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Elevation of serum adiponectin levels in Basedow disease

Takako Saito, Takahisa Kawano, Tomoyuki Saito, Aki Ikoma, Kazuyuki Namai, Hiroyuki Tamemoto, Masanobu Kawakami, San-e Ishikawa*

Department of Medicine, Jichi Medical School, Omiya Medical Center, Saitama 330-8503, Japan

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Abstract

The present study was undertaken to determine whether thyroid hormone affects serum adiponectin levels in the patients with Basedow disease. Sixty-four patients with Basedow disease were examined; 32 patients had hyperthyroid state and 32 patients had euthyroid state who had been treated with antithyroid drugs. In addition, 30 age- and sex-matched subjects served as a control. Serum adiponectin, free T4, free T3, thyroid-stimulating hormone, and thyroid-stimulating hormone receptor antibody (TRAb) were measured. Serum adiponectin levels were 12.9 ± 1.6 μg/mL in the hyperthyroid state, a value significantly greater than that of 8.2 ± 0.5 μg/mL in the euthyroid state ($P < .05$) and that of 8.6 ± 0.7 μg/mL in the control subjects ($P < .05$). Serum adiponectin levels had positive correlations with either of serum free T4 ($r = 0.453$, $P < .001$), free T3 ($r = 0.47$, $P < .001$), or TRAb ($r = 0.491$, $P < .001$), but not with body mass index. Multiple regression analysis showed TRAb had the strongest contribution to serum adiponectin concentration in the patients with Basedow disease. The present findings indicate that hyperadiponectinemia is closely associated with increases in serum thyroid hormone levels and TRAb in Basedow disease.

1. Introduction

Adipose tissue secretes a variety of biologically active molecules, including cytokines, growth factors, and complement factors into the circulation [1]. Among them, adiponectin is the most abundant adipocytokine in adipose tissue [2]. Adiponectin is a 244–amino acid protein, and serum adiponectin level has an extremely high concentration in healthy subjects [3]. Serum adiponectin levels do change in several pathological states; that is, serum adiponectin levels decrease in obesity, diabetes mellitus, ischemic heart disease, and dyslipidemia [3-9], and adiponectin plays an important role in a cluster of these common disorders linked to metabolic syndrome. Adiponectin has various potential effects, including antidiabetic effect, anti-inflammatory effects, anti-atherogenic effect, nitric oxide production, angiogenesis, and others [10-13].

Thyroid hormones have a permissive effect on adaptive thermogenesis and promote the activity of adrenergic receptor system [14]. A reduction in body weight is found in the patients with hyperthyroidism, and it is further associated with decreases in body fat and muscle [15]. Patients with hyperthyroidism frequently show changes in metabolic parameter, impaired glucose tolerance, dyslipidemia, and so on. There are a few reports showing the relation of serum adiponectin level with thyroid function, in which serum adiponectin levels increased or remained unchanged in the patients with hyperthyroidism [16-18]. We have focused on adipocytokines in hyperthyroidism. We reported an increase in serum leptin, the other adipocytokine, in hyperthyroidism [19]. The in vitro study in 3T3-L1 adipocytes showed thyroid hormone increases the leptin messenger RNA expression and leptin secretion [20]. Because adipose tissues have thyroid-stimulating hormone (TSH) receptors and thyroid hormone receptors [21], we wonder that serum adiponectin may be altered dependent upon thyroid hormones and thyroid autoantibodies in hyperthyroidism.

In the present study we determined whether thyroid function affects serum adiponectin levels in subjects with Basedow disease.

2. Subjects and methods

2.1. Subjects

Sixty-four patients with Basedow disease were enrolled in the present study between June 2003 and June 2004. They

* Corresponding author. Tel.: +81 48 647 2111; fax: +81 48 648 5166.
E-mail address: saneiskw@jichi.ac.jp (S.-e. Ishikawa).

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Table 1
Clinical features in the patients with Basedow disease and control subjects

	Control subjects	Basedow disease	
		Hyperthyroid state	Euthyroid state
n	30	32	32
Sex (male/female)	11/19	12/20	12/20
Age (y)	41.4 ± 2.3	41.2 ± 2.6	41.2 ± 2.1
BMI	22.7 ± 0.6	20.1 ± 0.4*,**	21.9 ± 0.8
Systolic blood pressure (mm Hg)	124.9 ± 3.6	128.4 ± 2.7	128.3 ± 3.1
Diastolic blood pressure (mm Hg)	69.1 ± 2.9	69.7 ± 2.0	71.2 ± 3.6
FT3 (pg/mL)	3.17 ± 0.09	9.48 ± 1.01*,**	3.76 ± 0.11
FT4 (ng/dL)	1.28 ± 0.03	2.70 ± 0.31*,**	1.13 ± 0.09
TSH (μU/mL)	1.52 ± 0.21	0.03 ± 0.02*,**	1.26 ± 0.35
TRAb (%)	–	39.1 ± 3.8**	24.4 ± 3.1
Total cholesterol (mg/dL)	199.5 ± 6.7	170.3 ± 5.9*,**	192.1 ± 5.7
HDL-C (mg/dL)	57.8 ± 2.8	56.8 ± 3.4	57.8 ± 2.1
Triglyceride (mg/dL)	120.6 ± 20.2	86.1 ± 8.1*,**	111.6 ± 15.4
Uric acid (mg/dL)	4.9 ± 0.3	4.6 ± 0.3	4.7 ± 0.2
Plasma glucose (mg/dL)	110.5 ± 3.1	117.1 ± 4.7	111.2 ± 5.5
Hemoglobin A_{1c} (%)	5.6 ± 0.2	5.8 ± 0.4	5.7 ± 0.2
Adiponectin (μg/mL)	8.6 ± 0.7	12.9 ± 1.6*,**	8.2 ± 0.5
% Adiponectin	100.5 ± 7.6	133.7 ± 14.3*,**	92.9 ± 6.1

Values are mean ± SEM. Analysis was performed by multivariate analysis of variance with post hoc testing.
* $P < .05$ vs the control subjects.
** $P < .05$ vs the euthyroid state of patients with Basedow disease.

were 24 males and 40 females, with a mean age of 41.5 ± 13.1 years (range, 20-72 years). They were subgrouped into 2 groups of hyperthyroid and euthyroid states. The hyperthyroid group consisted of 32 patients (20 females and 12 males; 41.2 ± 14.7 years). The euthyroid group consisted of 32 patients (20 females and 12 males; 41.2 ± 11.1 years). No significant differences in age and sex between hyperthyroid and euthyroid groups were found. The patients with complications such as diabetes mellitus or ischemic heart disease were excluded even if they had Basedow disease. Thirty age- and sex-matched subjects served as a control group. The control subjects were selected from the people who came to our hospital for medical examination. They were 11 males and 19 females, aged 41.4 ± 13.4 years ranging from 21 to 73 years. All of them had euthyroid state. The clinical and biochemical characteristics of the patients and the controls are summarized in Table 1.

2.2. Study design

Thirty-two patients with hyperthyroid state of Basedow disease were examined at the time of diagnosis. Thirty-two patients with euthyroid state of Basedow disease were examined after the normalization of thyroid function by antithyroid therapy. All subjects were from the outpatient clinic of Jichi Medical School Omiya Medical Center. Serum concentrations of free T4 (FT4), free T3 (FT3), TSH, and adiponectin were measured. Thyroid-stimulating hormone receptor antibody (TRAb), thyroid peroxidase antibody, and thyroglobulin antibody were also determined. On the basis of the influence of fat mass on adipocytokines, serum concentrations of adiponectin were adjusted for body mass index (BMI) to evaluate directly the role of thyroid hormones on adiponectin levels. The Ethical Committee of Jichi Medical School for human study approved the present study. We obtained informed consent from the subjects who joined the present protocol.

2.3. Hormone assays

Blood collections were obtained from an antecubital vein between 8:30 and 9:00 AM after an overnight fast. Blood samples were centrifuged immediately and their sera were stored at −20°C until assayed. Serum TSH, FT3, and FT4 were measured by an immunoenzymatic assay using Vitros TSH, Vitros FT3, and Vitros FT4 enzyme-linked immunosorbent assay (ELISA) kits (Ortho-Clinical Diagnostics, Tokyo, Japan), respectively. Maximal intra- and interassay coefficients of variation were 8% and 6.6% for TSH, 4.5% and 3.1% for FT3, and 6% and 4.8% for FT4, respectively. The sensitivities of the assay were 0.003 μU/mL, 0.39 pg/mL, and 0.03 ng/dL, respectively. Thyroid peroxidase antibody, thyroglobulin antibody, and TRAb were measured by an immunoenzymatic assay using Cosmic thyroid peroxidase antibody, Cosmic thyroglobulin antibody, and Cosmic TRAb ELISA kits (Cosmic Corporation, Tokyo, Japan), respectively. The serum concentration of adiponectin was measured using human ELISA kits (Otsuka Pharmaceutical, Osaka, Japan). The minimal sensitivity of the assay was 0.375 ng/mL.

2.4. Statistical analysis

All values were given as the mean ± SEM. The software of Statview 5.0 for Macintosh (Abacus Concepts, Berkeley, Calif) was used for the analysis. Comparisons of all 3 groups were made using an multivariate analysis of variance with post hoc testing. Simple linear regression analysis was performed to calculate correlations. Multiple regression analysis was used to evaluate determinants of the serum adiponectin level. The parameters including age, BMI, FT4, TSH, TRAb, total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglyceride, systolic blood pressure, diastolic blood pressure, and plasma glucose were entered into the model. A value of $P < .05$ was considered statistically significant.

3. Results

Table 1 shows the clinical features of the patients with Basedow disease. Serum levels of FT4 and FT3 were extremely high in the hyperthyroid group and they were in the reference ranges in the euthyroid group that had been treated with antithyroid drugs. Of the 32 hyperthyroid patients, 29 had a positive TRAb, and there was a significant difference in TRAb between the 2 groups of Basedow disease ($P < .05$). Serum adiponectin level was

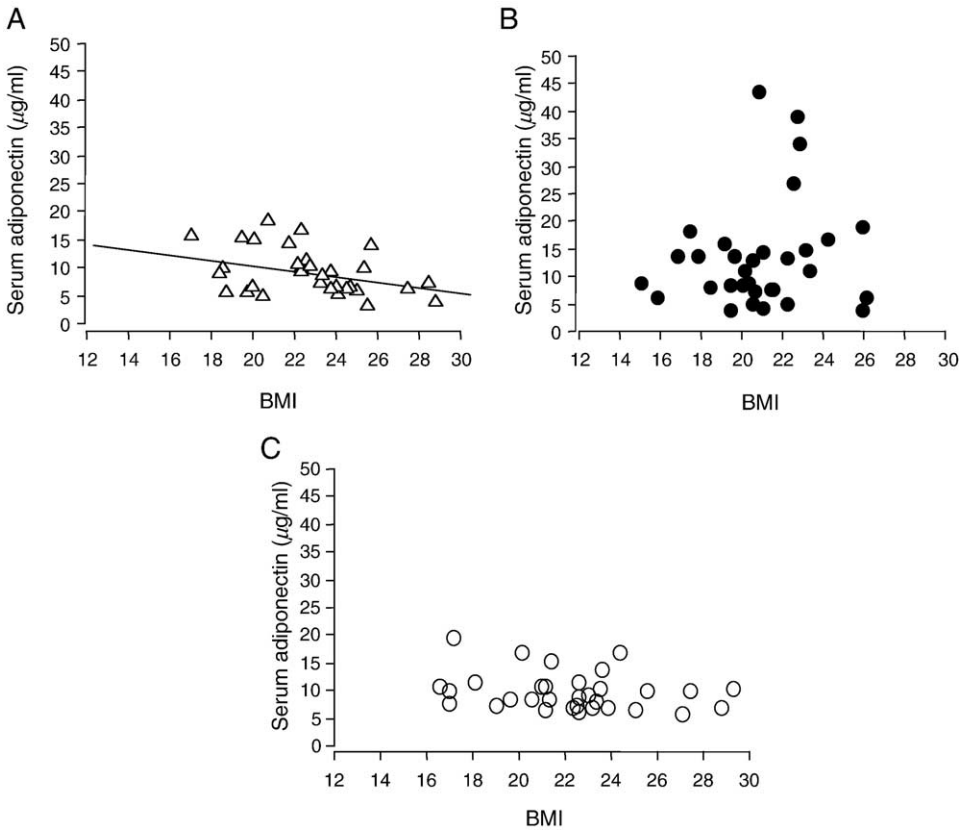

Fig. 1. Relationship between serum adiponectin levels and BMI in the control subjects (A) and patients with Basedow disease with hyperthyroid state (B) and euthyroid state (C). There was a negative correlation between serum adiponectin levels and BMI in the control subjects (serum adiponectin levels [μg/mL] = $-0.501 \times$ BMI + 20.018; n = 30, $r = 0.441$, $P < .05$), but not in the patients with Basedow disease with hyperthyroid and euthyroid states.

12.9 ± 1.6 μg/mL in the hyperthyroid group, which was greater than that of 8.2 ± 0.5 μg/mL in the euthyroid group ($P < .05$) and that of 8.6 ± 0.7 μg/mL in the control subjects ($P < .05$). There was no difference in serum adiponectin concentration between the patients with euthyroid state and the control subjects. There was a significant difference in serum total cholesterol and triglyceride between the hyperthyroid and the control subjects ($P < .05$). There were no differences in blood pressure, HDL-C, uric acid, plasma glucose, and hemoglobin A_{1c} levels among the 3 groups.

In the control subjects there was a negative correlation between serum adiponectin levels and BMI (Fig. 1A), but the correlation disappeared in the hyperthyroid and euthyroid state of Basedow disease (Fig. 1B and C). After adjusting serum adiponectin levels for BMI, it was expressed as the percentage of deviation (% adiponectin). The % adiponectin was 133.7% ± 14.3% in the hyperthyroid state, which was greater than that of 92.9% ± 6.1% in the euthyroid state ($P < .05$) and that of 100.5% ± 7.6% in the control subjects ($P < .05$) (Table 1). Therefore, the difference in serum adiponectin levels remained significant after adjusting for BMI.

Table 2 and Figs. 2 and 3 show the relationship of serum adiponectin levels with varying parameters in the patients with Basedow disease. Table 2 lists the analyses in which r values were significant among the 29 analyses. Among the parameters, serum adiponectin levels had positive correlations with serum FT4, FT3, or TRAb (Figs. 2 and 3). The highest correlation was found between serum adiponectin and TRAb ($r = 0.491$, $P < .001$). However, no correlation was found between serum adiponectin and TPO antibody and between serum adiponectin and thyroglobulin antibody. Furthermore, there were positive correlations between serum TRAb and FT4 ($r = 0.519$, $P < .001$) and between serum TRAb and FT3 ($r = 0.542$, $P < .001$). In addition, % adiponectin had significantly positive correlations with serum FT4, FT3, and TRAb in the patients with Basedow

Table 2
Linear regression analysis of plasma adiponectin levels with varying parameters in the patients with Basedow disease and control subjects

	Basedow disease		Control subjects	
	r	P	r	P
Adiponectin vs BMI	−0.156	.175	−0.441	.014
Adiponectin vs FT3	0.47	<.001	−0.134	.492
Adiponectin vs FT4	0.453	<.001	−0.188	.331
Adiponectin vs TRAb	0.491	<.001		
Adiponectin vs total cholesterol	−0.296	.013	−0.058	.77
Adiponectin vs HDL-C	−0.058	.681	0.444	.017
Adiponectin vs uric acid	−0.08	.544	−0.55	.013

The analyses in which r values were significant are listed among the 29 analyses.

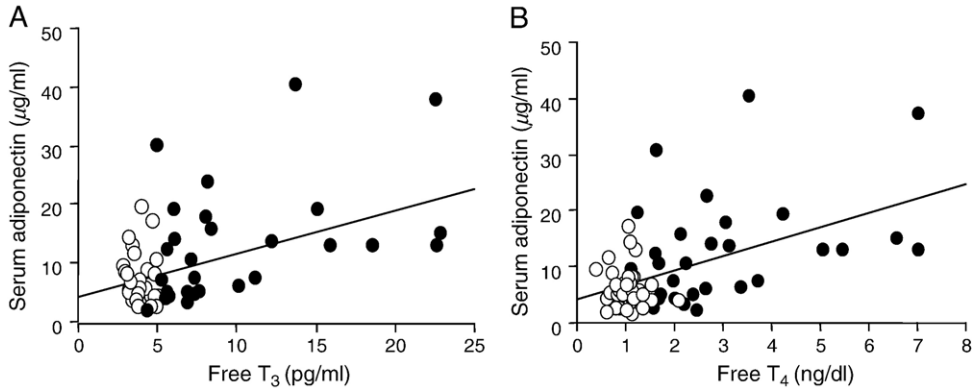

Fig. 2. Relationship between thyroid hormones and serum adiponectin concentrations in the patients with Basedow disease. Closed circles indicate the patients with hyperthyroid state (n = 32); open circles, patients with euthyroid state (n = 32). A, Correlations of serum adiponectin levels with serum FT3 (r = 0.47, P < .001). B, Correlations of serum adiponectin levels with serum FT4 (r = 0.453, P < .001).

disease (data not shown). In addition, serum adiponectin had a weak negative correlation with total cholesterol (Table 2). We further studied multiple regression analysis. Multiple regression analysis was enrolled with 11 parameters. Total cholesterol, FT4, TSH, and TRAb were significant parameters in the analysis. Thyroid-stimulating hormone receptor antibody has the strongest contribution to serum adiponectin concentration in the patients with Basedow disease (Table 3).

4. Discussion

In healthy subjects, serum adiponectin levels are widely scattered and negatively correlate with BMI and body fat [3]. Serum adiponectin levels are higher in females than males with the same BMI [3]. There is a considerable variability in serum adiponectin levels corresponding to each BMI, suggesting that some unknown hormonal, genetic, and/or environmental factors may be involved in the determinants of serum adiponectin concentration. In the present study, we demonstrated hyperadiponectinemia in the patients with Basedow disease. Serum adiponectin levels were increased in the untreated subjects with hyperthyroid state, and they were reduced after the normalization of thyroid hormone levels. Serum adiponectin levels had positive correlations with serum FT4, FT3, and TRAb. Particularly, the coefficient value was the highest between serum adiponectin and TRAb in the simple linear regression analysis. Multiple regression analysis added an independent contribution of FT4 and TRAb to serum adiponectin levels. However, there was no correlation between serum adiponectin and thyroid peroxidase antibody and between serum adiponectin and thyroglobulin antibody.

The present study demonstrated that serum adiponectin levels were increased in the patients with Basedow disease with a hyperthyroid state. As hyperthyroidism causes an increase in energy expenditure and decreases body weight, we firstly analyzed the relationship between BMI and serum adiponectin levels. There was a negative correlation in healthy subjects, but its correlation disappeared in the patients with Basedow disease. This may indicate that thyroid function is one of independent factors for determining serum adiponectin levels in the patients with Basedow disease. Similar results were obtained by Fernandez-Real et al [18], that the subjects having higher levels of serum adiponectin had higher levels of serum FT4. There were, however, controversial results regarding thyroid function and serum adiponectin. No significant difference in serum adiponectin levels was found among hyperthyroid, hypothyroid, and controls subjects [16,17]. In contrast, leptin, the other adipocytokine, inhibits food intake and increases energy expenditure in rodents [22,23]. Serum leptin levels

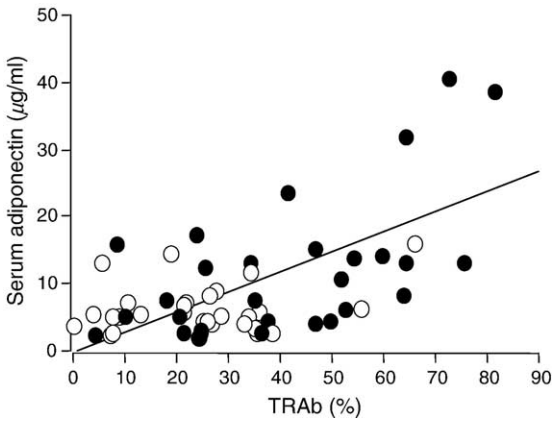

Fig. 3. Relationship between TRAb and serum adiponectin concentrations in the patients with Basedow disease. Closed circles indicate hyperthyroid state; open circles, euthyroid state (r = 0.491, P < .001).

Table 3
Multiple regression analysis for the determinants of serum adiponectin levels in the patients with Basedow disease

Parameter	Regression coefficient	SE	P
Intercept	−68.91	24.284	.022
Total cholesterol (mg/dL)	0.313	0.114	.025
FT4 (ng/dL)	2.853	1.228	.048
TSH (μU/mL)	−52.23	22.58	.049
TRAb (%)	0.253	0.074	.009

R^2 = 0.794, P < .01.

had a positive correlation with BMI in control subjects [24]. In addition, serum leptin concentration was increased in the patients with hyperthyroidism, dependent probably on the direct action of thyroid hormone [19,25,26]. Like leptin, there might be a direct modulation by thyroid function of serum adiponectin levels in hyperthyroidism.

What is the mechanism of hyperadiponectinemia in hyperthyroidism? The present clinical study had a limitation to elucidate the mechanism of the effect of thyroid hormones on adiponectin expression in adipose tissue. At present, we may consider 4 possibilities. First, because adipose tissue has receptors for TSH [21], TRAb may cross-react with TSH receptors in adipose tissue to affect adiponectin production. This scenario is highly likely because there was a significant correlation between TRAb and serum adiponectin levels in our study. The findings may indicate the state of hyperthyroid induces the adiponectin production in adipose tissue. There is an evidence for TRAb stimulation on thymus via TSH receptors, that is, thymic enlargement in patients with hyperthyroidism [27]. Second, thyroid hormone itself directly may stimulate the production of adiponectin. Thizolidinediones, peroxisome proliferator–activated receptor γ (PPAR-γ) agonists, have been shown to increase plasma adiponectin levels by transcriptional induction in adipose tissues because there is a functional PPAR-responsive element in human adiponectin promoter [28]. Thyroid hormone can induce the PPAR-γ expression in hepatocyte [29]. Therefore, there may be a cross talk between the thyroid hormone and peroxisome proliferator signaling pathways in the regulation of peroxisome proliferator–responsive genes [30]. In mouse adiponectin promoter, there also are binding sites of ADD1/SREBP1c and CCAAT enhancer, in addition to PPAR-γ [31]. ADD1/SREBP1c controls adiponectin gene expression in differentiated adipocytes [31]. It also has reported that thyroid hormone stimulates an increase in the mature SREBP-1 in hepatocyte [32]. It is likely that thyroid hormone directly increases transcriptional induction of adiponectin through PPAR-γ or SREBP stimulation. Third, thyrotoxicosis activates the adrenergic receptor system and lipolysis. Adiponectin is produced from small adipocytes, but not large well-differentiated adipocytes. Thyrotoxicosis could induce the increment of small adipocytes, which can produce adiponectin. Fourth, thyroid function affects serum lipid profile. Serum total cholesterol may be a determinant for serum adiponectin levels because serum total cholesterol had negative correlation with serum adiponectin levels in the patients with Basedow disease. Thyroid function may alter serum adiponectin levels by mediating lipid metabolism. However, the mechanism still remains an open question, and further examinations will be necessary to elucidate the exact mechanism of hyperadiponectinemia in hyperthyroidism.

In conclusion, the present study demonstrated hyperadiponectinemia in the patients with Basedow disease. Serum adiponectin levels were closely associated with thyroid hormone and TRAb. These findings may indicate that hyperadiponectinemia is closely associated with increases in serum thyroid hormone levels and TRAb in Basedow disease.

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