

## Study of serum adiponectin and lipid profile in newly diagnosed hyperthyroid patients

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### Abstract

**Introduction:** Thyroid dysfunction is associated with metabolic changes that affect lipid and carbohydrate metabolism as well as adipocyte function. Adiponectin, an adipocyte derived hormone has been shown to decrease body weight by increasing thermogenesis and lipid oxidation. Changes in profile of lipid and adiponectin have been reported in patients with thyroid dysfunction. But the evidence is controversial. The present study aimed to explore the relationships between thyroid function and lipid profile and serum adiponectin levels in hyperthyroid patients.

**Materials and Method:** A case control study was carried out on patients attending OPD, Department of Medicine RMRI, Bareilly. 100 cases of newly diagnosed hyperthyroid patients and 100 cases of age, sex matched apparently healthy controls were selected for analysis of biochemical parameters (plasma glucose, thyroid profile, adiponectin, lipid profile). Statistical analysis was performed using SPSS version 20.0.

**Results:** We found that serum adiponectin level was significantly higher in hyperthyroid patients as compared to control ( $p < 0.0001$ ). Positive correlation was observed between thyroid hormones and serum adiponectin level. No significant differences was observed in lipid profile among hyperthyroid patients and control group.

**Conclusion:** The present study demonstrated that hyperadiponectinemia is associated with hyperthyroidism. Regarding lipid profile no significant changes was observed in hyperthyroid patients as compared to control, though more extensive study with increased sample size may provide more insights.

**Keywords:** Hyperthyroidism, Adiponectin, Lipid profile

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### Introduction

Hyperthyroidism is a pathological disorder characterized by excess of thyroid hormones by thyroid glands. About 1.2 percent of people in the United States have hyperthyroidism.<sup>(1)</sup> In an epidemiological study from Cochin, overt hyperthyroidism were present in 1.3% of subjects participating in a community survey.<sup>(2)</sup> Thyroid hormones serve as a regulator of various processes in our body. The main function of thyroid hormones are to stimulate resting metabolic rate and increase heat production.<sup>(3)</sup> In addition thyroid hormones influence cell proliferation and development, modulate response to other hormones. Thyroid hormones also play a significant role in changing metabolism of carbohydrate, protein and lipid.<sup>(4)</sup> Hyperthyroidism is a catabolic state that lead to breakdown of fat and lean mass. Excess thyroid hormone can also induce insulin resistance.<sup>(5)</sup> Thyroid dysfunction is associated with metabolic alteration that affect not only lipid and carbohydrate metabolism but also adipocyte function. Adipose tissue is nowadays recognized as a highly active metabolic and endocrine gland which secretes a variety of biologically active substances, including adipocytokines, growth factors into blood stream. Among the various adipokines, adiponectin is the most abundant adipocytokines which shows anti-inflammatory and anti-atherogenic properties.<sup>(6)</sup> Though adiponectin is a product of adipose tissue its levels are

surprisingly reduced in obesity and also in type 2 diabetes.<sup>(7,8)</sup> These adiponectin and thyroid hormones share common physiological role such as regulating energy expenditure and metabolism of glucose and lipids.<sup>(9)</sup> The in vitro study in 3T3-L1 adipocytes showed that thyroid hormone elevates the leptin messenger RNA expression which leads to increase leptin secretion.<sup>(10)</sup> So it might be possible that there is interaction between thyroid axis and action of adipose tissue. It is conceivable that thyroid hormones can modulate synthesis and secretion of adiponectin also. In addition adipose tissue have thyroid stimulating hormone receptors and thyroid hormone receptors.<sup>(11)</sup> This indicate the probable interaction of thyroid hormones in regulation of adipocyte functions including secreting of adiponectin. Another effect of thyroid hormones is on lipid profile which is manifested in thyroid dysfunction.<sup>(12)</sup> Though there are some controversy, in most cases serum levels of lipids are found to be decreased in hyperthyroidism.<sup>(13)</sup>

Studies regarding thyroid disorders and their consequences on adiponectin profile are limited. Results are highly variable and conflicting.<sup>(14,15)</sup> In this context the objective of our present study was to evaluate serum adiponectin levels in newly diagnosed hyperthyroid patients. Furthermore we also evaluated serum lipid profile in hyperthyroid patients to find out any association.

## Materials and Method

This case control study was conducted in the Department of Biochemistry from February 2015 to September 2016 in collaboration with Medicine department of Rajshree Medical Research Institute, Bareilly. Ethical clearance was procured from Institutional Ethical Committee with vide reference no RMRI. Bly/2014-15/101.

100 cases of newly diagnosed hyperthyroid patient's age group between 25 to 45 years were selected. Selection criteria of the patients were based on biochemical laboratory investigation and clinical sign and symptoms. Hyperthyroid subjects were primarily diagnosed with T3, T4, fT3 and fT4 above the normal range and TSH below the normal range. Normal range for T3 was 0.52-1.85 ng/ml, T4 was 4.4-10.8 µg/dl (male) and 4.8-11.6 µg/dl (Female) and TSH was 0.39-6.16 µIU/ml. 100 age, sex matched apparently healthy euthyroid controls were taken and all the biochemical parameters (Plasma glucose, Adiponectin, Cholesterol, Triglyceride, HDL-C, LDL-C, LDL-C, VLDL) were measured in both the groups. The control subjects were selected from the people who came to the hospital for medical health checkup.

### The following patients were excluded from our study:

1. Subjects taking medication affecting thyroid hormone levels and hypolipidemic agents were excluded from our study.
2. Diabetes, Tuberculosis, hypertension, cancer, known cases of HIV.
3. Pregnant women and women with contraceptive pills
4. Obese subject BMI >35.

All the patients were explained about aim, objective of the study and written consent was obtained. Detail history was taken from all the patients. Height and weight of all the subjects were measured. The body mass index (BMI) of the subjects was calculated as per convention:

$$\text{BMI} = \frac{\text{Weight in Kg}}{\text{Height in m}^2}$$

**Biochemical analysis:** After an overnight fast 5 ml of blood was collected from an antecubital vein with full aseptic precaution without anticoagulant and allowed it to clot. Clotted blood was centrifuged and clear serum was collected. The serum was stored at -20°C until analyzed. Thyroid profile (T<sub>3</sub>, T<sub>4</sub>, fT<sub>3</sub>, fT<sub>4</sub>, TSH) test was done using ELISA method (Avantor, USA). Serum adiponectin level was estimated by quantitative sandwich ELISA method (CUSA Biotech, USA). Plasma fasting glucose level was done by glucose oxidase/oxidase method (ACCUREX, India). Total cholesterol was estimated by enzymatic end point cholesterol esterase-peroxidase method (ACCUREX, India). Triglycerides were measured by glycerol phosphate oxidase-peroxidase method (ACCUREX, India). HDL-C was estimated by direct enzymatic end point assay based on precipitation method (ERBA,

Germany). LDL-C and VLDL were calculated using Friedewald's formula.<sup>(16)</sup>

**Statistical Analysis:** Statistical analysis was performed using SPSS version 20.0. All data were expressed as "mean ±SD". Student t-test and Pearson's correlation coefficient was used to find out statistical significance. A value of  $p \leq 0.05$  was considered to be statistically significant. ROC curve analysis was done to find out the cut off value of various parameters.

## Results

The demographic characteristics and BMI of our study population for hyperthyroid patients and control group is shown in Table 1. The mean age group of hyperthyroid cases was 37.07 years and mean age of controls was 36.63 years. There was no significant change in mean BMI in both the groups and p value was statistically insignificant ( $p=0.54$ ). Table 2 shows the age and sex distribution of controls and hyperthyroid patients. The maximum number of patients in our study was in the age group between 36 to 45 years ( $n=60$ ).

Table 3 shows the normal values of T<sub>3</sub>, T<sub>4</sub>, fT<sub>3</sub>, fT<sub>4</sub> and TSH as well observed values in hyperthyroid subjects and controls. We found that TSH was significantly low ( $p < 0.0001$ ) and other thyroid hormones (T<sub>3</sub>, T<sub>4</sub>, fT<sub>3</sub> and fT<sub>4</sub>) were significantly high ( $p < 0.0001$ ) in hyperthyroid subjects. The biochemical analysis of plasma glucose, serum adiponectin and lipid profile is shown in Table -4. Plasma glucose level in both controls and hyperthyroid subjects was within normal reference range (70-100mg/dl). Though in hyperthyroid patients the plasma glucose level ( $85.44 \pm 12.84$ mg/dl) was slightly raised compared to control group ( $83.25 \pm 10.76$ mg/dl) but p value was statistically insignificant ( $p=0.19$ ). Serum adiponectin level was  $8.16 \pm 1.64$  (µg/ml) in hyperthyroid patients which was greater than that of  $6.59 \pm 1.44$  (µg/ml) in control group. When compared with unpaired student 't' test p value was  $< 0.0001$  which is highly statistically significant. In control group a negative correlation was observed between serum adiponectin and BMI ( $r=-.21$ ) but the correlation disappeared in hyperthyroidism ( $r=0.02$ ). Among the parameters serum adiponectin levels had positive correlation with serum T<sub>3</sub>, T<sub>4</sub>, fT<sub>3</sub> and fT<sub>4</sub> (Fig. 1, 2, 3 and 4). Very significant positive correlation it showed with serum T<sub>4</sub> ( $r=0.85$ ). In addition serum adiponectin also had weak negative correlation with serum total cholesterol (-0.30) and LDL cholesterol ( $r=-0.32$ ) but no significant correlation was found with HDL cholesterol.

There was no significant change was observed in serum cholesterol, triglyceride and LDL cholesterol level between hyperthyroid patients and control group and p value was statistically insignificant (Table 4). Though in our hyperthyroid patients these values were slightly increased and HDL cholesterol was marginally decreased but statistically insignificant ( $p=0.40$ ). When plotted in ROC curve in hyperthyroid group vs. control

group the best cut off value for serum adiponectin was 7.48  $\mu\text{g/ml}$  (Sensitivity 60% and specificity 78%) and AUC was 0.778 (Fig. 5).

**Table 1: Demographic characteristic and BMI of study population**

Parameters	Controls (mean $\pm$ SD)	Hyperthyroid cases (mean $\pm$ SD)
Age(Yrs)	36.63 $\pm$ 5.38	37.07 $\pm$ 5.28
Mean age of Males	36.06 $\pm$ 5.48	37.45 $\pm$ 5.97
Mean age of Females	37.07 $\pm$ 5.31	36.71 $\pm$ 4.78
BMI(Kg/ m <sup>2</sup> )	23.52 $\pm$ 1.56	23.39 $\pm$ 1.42

**Table 2: Age and Sex distribution in Hyperthyroid cases and controls**

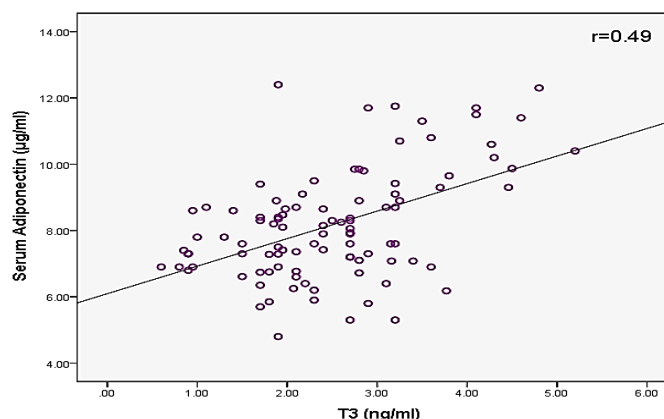
Age(Years)	Controls Total= 100		Hyperthyroid cases Total=100	
	Males	Females	Males	Females
25-30	7	8	10	6
31-35	14	12	5	19
36-40	11	18	14	17
41-45	12	18	15	14
Total	44	56	44	56

**Table 3: Thyroid profile in hyperthyroid cases and control**

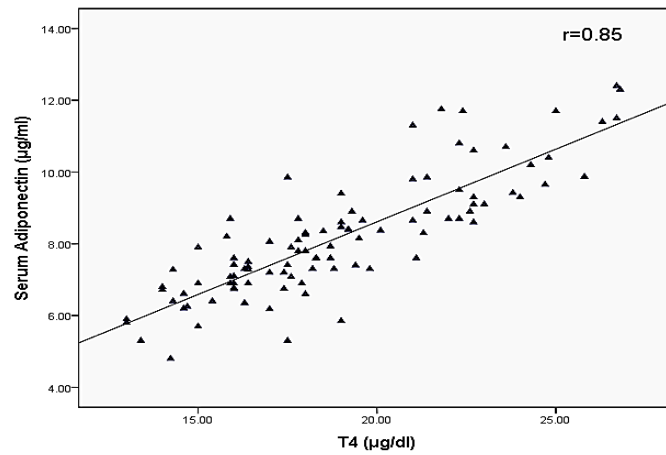
Parameter	Normal range	Controls (mean $\pm$ SD)	Hyperthyroid cases (mean $\pm$ SD)	p-value
T3 (ng/ml)	0.52-1.85	1.83 $\pm$ 0.32	2.49 $\pm$ 0.98	<0.0001
T4 ( $\mu\text{g/dl}$ )	Males: 4.4-10.8 Females: 4.8-11.6	7.25 $\pm$ 1.98	18.89 $\pm$ 3.44	<0.0001
FT3(pg/ml)	1.4-4.2	2.96 $\pm$ 1.10	5.39 $\pm$ 1.87	<0.0001
FT4(ng/dl)	0.8-2.0	1.33 $\pm$ 0.42	3.62 $\pm$ 2.91	<0.0001
TSH ( $\mu\text{IU/ml}$ )	0.39-6.16	2.71 $\pm$ 1.35	0.23 $\pm$ 0.10	<0.0001

**Table 4: Comparison of biochemical parameters between two groups**

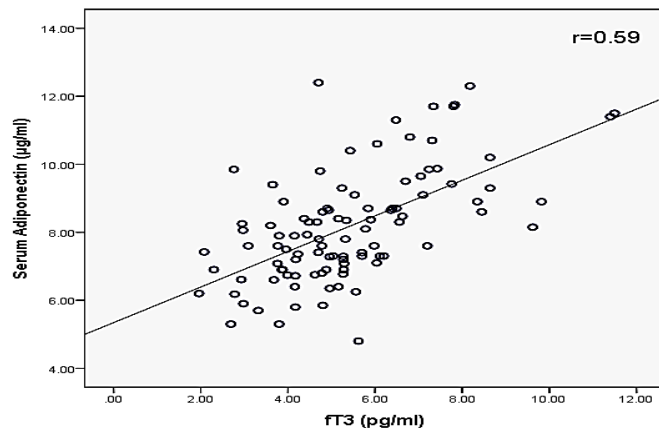
Parameters	Controls (mean $\pm$ SD)	Hyperthyroid cases (mean $\pm$ SD)	p- value
Fasting plasma glucose (mg/dl)	83.25 $\pm$ 10.76	85.44 $\pm$ 12.84	0.19
Adiponectin ( $\mu\text{g/ml}$ )	6.59 $\pm$ 1.44	8.16 $\pm$ 1.64	<0.0001
Total Cholesterol (mg/dl)	172.42 $\pm$ 32.62	180.85 $\pm$ 30.78	0.061
Triglyceride (mg/dl)	132.95 $\pm$ 38.33	142.46 $\pm$ 42.53	0.098
HDL-C (mg/dl)	46.30 $\pm$ 10.63	45.17 $\pm$ 8.48	0.40
LDL-C (mg/dl)	99.52 $\pm$ 30.79	107.23 $\pm$ 29.62	0.07
VLDL-C(mg/dl)	26.59 $\pm$ 7.66	28.46 $\pm$ 8.51	0.10



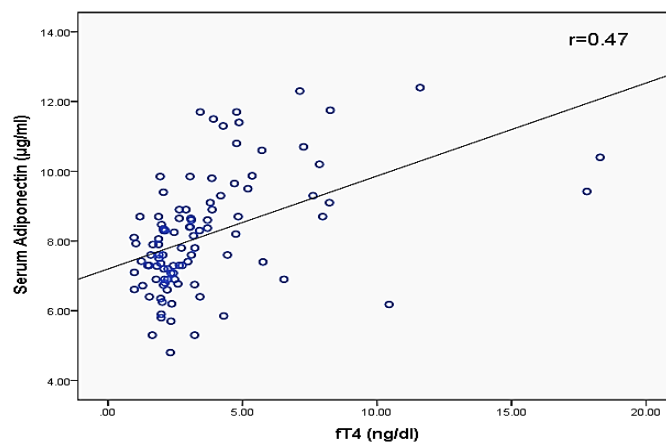
**Fig. 1: Relationship between T3 and serum adiponectin in Hyperthyroid patients**



**Fig. 2: Relationship between T4 and serum adiponectin in Hyperthyroid patients**



**Fig. 3: Relationship between FT3 and serum adiponectin in Hyperthyroid patients**



**Fig. 4: Relationship between FT4 and serum adiponectin in Hyperthyroid patients**

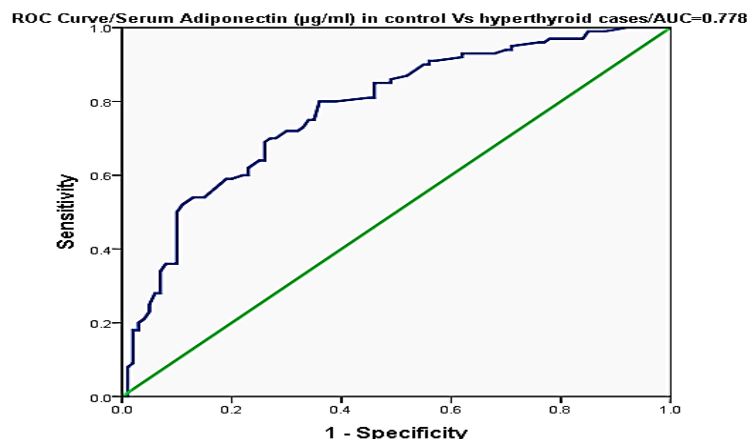


Fig. 5: ROC curve/ Serum adiponectin in control Vs hyperthyroid cases

### Discussion

Hyperthyroid patients are known to have elevated blood glucose levels.<sup>(17)</sup> The increase level is due to the endogenous glucose production by rapidly occurring glycogenolysis and gluconeogenesis.<sup>(18)</sup> In our present study the plasma glucose was slightly elevated than the control group but p value is statistically insignificant ( $p=0.19$ ). Another important finding is that serum adiponectin level was increased significantly in hyperthyroid group ( $8.16 \pm 1.64 \mu\text{g/ml}$ ) in comparison with control ( $6.59 \pm 1.44 \mu\text{g/ml}$ ) which is statistically significant. As hyperthyroidism causes an increase in energy expenditure and decrease in body weight, we analyzed the relationship between BMI and serum adiponectin levels. In control group we found negative correlation but no significant correlation was observed between serum adiponectin levels and BMI in hyperthyroid patients which was in agreement with the results obtained by Takako et al.<sup>(19)</sup> This indicate that thyroid function is one independent factor for determining serum adiponectin level in hyperthyroid patients. Serum adiponectin levels had positive correlations with serum T3, T4, fT3 and fT4. Takako et al. found that hyperadiponectinemia was associated with Basedow disease in hyperthyroid patients.<sup>(19)</sup> They also got strong positive correlation between serum adiponectin level and TRAb. However no correlation was found between serum adiponectin and TPO antibody and serum adiponectin and thyroglobulin antibody in their study. Our results are in accordance to study conducted by Yanyan Chen et al, where they found that serum levels of adiponectin were significantly increased in patients with hyperthyroidism.<sup>(20)</sup> In another study conducted by Haiying et al showed that hyperthyroidism was associated with a 95% increase of serum adiponectin level.<sup>(21)</sup> In animal studies carried out by Aragao CN et al. showed that hyperthyroidism induced an important elevation in the serum adiponectin concentration on experimental rats.<sup>(22)</sup> Seifi S et al. studied the gene expression on experimental rats and showed that adiponectin gene expression was increased with increase

in thyroid hormone concentration.<sup>(23)</sup> Their study provide evidence that adiponectin gene expression in adipose tissue is regulated by thyroid hormones at the translational level and the lipid and carbohydrate disturbances in hyperthyroid patients may be due to adiponectin gene expression changes. Our findings contradict the study conducted by Santini F et al. who concluded that metabolic changes associated with thyroid dysfunction are not due to alterations of serum levels of adiponectin.<sup>(24)</sup> Iglesias et al carried our similar study but their findings contrast our results where no significant changes were found in serum adiponectin level.<sup>(25)</sup> In contrast serum leptin, another adipocytokine was increased in the patients with hyperthyroidism probably due to excess thyroid hormone secretion.<sup>(26)</sup> So it can be postulated that like leptin, there might be a direct modulation by thyroid hormones on serum adiponectin levels in hyperthyroidism. Upon ROC curve analysis in hyperthyroid group vs. control group we found the best cut off value for serum adiponectin was  $7.48 \mu\text{g/ml}$  with 60% sensitivity and 78% specificity.

The reason for adiponectin elevation in hyperthyroidism is unclear and our present 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 few possibilities. First as TSH receptors are present on adipose tissue and TRAb may cross react with TSH receptors to produce more adiponectin.<sup>(11)</sup> This scenario is highly likely because study conducted by Takako et al. showed significant correlation between serum adiponectin and TRAb.<sup>(19)</sup> Second study conducted by Seifi S et al. on experimental rats showed that thyroid hormone itself may stimulate the synthesis of adiponectin by increasing gene expression with increase in thyroid hormone concentration.<sup>(23)</sup> Third excess thyroid hormones activates the adrenergic receptor system and lipolysis. Adiponectin is produced from small adipocytes, but not well differentiated adipocytes. Thyrotoxicosis could induce the increment of small adipocytes, which can produce adiponectin.<sup>(19)</sup>

In our present study surprisingly we found that total cholesterol, triglyceride and LDL cholesterol values were slightly higher when compared with euthyroid control but they were not statistically significant. The lipid profile values of both the groups are within normal reference range.<sup>(27)</sup> Our findings are in accordance with the study conducted by Sridevi V. Udupa et al. where they found LDL cholesterol and total cholesterol remain elevated in hyperthyroid patients.<sup>(28)</sup> HDL cholesterol level was marginally decreased in our present study in comparison with control group which is statistically insignificant. Most of the studies have reported lower total cholesterol level and LDL cholesterol level as compared to those in the euthyroid control.<sup>(13,29)</sup> Slightly different results observed in our study in lipid profile might be due to differences in patients' characteristics, which include duration and degree of thyroid dysfunction and also metabolic effect of other hormones. We also observed negative correlation between total cholesterol and serum adiponectin and also between LDL cholesterol and serum adiponectin. The result is an anti-atherogenic lipid profile, which may be mediated through both thyroid hormones as well as adiponectin.

In hyperthyroidism though the main rate limiting enzyme of cholesterol biosynthesis i.e. HMG CoA reductase activity is increased but total cholesterol, LDL cholesterol levels are decreased. Thyroid hormone are able to regulate expression of LDL receptors and excess thyroid hormone leads to increase LDL receptor gene expression which results in enhanced LDL receptor mediated catabolism of LDL particles.<sup>(30)</sup> Hyperthyroidism is associated with decrease level of HDL cholesterol. In hyperthyroidism thyroid hormones modulate HDL cholesterol metabolism. The mechanism is by increased activity of cholesteryl ester transfer protein and also due to increased hepatic lipase mediated catabolism of HDL<sub>2</sub>.<sup>(30)</sup>

## Conclusion

In conclusion result of our study indicates significant relationship between serum adiponectin and thyroid hormones. The present study demonstrated that hyperadiponectinemia is associated with hyperthyroidism. Significant positive correlation was observed between thyroid hormones and serum adiponectin levels. We could not find any significant changes in lipid profile between hyperthyroid patients and control group but negative correlation was observed between total cholesterol and serum adiponectin and between LDL cholesterol and serum adiponectin level. The limitation of our study is limited sample size and study was conducted in a single region. Larger sample size and multi-centric studies could be done to obtain wider insights.

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