ISSN 2348-313X (Print)
International Journal of Life Sciences Research ISSN 2348-3148 (online)
Vol. 5, Issue 1, pp: (1-9), Month: January - March 2017, Available at: www.researchpublish.com

Association of Dyslipidemia with Hypothyroidism: Comparative Study

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Abstract: **Thyroid hormones enhance the basal metabolic rate. This study aimed to evaluate lipid profile in hypothyroidism in humans and experimental rats.**

Materials and methods: This study included 48 subjects age range 24-48 years (24 healthy controls and 24 hypothyroid patients) and two groups of male Wister rats (normal and experimental induced hypothyroidism). Blood was collected for determination of thyroid profile (TSH, FT_4 and FT_3), glucose, total cholesterol, triglycerides, LDL-c and HDL-c.

Results: The levels of plasma total cholesterol, triacylglycerol and LDL-c were statistically significantly higher ($p<0.001$) in hypothyroidism than control in human and rats. Treatment of hypothyroid rats with thyroxin, the level of lipids reduced to be normal. Therefore, treatment of thyroid dysfunction should be taken into consideration in the cases of dyslipidemia in order to decrease the risk of coronary heart diseases.

Conclusion: Finding a laboratory model that has common characteristics with humans can be useful in pharmacological research for thyroid disorders, dyslipidemia and coronary heart diseases.

Keywords: **Hypothyroid, lipid profile- rats-humans.**

1. INTRODUCTION

Thyroid gland produces thyroid hormones, which play central role in human growth and development. Several studies show that these hormones in animals and humans are critical for many functions in cardiovascular, nervous, immune, and reproductive systems (Jannini et al. 1995, Metz et al. 1996, Krassas 2000). For example, thyroid hormones regulate body metabolism and body energy and have direct anti-atherosclerotic effects such as blood vessel dilatation and synthesis of vasodilator molecules (Choksi et al. 2003, Kim 2008, Ichiki 2010). Therefore, thyroid diseases can lead to various clinical conditions.

Hypothyroidism (or underactive thyroid) which is one of the major disorders of the thyroid glands can influence many different metabolic pathways involved in food intake, energy consumption, and glucose and lipid metabolism (Kim 2008, Lopez et al. 2013). The estimated prevalence of hypothyroidism is 2% and it is more likely to develop in women than men, with a ratio of 10:1 (Canaris et al. 2000, Pucci et al. 2000). Hypothyroidism results when the production of the thyroid hormones is not sufficient to perform regular functions (Vanderpump 2011). However, thyroid gland requires iodine to synthesize the thyroid hormones: thyroxine (T_4, inactive form) and triiodothyronine (T_3, active form). Production of these two hormones is stimulated by another hormone, thyroid-stimulating hormone (TSH) that is synthesized by the pituitary gland. Hypothyroidism is characterized by abnormally low level of free thyroxine (FT_4) and high level of thyroid-stimulating hormone (TSH) levels (Boelaert and Franklyn 2005, Vanderpump 2011).

The basal metabolic rate (BMR) is a measure of the rate of oxygen consumption of an individual at complete rest, 12 hours after meal, in relation to the surface area of the body. T_4 and T_3 have an effect on the BMR. When large quantities of these hormones are secreted, the BMR may increase as much as 60-100% above normal level and the energy utilization

rate is greatly accelerated. On the other hand, when no thyroid hormone is produced, the BMR falls to almost one-half normal. However, individuals suffering from hypothyroidism have an elevated BMR. All aspects of fat metabolism are enhanced under the influence of the thyroid hormones. Because fats are the major source of long term energy supplies, the oxidation of free fatty acids by the cells is greatly accelerated by the thyroid hormones. Decreased thyroid secretion significantly increases the levels of cholesterol, triacylglycerols, and phospholipids and almost always causes excessive deposition of fats in the liver (Hulbert and Else 2004, Mullur et al. 2014, McAninch and Bianco 2016).

Hypothyroidism has been associated with accelerated and pre-mature coronary atherosclerosis. Indeed, it is a common cause of secondary dyslipidemia(Stone 1994, Tsimihodimos et al. 1999). The hypothyroid state induces changes in the lipid concentrations that may directly or indirectly promote atherogenesis. The number of LDL receptors is minimized in hypothyroidism and results in increased levels of apoprotein B, cholesterol, and LDL-cholesterol. Impaired catabolism of VLDL by lipoprotein lipase (LPL) results in increased level of triacylglycerol. Hepatic secretion of cholesterol and its conversion to bile acids is also reduced in hypothyroidism and improved by administration of L-thyroxine which converts T_4 to T_3 by organs (Smitz et al. 1989, de Bruin et al. 1993).

This study aims to provide an overview of the impact of hypothyroid hormones on lipid levels in the blood of both rats and humans. The study also aimed to assess the lipid levels in hypothyroid rats when hypothyroidism was reversed with the injection of thyroxine, the current standard hormone replacement recommended by the British National Formulary (BNF).

2. MATERIALS AND METHODS

Subjects:

A total of 48 male and female subjects (24 males and 24 females), age range 20-60 years, were recruited in this study from King Fahad Hospital in Jeddah. The handling of human samples were done according to the ethical rules approved by King Abdulaziz University.

These subjects were divided into two groups as follows:

- Normal control subjects, a total of 24 subjects (12 males and 12 females) – they were healthy subjects who were suffering from no major illness and were without any medication. They were staff, nurses and students.

- Hypothyroid patients, a total of 24 (12 males and 12 females).

Samples (serum or plasma) were collected from venous blood after overnight fasting from 12 to 14 hours. Samples were removed after centrifugation at 3000 g for 4 minutes at 4°C and stored at -20°C until assays. Serum samples were used to determine the levels of TSH, FT_4 and FT_3 while plasma samples were used to determine the levels of glucose, total cholesterol, triglycerides and HDL-cholesterol.

Animal model:

A total of 27 male and female Wistar rats (180-250 g) were obtained from King Fahd Medical Research Center, King Abdulaziz University, Jeddah, Saudi Arabia. They were fed *ad libitum* on a standard laboratory diet (Grain Soils and Flour Mills Organization, Jeddah, Saudi Arabia) with free access to water and they were housed individually in an environment in which the temperature was maintained at a constant temperature of 24±1°C, with lighting for 12 hours each day.

Rats were divided into two groups: a control group (n=7) and a hypothyroid group (n=20). The hypothyroid rats were divided into two sub-groups: untreated rats (n=10) and treated rats with Thyroxine (n=10). Experimental hypothyroidism was induced by administration of 6-n-propyl-2-thiouracil for 4-5 weeks. The drug was dissolved in warm ethanol (1% v/v) and added to the drinking water (0.5 mg/ml). For the pair-fed control rats ethanol was added to the drinking water at the same final concentration (1%). 6-n-propyl-2-thiouracil is an anti-thyroid drug that blocks hormone synthesis at the steps of iodine organization and iodotyrosine coupling. It has been shown that it inhibits the extra-thyroidal conversion of thyroxine to triiodothyronine (Chopra et al. 1985). The effect of hypothyroidism was reversed with three intraperitoneal

(I.P.) injections of thyroxine (5 µg/kg body weight in distilled water). The handling of animals was done according to the ethical rules approved by King Abdulaziz University.

Thyroxine Treatment:

Thyroxine was injected into hypothyroid rats on daily basis for three consecutive days. Hypothyroid rats were sacrificed after 28 days while hypothyroid rats treated thyroxine were sacrificed one day after the final injection of thyroxine.

Blood samples were collected from rats by cardiac puncture under light ether anesthesia into plain tubes. Serum was obtained by centrifugation for 20 minutes at 3000 ×g, and stored at -20°C until analyzed. To extract liver, rats were anaesthetized with Sagatel (0.1 ml/100 g body weight) and then livers were excised and directly frozen in liquid N_2 until use.

Determination of biochemical blood analysts:

Kits for glucose and lipids profile were purchased from Siemens (UK) whereas kits for thyroid hormones were purchased from Roche (USA).The concentrations of glucose, total cholesterol, triglycerides, and HDL-cholesterol were determined spectrophotometrically using an automated enzymatic procedure by Dimension instrument (Dade Behring Dimension RXL Chemistry Analyzer) according to standard enzymatic colorimetric tests. The value for LDL-cholesterol was calculated using Friedwald's equation. Concentrations of all serum hormones, free tri-iodothyronine (FT_3), total tri-iodothyronine (TT_3), free thyroxine (FT_4), total thyroxine (TT_4), TSH, and insulin were measured either by Electrochemiluminescence immunoassay (ECLIA) (Boehringer Mannheim Elecsys 2010, Roche, USA) or by radioimmuno assay (RIA) technique (Diagnostic Products Corporation (DPC), USA). Radioactivity was determined in Wallac Wizard, gamma counter model 1470.

Statistical analysis:

Results are given as mean ± standard error of mean (SEM) for the indicated number of observations. Comparisons between treated animals and their matched controls were made by using Student's t-test. For human subjects, LSD test procedure using T-test between groups followed a significant ANOVA test when the values of the measured parameter were normally distributed.

3. RESULTS

Table 1 shows general characteristics of the rats that were made hypothyroid by administration of 6-n-propyl-2-thiouracil. The body weight gain of the hypothyroid rats was significantly less than that of their pair-fed control ($P< 0.01$). No significant differences were detected in the serum concentrations of glucose while serum concentrations of insulin were significantly decreased ($P<0.001$). The serum concentrations of TT_3, FT_3, TT_4 and FT_4 were significantly decreased ($P< 0.001$) in hypothyroid rats, whereas that of TSH was significantly increased ($P < 0.001$).

Table 2 showed changes in serum lipid concentrations among hypothyroid rats and hypothyroid rats treated with thyroxine. Hypothyroidism resulted in significantly increased concentration of total cholesterol ($P<0.05$), significantly decreased concentrations of triacylglycerol and phospholipids ($P<0.001$) and a non-significant change in HDL- c concentration. However, when hypothyroid rats were treated with thyroxine, the total concentration of cholesterol was decreased and became insignificantly different from control rats, whereas triacylglycerol and phospholipids concentrations were markedly increased than those of hypothyroid rats, while HDL-cholesterol concentration was still insignificantly different from control rats.

The concentration of serum TSH was significantly increased in hypothyroid rats and was sharply decreased in hypothyroid rats treated with thyroxine (data not shown). However, when serum TSH concentration was high, serum concentration of total cholesterol was high. Higher total cholesterol concentration coincides with higher serum TSH concentration. In contrast to total cholesterol, the concentration of triacylglycerol and phospholipids were shown to be lower with high serum TSH concentration and to be higher with low TSH concentration. The relationship between serum TSH concentration and HDL-cholesterol was not clearly evident.

The concentration of serum FT_4 was significantly decreased in hypothyroid rats and then noticeably increased in hypothyroid rats treated with thyroxine. However, when serum TT_4 concentration was low, serum concentrations of total cholesterol were higher. Higher total cholesterol coincides with lower serum TT_4 concentration. In contrast to total cholesterol, the concentration of triacylglycerol and phospholipids were shown to be lower with low serum TT_4 concentration and to be higher with high TT_4 concentration (data not shown). The relationship between serum TT_4 and HDL-cholesterol was not clearly evident. For human subjects, the serum concentrations of FT4, FT3 and TSH were measured (Table 3) as well as plasma concentrations of total cholesterol, triacylglycerol, LDL-cholesterol, HDL-cholesterol and glucose (Table 4) in hypothyroid and normal controls. The concentration of serum TSH in hypothyroid was significantly higher than normal controls ($p<0.001$), while the concentrations of serum FT4 and FT3 in hypothyroid were significantly lower than normal controls ($p<0.001$) (Figure 2 A and B).

The concentrations of plasma total cholesterol, triacylglycerol and LDL-cholesterol were statistically significantly higher ($p<0.001$) in hypothyroid than control humans. There was no significant difference in the concentrations of plasma of both HDL-cholesterol and glucose between hypothyroid and normal controls (Figure 1).

Similar to rat model, when TSH concentration was high and FT_4 concentration was low, the concentration of total cholesterol in humans was high while in contrast to rats, triacylglycerol concentration was also significantly high in humans ($p<0.001$).

Table 1: General characteristics of control and hypothyroid rats

	Control Rats (n=7)	Hypothyroid Rats (n=20)
Initial body wt. (g)	158±3.00	155±3.00 n.s.
Final body wt. (g)	264±4.00	197±2.00 **
Liver wt. (g)	7.00±0.13	5.30±0.12 ***
Serum glucose (mmol/I)	9.60±0.69	8.1±0.13 n.s.
Serum insulin (µIU/ml)	51.5±4.22	23.7±2.14 ***
Serum TT_3 (nmol/I)	3.30±0.15	0.78±0.02 ***
Serum FT_3 (pmol/l)	4.14±0.31	0.16±0.03 ***
Serum TT_4 (nmol/l)	106±7.2	2.7±0.38 ***
Serum FT_4 (pmol/l)	22.9±1.68	0.46±0.03***
Serum TSH (µIU/ml)	0.62±0.25	3.78±0.25 ***

Values are presented as means ± SEM. Values significantly different from control are shown:

n.s.: non-significant, ** P < 0.01, *** P < 0.001.

Table 2: Serum concentrations of total cholesterol, triacylglycerol, HDL-cholesterol and phospholipids of control, hypothyroid and hypothyroid rats treated with thyroxine

	Control Rats	Hypothyroid Rats	Hypothyroid Rats treated with Thyroxine
Total Cholesterol(mmol/l)	1.98±0.07 (7)	2.27±0.09 (10)*	1.79±0.08 (10) n.s.
Triacylglycerol (mmol/l)	2.18±0.34 (6)	0.67±0.02 (10)***	1.21±0.18 (8)**
HDL-cholesterol (mmol/l)	0.89±0.10 (7)	0.85±0.03 (10) n.s.	0.93±0.03 (10) n.s.
LDL-cholesterol (mmol/l)	0.65±0.10 (6)	1.29±0.07 (10) ***	0.62±0.10 (8) n.s
Phospholipids (mmol/l)	2.01±0.04 (7)	1.62±0.03 (10) ***	1.72±0.07 (10) ***

Values are presented as means± SEM with number of rats given in parenthesis. Values significantly different from control are shown: n.s.: non-significant, * P < 0.05, ** P < 0.01, *** P < 0.001.

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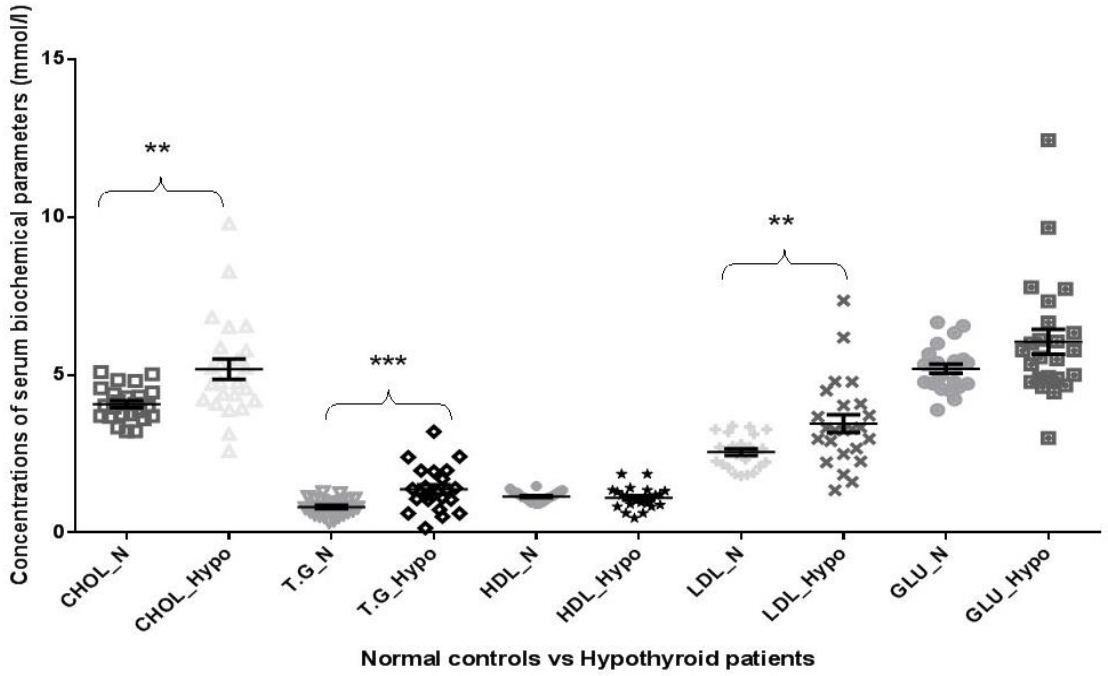

Figure 1: Biochemical parameters concentrations of hypothyroid (n=75) and normal control (n=100). Results are presented as means ± SEM. Significant difference between hypothyroid and normal control were made by Mann Whitney test: *p<0.5, **p<0.01and ***p<0.001, n.s= non-significant

Table 3: Serum levels of thyroid hormones of normal control and hypothyroid humans.

	Control Humans (n=24)	**Hypothyroid Humans (n=24)**
Serum glucose (mmol/I)	5.20±0.14	6.05±0.39 $^{n.s}$
Serum FT_3 (pmol/l)	4.96±0.16	3.66 ±0.18***
Serum FT_4 (pmol/l)	14.89±0.33	11.86 ±0.75***
Serum TSH (µIU/ml)	2.19±0.21	11.30±1.57 ***

Values are presented as means± SEM.Significant difference between hypothyroid and normal control were made Mann Whitney test: *p<0.5, **p<0.01and ***p<0.001, n.s= non-significant.

Table 4: Serum levels of plasma levels of some biochemical parameters of normal control and hypothyroid humans

	Control Humans (n=24)	**Hypothyroid Humans (n=24)**
Total Cholesterol (mmol/l)	4.08±0.11	5.19±0.32 **
Triacylglycerol (mmol/l)	0.81±0.05	1.38 ±0.14 ***
HDL-cholesterol (mmol/l)	1.15±0.03	1.10±0.07 $^{n.s}$
LDL-cholesterol (mmol/l)	2.56±0.10	3.35±0.28 **

Values are presented as means± SEM.Significant difference between hypothyroid and normal control were made Mann Whitney test: *p<0.5, **p<0.01and ***p<0.001, n.s= non-significant.

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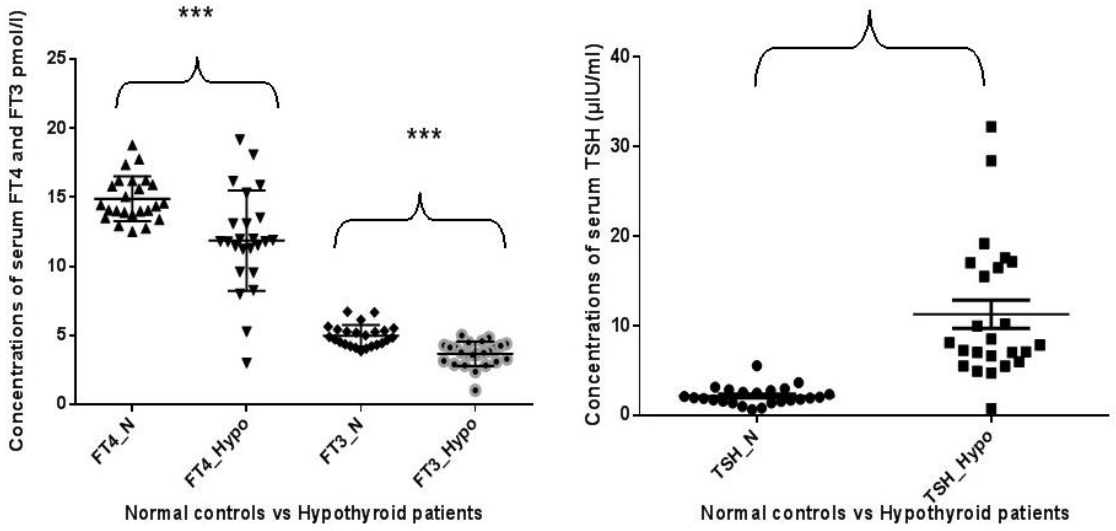

Figure 2: Serum thyroid hormones concentrations of hypothyroid (n=75) and normal control (n=100). Results are presented as means ± SEM. Significant difference between hypothyroid and normal control were made by Mann Whitney test: *p<0.5, **p<0.01and ***p<0.001, n.s= non-significant.

4. DISCUSSION

Thyroid hormones can affect various physiological and metabolic functions. Such effects include modulation of basal metabolic rate (BMR), stimulation of the oxygen consumption of cells in the body, controlling body temperature, changing of the heart rate, muscle activity, protein turnover and energy metabolism. Moreover, thyroid hormones increase the sensitivity of cardiovascular and central nervous system to catecholamine's (Psaltopoulou et al. 2007, Kim 2008, Lopez et al. 2013, Mullur et al. 2014).Hypothyroidism is a common metabolic disorder showing an age and sex dependence in the general population (Chiche et al. 2009). It is strongly associated with an unfavorable effect on lipids. Abnormal levels of thyroid hormones effect lipid synthesis, mobilization and degradation leading to quantitative/qualitative changes of cholesterol, triacylglycerol, phospholipids and lipoproteins. This may explain the high risk for cardiovascular disease in thyroid patients. Hypothyroidism is associated with elevated risk for atherosclerosis and ischemic heart disease (Hollowell et al. 2002, Liberopoulos and Elisaf 2002, Psaltopoulou et al. 2007, Chiche et al. 2009, Ichiki 2010, Peppa et al. 2011, Rizos et al. 2011, Lopez et al. 2013), while hyperthyroidism is associated with a hyper-dynamic cardiovascular state (Gomberg-Maitland and Frishman 1998, Ichiki 2010).

Cardiovascular diseases are one of the most important health problems and remain the major cause of death and disability in many countries all over the world. Atherosclerosis and thrombosis are the two etiological causes of coronary heart disease. Atherosclerosis is principally a disease of the large arteries in which lipids deposits called atheromatous plaque in the intimal layer of the arteries. Atherosclerosis is associated with modification of the LDL-cholesterol. Thus, high levels of LDL-cholesterol and low levels of HDL-cholesterol are considered as risk factors for atherosclerosis (Hu et al. 2002, Lopez et al. 2013).

In this study, rat has been chosen as an animal model since rats are most widely used in the study of thyroid physiology and in the actions of the thyroid hormones. Some results on rats are in agreement with the result on humans. Results obtained from this study show a significant decrease in serum concentrations of FT4 and FT3 combined with a significant increase in serum concentration of TSH in both rats and humans. These results correspond well with all other investigations.

Likewise, the concentrations of total cholesterol and LDL-cholesterol of hypothyroid rats and humans were increased significantly compared to control subjects. Despite the reduced activity of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase (which involved in the first step of cholesterol biosynthesis), the total cholesterol level is elevated (Liberopoulos and Elisaf 2002, Rizos et al. 2011). This is probably due to increased production of LDL-cholesterol,

impaired catabolism of LDL-cholesterol and minimized number of LDL-receptors in the liver. These results are in agreement with other reported results (Engler and Riesen 1993, Prakash and Lal 2006, Cheserek et al. 2015, Bandi A and R. 2016).

Jiang and his colleagues reported that Amiodarone and Dronedarone drugs effect lipid metabolism, increase the concentrations of cholesterol, LDL- and HDL-cholesterol and this may be associated with thyroid dysfunction in rats (Jiang et al. 2016). In contrast, upon treatment of hypothyroid rats with thyroxine, the serum total cholesterol level was reduced to nearly normal concentration. This reduction of total cholesterol concentration could be a result of reduced and/or increased removal of LDL-cholesterol concentration since thyroxine substitution decreases both LDL-cholesterol and apo-protein B if the number of LDL-receptors is reduced in hypothyroidism.

On the other hand, triacylglycerol showed different pattern between rats and humans. Interestingly, experimental hypothyroidism in rats displayed hypotriacylglycerolemia as well as hypophospholipidemia. When thyroxine was injected into hypothyroid rats, the concentrations of serum triacylglycerol and phospholipids were significantly lower than control rats. It is probably expected that the reason for this reduction in serum triacylglycerol and phospholipids during hypothyroidism is the reduction in the synthesis of these lipids from the liver since the liver weight was decreased by one third in hypothyroid rats. It is also suggested that triacylglycerol and phospholipids are greatly utilized during hypothyroidism (Nikkila and Kekki 1972). It has been reported that the rate of glycolysis was impaired and the activity of 6-phosphofructo-1-kinase was diminished in hypothyroid rats (Kjos et al. 1993). This result would also lead to reduction in the synthesis of pyruvate and acetyl CoA which are known as starting materials for triacylglycerol biosynthesis. On the contrary, in the case of hypothyroid patients, hypertriglyceridemia occurs because the synthesis of triacylglycerol is normal but the fraction removal is markedly diminished. This might be explained by the finding that a normal decrease in lipoprotein lipase (LPL) activity in the adipose tissues reduces the clearance of triglycerides-rich lipoproteins (Kuusi et al. 1980, Santamarina-Fojo et al. 2004, Rizos et al. 2011).

The association between hypothyroidism and HDL-cholesterol is controversial. In this study, the level of HDL-cholesterol did not exhibit any difference between subjects with hypothyroidism and controls in both rats and humans. In most studies, hypothyroid subjects usually exhibit elevated level of HDL-cholesterol possibly due to a reduction in hepatic lipase (HL) activity, a decrease in HDL catabolism, and decreased activity of cholesteryl ester transfer protein (CETP) which converts cholesteryl esters from HDL to VLDL-cholesterol (Kuusi et al. 1980, Liberopoulos and Elisaf 2002).

In conclusion, association of thyroid hormones with lipid profile is necessary to avoid the risk of cardiovascular diseases since thyroid dysfunction leads to qualitative and quantitative changes in lipids. Thyroid hormone profile are highly conserved in rats and humans. Finding a laboratory model that has common characteristics with humans can be useful in pharmacological research for thyroid disorders, dyslipidemia and coronary heart diseases.

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