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Effects of Hyperthyroidism on Lipid Profile, Adiponectin and Liver Function Tests of Male Rats

KEYWORDS: hyperthyroidism, Lipid profile, Adiponectin and kidney function tests.

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ABSTRACT *Introduction: Thyroid hormone influences the function of all body organs and cells. Thyroid abnormalities are accompanied by changes in intermediary metabolism including alterations in body weight and lipid profile.*

Aim: to investigate the effect of hyperthyroidism on serum or plasma lipids profile, adiponectin and liver function tests as compared to controls.

Materials and Methods: 40 rats weighing 220-250gm, divided into 2 groups (20 rats each). G1: control normal group; and G2: hyperthyroid rats group. Body weights were recorded on weekly bases. Serum or plasma FT3, FT4, TSH, total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C) triacylglycerols (TG), adiponectin, alanine and aspartate aminotransferase (ALT and AST) were measured using appropriate kits.

Results and Discussion: Results reveals significant decreased level of TC, HDL-C, LDL-C, VLDL-C, and TG in hyper thyroid rats when compared with the normal control group. Also a significant increase in ALT and AST levels were found in hyper thyroid rats when compared with the normal control group. Hyperthyroidism was associated with a 51.75% increase in adiponectin (P< 0.0001). Adiponectin correlated with FT3 (r= 0.84, P< 0.0001) and FT4 (r= 0.96, P< 0.0001). Adiponectin was negatively correlated with TSH (r= 0.84, P< 0.0001), total cholesterol (r= -0.55, P< 0.0001), LDL-C (r= -0.46, P< 0.0001) and triacylglycerol (r = -0.38, P < 0.0001) in hyperthyroid rat group.

Conclusion: Hyperthyroidism is associated with abnormal lipid profile, high adiponectin, urea and creatinine levels. This may be a possible explanation for the high cardiovascular morbidity among hyperthy¬roidic subjects. This study indicates that monitoring of lipid level in patients with thyroid dysfunction would be helpful in preventing cardiovascular diseases.

Introduction

The thyroid gland secretes two iodine containing amine hormones, L-thyroxine (T4) and tri-iodothyronine (T3). Free T3 and T4 enter all cells through the plasma membrane and bind to a nuclear T3 receptor. Thyroid diseases are primarily conditions that affect the amount of thyroid hormones being produced. Excess production leads to hyperthyroidism while diminished production leads to hypothyroidism (1). Thyroid function regulates some metabolic parameters as lipoprotein metabolism (so any disturbance in thyroid hormones leads to dyslipidemia) and some cardiovascular disease (CVD) risk factors (2,3). Hyperthyroidism is characterized by decreased body weight, as well as decreases in plasma lipids such as plasma cholesterol and triacylglycerols (2).

Through internet searching, a few studies were available dealing with the effect of thyroid gland disorder (hormones especially in case of hyperthyroidism) on liver, since thyroid hormones affect metabolic rate of cells including hepatocytes. Thyroid gland hormones (T3 and T4) have an important rule in maintaining the natural liver function (4) and also their effect on adiponectin.

Adiponectin is an adipose tissue hormone with multiple functions (5). Plasma adiponectin has been reported to correlate positively with plasma lipids, in particular HDL cholesterol (HDL-C) (6). Adiponectin has been suggested to increase fatty acid oxidation and alter energy expenditure (7).

The aim of this study was to investigate the effect of hyperthyroidism on serum lipids profile, adiponectin and liver function tests as compared to controls.

Materials and Methods

This study was approved by the high society of scientific ethic committee of NNI (National Nutrition Institute) & GOTHI (General Organization for Teaching Hospitals and Institutes).

This study was carried out on 40 adult male albino rats weighing 220- 250 gm at start of the study and housed individually in suspended wire-mesh cages and maintained under standard conditions of boarding. All rats were fed standard rat chow before starting the experiment for 10 days (adaptation period). The standard rat chow diet (AIN-93 M diet formulated for adult rodents) was prepared according to (8,9). Water and diet were given ad libiyum.

The rats were allocated into 2 groups

1. Group 1: include control rats (n=20). These rats were treated with intraperitoneal injection of normal saline in a similar volume as test group.
2. Group 2 include untreated hyperthyroid rats (n=20). Hyperthyroidism was induced by daily intraperitoneal injection of tetra-iodo-thyronine in a dose of 10 µg/100 g BW for 30 days (40 µg dissolved in 1 ml normal saline) as described by (10).

Weights of the rats and diets were recorded on a weekly base. The experiment lasted for 4 weeks (30 days) and at the end of the experiment, rats were fasted overnight, and then sacrificed, anesthetized under diethyl ether; the blood was collected and kept in tubes with and without anticoagulant. They were kept at –80 °C if not analyzed immediately. Liver was removed, washes with saline, dried and then weighed. Relative liver weights (RLW) were calculated as follow: RLW= [liver weight (LW)/Final Body Weight (FBW)] X 100.

Biochemical Analysis

The following parameters were monitored: Serum or plasma FT_3, FT_4, TSH, total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C) triacylglycerols (TG), adiponectin, alanine and aspartate aminotransferase (ALT and AST). FT_3 was determined using Rat Free Thyroxine, FT_3 ELISA Kit, supplied by Antibodies-online.com for the in vitro quantitative determination of Rat Free Thyroxine, FT_3 concentrations in cell culture supernates, serum, plasma and other biological fluids, Catalog No: ABIN572358.

FT4 was determined using Rat Free Thyroxine (FT4) ELISA

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Kit, supplied by CUSABIO BIOTECH CO., Ltd. for the in vitro quantitative determination of rat FT4 concentrations in serum, plasma and other biological fluids, Catalog No. CSB-E05079r. TSH was determined using kits supplied by ALPCO IMMUNOASSAYS, ALPCO Diagnostics. Thyroid Stimulating Hormone (Rat) ELIZA for the quantitative determination of TSH in rat serum and plasma, Catalog No. 55-TSHRT-E01. Adiponectin was determined using kits supplied by ALPCO IMMUNOASSAYS, ALPCO Diagnostics. Rat Adiponectin ELISA for the quantitative determination of adiponectin in rat serum and plasma, Catalog No. 22-ADPRT-E01. The serum total cholesterol (TC) and serum high density lipoprotein cholesterol (HDL-C) level was determined using colorimetric enzymatic kits (SGM Italia, Rome, Italy), according to the method described by (11,12) respectively. The serum low density lipoprotein cholesterol (LDL-C) level was determined using colorimetric enzymatic kits (SGM Italia, Rome, Italy), according to the method described by (13). The serum triacylglycerol (TG) level was determined using colorimetric enzymatic kits (SGM Italia, Rome, Italy), according to the method described by (14). Very low density lipoprotein cholesterol (VLDL-C) level was calculated using the following equation: VLDL-C= TC–(HDL-C+LDL-C). ALT and AST activities were measured spectrophotometrically by the methods of (15).

Statistical analysis

Data are expressed as Mean ±SEM. All statistical data and significance tests (T Test for comparison between individual groups and control group; and correlation co-efficient) were performed using the Statistical Package for the Social Sciences version 11 (SPSS Inc, Chicago, IL, USA). Statistical significance was accepted at $P < 0.05$.

Results

Results of Table (1) reveal significant decrease in body weight, the decrease reach 32.33% compared to control group, and a significant increase in liver weight of hyperthyroid group compared to normal euthyroid group. The increase reach 17.66% compared to control group.

Based on diagnosis of hyperthyroidism, FT_3 and FT_4 were above normal, while TSH was below normal when compared with normal euthyroid control group ($P< 0.0001$, Table 2). FT_3, FT_4 and adiponectin levels were significantly increased as compared to normal euthyroid control group ($P< 0.0001$). FT_3 and FT_4 increase reach 70.48 and 26.7% respectively when compared with the normal control group. A significant, direct correlation was found between adiponectin and FT_3 and FT_4 in hyperthyroid group. A significant, inverse correlation was found between adiponectin and TSH, TC, LDL-C and triacylglyerols in hyperthyroid group (Table 3).

Results of Table (4) reveal significant decrease ($P< 0.0001$) in TC, HDL-C, LD-C, VLDL-C and triacylglycerols levels of hyperthyroid rats group when compared with the normal control group.

Results of Table (5) reveal significant increase ($P< 0.0001$) in ALT and AST levels of hyperthyroid rats group when compared with the normal control group. The increase reach > 2 X (fold) normal level of control group.

Discussion

The diagnosis of hyperthyroidism was made on the basis of clinical examination, elevated levels of free thyroxine (FT_4), free triiodothyronine (FT_3) and suppressed TSH levels.

Hyperthyroid rats showed significant decreases in body weight throughout the period of the study and at the end of the study, despite significant increase in food intake (un-presented data). These findings indicate negative energy balance due to increased metabolic rate & energy expenditure (16). The results of the experiment agree with (17).

The increased liver weight of hyperthyroid rats can be explained by the recent research which used triiodothyronine as a hepatic growth factor and showed that T3 might be a primary mitogen for the liver in animal models (i.e. it induces hepatocyte proliferation and increases liver mass when administered at high doses in the absence of hepatic injury) (18).

The significant rise in thyroid hormones (FT3 and FT4) and significant decrease in TSH levels in hyperthyroid rat group are due to the negative feedback mechanism along the hypothalamic-pituitary-thyroid axis (17).

During searching in the internet, only few data is present regarding the effect or relationship of hyperthyroid and adiponectin. The increased levels of adiponectin in hyperthyroidism are consistent with the increased metabolic rate that is characteristic of hyperthyroid patients. Our results agree with (19,20) and disagree with (21,22) where they reported no significant changes were found in hyperthyroid human patients.

Thyroid hormones play a role in the regulation of adiponectin expression as suggested by (23), where they reported increased adiponectin level in mice exposed to cold. Yoda et al., 2001 and Yu et al., 2006 (23, 20) found that insulin level increased significantly in hyperthyroid patients. Insulin has been reported to stimulate adiponectin secretion. The significant increased level of insulin stimulate adiponectin secretion since insulin is this case act as stimulus as reported by (24).

Adiponectin correlated with FT_3 ($r = 0.84$, $P< 0.0001$) and FT_4 ($r= 0.96$, $P< 0.0001$). Adiponectin was negatively correlated with TSH ($r= 0.84$, $P< 0.0001$), total cholesterol ($r= -0.55$, $P< 0.0001$), LDL-C ($r= -0.46$, $P< 0.0001$) and triacylglycerol ($r = -0.38$, $P < 0.0001$) in hyperthyroid rat group.

The TC, HDL-C, LDL-C, VLDL-C and TG levels were found to be decreased in hyperthyroidism and this may be due to the rapid clearing of chylomicron remnants from blood stimulating cholesteryl ester transfer which in turn stimulate lipoprotein lipase. The main cause of the differences in total cholesterol concentrations is the alterations of LDL-C levels due to the increase in LDL receptor mRNA gene expression, which leads to an increase in activity and number of LDL receptors and enhance LDL receptor-mediated catabolism of LDL particles (1,25). This in turn, leads to a decrease in concentrations of LDL-C and TC levels. Moreover, no difference in LDL subfraction distribution has been observed between hyperthyroid versus euthyroid subjects (26). Furthermore, hyperthyroidism results in enhanced LDL oxidability, which is related to FT4 levels (27).

In hyperthyroid a decrease in HDL-C levels is also observed (28). This decrease suggested being due to due to increased cholesteryl ester transfer protein (CETP)- mediated transfer of cholesteryl esters from HDL to VLDL and increased hepatic lipase (HL)- mediated catabolism of HDL2 (29), or due to increased hepatic triglyceride lipase activity. Through the effects of thyroid hormones, hepatic lipase, a decrease, in HDL2/ HDL3 is reported. The most prominent alteration in HDL-C is due to the changes in HDL2 subfraction (30). The result of this study disagrees with (31) where he found no change in overt hyperthyroid or significant increase in subclinical hyperthyroid human patients.

In this study adiponectin correlates inversely with total cholesterol and triacylglycerols which agree with (20) and this may relates to the disruption of the usual elevated triglyceride/low HDL-C relationship, which is a feature of hyper/hypothyroidism (1,2). Yu et al., 2006 (20) reported an increase in non-esterified fatty acids (NEFA) and the enhanced release of NEFA from adipose stores, coupled to increased adiponectin may stimulate fatty acid oxidation in muscle and liver (7) with a comparable decrease in lipoprotein production (32)

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and this result is an anti-atherogenic lipid profile, which may be mediated through both thyroid hormones as well as adiponectin.

The decreased level of TG levels could be due to the action of thyroid hormone on VLDL. Catabolism of VLDL is accelerated in hyperthyroidism which is probably related to changes in activity of lipoprotein lipase (LPL) and/ or hepatic TG lipase (33).

The results also pointed to significant increase (P< 0.001) in AST and ALT enzyme activity in the serum of hyperthyroid group, may be due to metabolism increasing in hepatocytes which lead in turn to increase ALT & AST (4), or due to the damage which may happen in the hepatocytes leading to leakage of enzymes from the cells (34). The results of this experiment disagree with (35) where they found non significant increase in AST and no change in ALT in hyperthyroid rats.

Conclusion

Hyperthyroidism is associated with abnormal lipid profile, high adiponectin, urea and creatinine levels. This may be a possible explanation for the high cardiovascular morbidity among hyperthyroidic subjects. This study indicates that monitoring of lipid level in patients with thyroid dysfunction would be helpful in preventing cardiovascular diseases.

Table (1): Effect of hyperthyroidism on final body weight (FBW), Body weight gain (BWG), liver weight (LW) and relative liver weight (RLW) compared to normal group.

	IBW (gm)	FBW (gm)	BWG (gm)	LW (gm)	%LW
Mean±SEM	236.20±1.73	295.10±2.02	58.90±1.37	6.93±0.04	2.35±0.02
Mean±SEM	236.25±1.21	199.70±1.35 [a]	-36.55±1.31 [a]	8.15±0.10 [a]	4.09±0.06 [a]
P<	NS	0.0001	0.0001	0.0001	0.0001
% Change	0.02	-32.33	-162.05	17.66	73.94
X Fold	1.00	0.68	-0.62	1.18	1.74

G1: Normal control group; G2: Hyperthyroid Group; a: Significant from G1

Table (2): Comparison of FT^3, FT^4, TS^H, T^3/T^4 and adiponectin between normal and hyperthyroid rats.

		FT^3	FT^4	TS^H	$T3/T^4$	Adiponectin
		pg/ml	ng/dl	µIU/ml		ng/ml
G 1	Mean±SEM	4.81±0.07	7.58±0.15	3.26±0.13	0.64±0.02	4.99±0.06
G 2	Mean±SEM	8.21±0.05 [a]	9.61±0.22 [a]	2.16±0.07 [a]	0.86±0.02 [a]	7.57±0.05 [a]
	P<	0.0001	0.0001	0.0001	0.0001	0.0001
	% Change	70.48	26.70	-33.78	34.50	51.75
	X Fold	1.70	1.27	0.66	1.35	1.52

G1: Normal control group; G2: Hyperthyroid Group; a: Significant from G1

Table (3): Pearson Correlation co-efficient between adiponectin and FT_3, FT_4, TSH and lipid profi le.

	FT_3	FT_4	TSH	TC	HDL-C	LDL-C	TG
G 1	0.2	0.096	-0.33	-0.16	-0.03	-0.19	-0.23
P <	NS	NS	0.05	NS	NS	0.05	0.05
G 2	0.84	0.96	-0.87	-0.55	-0.27	-0.46	-0.38
P <	0.001	0.001	0.001	0.002	0.01	0.002	0.01

G1: Normal control group; G2: Hyperthyroid Group; a: Significant from G1

Table (4): Comparison of mean lipid profiles between normal and hyperthyroid rats.

	Cholesterol	HDL-C	LDL-C	VLDL-C	TG	TG/HDL-C
	gm/dl					
Mean±SEM	92.68±1.24	44.55±0.65	31.75±1.41	16.38±0.44	77.73±1.16	2.20±0.04
Mean±SEM	62.95±0.75 [a]	31.57±0.40 [a]	22.40±0.99 [a]	8.98±0.42 [a]	55.92±0.75 [a]	2.41±0.04 [a]
P<	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
% Change	-32.08	-29.14	-29.45	-45.19	-28.06	9.68
X Fold	0.68	0.71	0.71	0.55	0.72	1.10

G1: Normal control group; G2: Hyperthyroid Group; a: Significant from G1

Table (5): Effect of hyperthyroidism on liver function tests as alanine and aspartate aminotransferease compared with normal group.

		AST	ALT
		IU/ml	
G 1	Mean±SEM	38.22±0.72	27.24±0.60
G 2	Mean±SEM	83.77±1.18 [a]	64.32±1.40 [a]
	P<	0.0001	0.0001
	% Change	119.20	136.17
	X Fold	2.19	2.36

G1: Normal control group; G2: Hyperthyroid Group; a: Significant from G1

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