and adiponectin levels were higher in hyperthyroid state than hypothyroid state; (b) leptin levels did not change with the thyroid function status; (c) resistin and adiponectin levels correlate with thyroid hormone levels; (d) insulin resistance index by HOMA-R did not correlate with adiponectin or resistin but correlated with free t4 and t3 during hyperthyroid state.

Previous studies of serum leptin during abnormal thyroid function have shown conflicting results. Leptin levels correlate with the body mass index [Mantzoros et al., 1997; Zimmermann-Belsing et al., 1998]. In our subjects, there is no significant difference in the levels of leptin between hyperthyroid and hypothyroid state. Leptin levels did not correlate with thyroid function tests or with resistin or adiponectin. Lack of change in leptin levels with the thyroid functional status probably reflects lack of change in the fat mass from hyperthyroid state to hypothyroid state in our subjects as the hypothyroidism is of recent onset following radioiodine therapy. Thus, the change in energy expenditure with changes in the thyroid state does not operate through variation in leptin levels. This observation is consistent with observations of some of the previous studies [Corbetta et al., 1997; Seven, 2001; Wahrenberg et al., 2002].

Adiponectin levels are reduced in obesity and restored to normal levels with weight loss [Yang et al., 2001]. Adiponectin levels are related inversely with the degree of adiposity and associated positively with insulin sensitivity both in healthy subjects and in diabetic patients and negatively correlated with obesity [Arita et al., 1999; Weyer et al., 2001]. Weyer et al. [2001] noted that the degree of hypo adiponectinemia is more closely related to the degree of insulin resistance and hyperinsulinemia than to the degree of adiposity and glucose intolerance. Decreased adiponectin levels were also reported in subjects with coronary artery disease [Ouchi et al., 1999]. Our results show that adiponectin levels were higher in hyperthyroid state than hypothyroid state (5.71 ± 1.11 vs. 3.0 ± 0.5 ng/ml, $P < 0.03$). Adiponectin levels correlate positively with free t4 ($r = 0.33$, $P < 0.01$) and free t3 ($r = 0.44$, $P < 0.01$) and not with TSH. There is no significant correlation of levels of adiponectin with leptin or resistin. These results are in contrast to the recent publication of Iglesias et al. [2003]. Bruun et al. [2003] in their study on obese subjects noted that the adiponectin levels correlate inversely with adiposity, insulin sensitivity, and IL-6 and tumor necrosis factor-alpha (TNF-alpha).

Overproduction of TNF-α by adipose tissue has been suggested in the development of insulin resistance [Hotamisligil et al., 1993]. Cytokines interleukin-6 (IL-6) and TNF-alpha are elevated in Graves' disease [Celik et al., 1995; Komorowski et al., 1998; Salvi et al., 2000]. Since these cytokines are suggested to regulate adiponectin [Bruun et al., 2003], decreased levels of adiponectin can be explained in subjects with Graves' disease. In addition, in our group of hyperthyroid patients, no correlation between adiponectin and insulin and the HOMA-R index was found. However, because of the small size of the sample, these results must be interpreted with caution. Similar results with lack of correlation of adiponectin with markers of insulin resistance was noted recently by Iglesias et al. [2003].

Resistin, a recently discovered adipocyte hormone considered potentially to link obesity and diabetes is considered to play a role in insulin resistance [Steppan et al., 2001; McTernan et al., 2002a,b; Steppan and Lazar, 2002]. The mechanism by which this hormone affects insulin sensitivity has not been well established. Resistin levels seems to correlate with hepatic but not muscle insulin resistance [Rajala et al., 2003; Smith et al., 2003]. Resistin is severely decreased in hyperthyroid rats and

elevated in drug-induced hypothyroid rats [Nogueiras et al., 2003]. Our study shows a significant reduction in resistin levels with hypothyroid state compared to that of hyperthyroid state and levels do not correlate with the insulin resistance index. In contrast to our results, resistin levels were reported to correlate with insulin resistance [Iglesias et al., 2003]. As the sample size is small, these results must be interpreted with caution.

Summary

In summary, our observations suggest that the leptin levels do not change with thyroid functional status. Change in the levels of resistin with thyroid functional status and correlation with thyroid function tests reflects the effect of thyroid hormone on the resistin. The mechanism of insulin resistance in these subjects with hyperthyroidism may not be related to adiponectin or resistin but with a different mechanism.

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