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ESTIMATION OF THYROID HORMONES AND LIVER ENZYMES LEVELS IN HYPO AND HYPERTHYROIDISM IN IRAQI WOMEN

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ABSTRACT

Thyroid hormones are secreted to control tissues metabolism rate ,so that any alteration in their action will affect the system of many organs and change many enzymes level included liver enzymes aspartate amino transferase(AST), alanine amino transferase (ALT) and alkaline phosphatase (ALP) and total serum bilirubin(TSB). The study is conducted to estimate the correlation between thyroid hormones levels alteration with liver enzymes levels and lipid profile. This study includes(60)hypo and hyperthyroidism patients compared with 30 apparently healthy control group who have attended to Nursing Home Hospital in Baghdad Medical City. Thyroid hormones are measured by automated system(TOSO),while lipid profile and liver enzymes are measured by auto analyzer by (COBAS 11). Results show increase in the enzymes ALP,AST, ALT ,and TSB levels in both hyper and hypothyroid ismpatients , lipid profile LDL,TG,TC levels increase in all cases, but HDL increase in hypothyroidism and decrease in hyperthyroidism patients. Thyroid hormones levels are significantly correlated with liver enzymes level and lipid profile in hyper and hypothyroidism patients ($p<0.05$)($p<0.01$) respectively. The current study demonstrates that there is an appositive association between thyroid hormones levelsand liver enzymes levels(ALT, AST and ALP) and TSB levels.

KEYWORDS: **hyperthyroidism, hypothyroidism, liver enzymes and lipid profile**

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INTRODUCTION

Hyperthyroidism is defined as an over activity of the thyroid gland . The metabolism of a person with hyperthyroidism is sped up from too much thyroid hormone in their system, so that everything in the body is running at overdrive. [1] The vast majority of people with hyperthyroidism (95%) experience Graves' disease as the cause. [2] It is an autoimmune disease caused by antibodies created by the immune system attached to the thyroid gland and stimulates it to produce excessive amounts of hormone. [3] Hypothyroidism is a gradual disorder, it can be severe with obvious, or moderate to mild or can be sub-clinical hypothyroidism. Deficiency of thyroid hormones affects entire metabolism of the body.[4] It has been associated with altered ovulatory function, menstrual irregularities, subfertility, and higher (recurrent) miscarriage rates. Usually, treatment corrects these problems. More recent studies have reported a lower frequency of menstrual abnormalities. [5] Subclinical hypothyroidism (SCH) is defined by an increase in serum thyroid stimulating hormone (TSH) concentrations with normal free thyroxine (FT4) levels. The prevalence of SCH in sub fertile women has been reported to vary from 0.7% to 43% [6.] The wide range of prevalence is due to the differences in sensitivity of serum TSH measurement. The revised clinical practice guidelines of the Endocrine Society have recommend the measurement of serum TSH in order to screen for thyroid dysfunction in women over the age of 30 years with infertility or a prior history of miscarriage. [7] Nonalcoholic fatty liver disease (NAFLD) is characterized by excessive hepatic accumulation of triglycerides and free fatty acids in the liver. [8] The incidence of NAFLD increases rapidly, and it is the most common cause of abnormal liver function results worldwide. [9] The increase in the prevalence of NAFLD has been attributed to the global increase in the prevalence of obesity and other metabolic risk factors. Advanced age and metabolic disorders such as type 2 diabetes mellitus, impaired glucose tolerance, and central obesity, are among the risk factors for NAFLD.[10] Cryptogenic cirrhosis is a term used to signify patients with liver cirrhosis who lack any identifiable viral, alcoholic, autoimmune or drug-related causes for the condition. Many clinicians now believe that a considerable number of these patients have cirrhosis due to nonalcoholic steatosis hepatitis (NASH). [11] Thyroid glands release Triiodothyronine (T3) and Thyroxine, which can sometimes be referred to as tetraiodothyronine (T4), are significantly involved in energy homeostasis, lipid, carbohydrate metabolism, regulation of body weight, and adipogenesis. Subclinical and overt hypothyroidism has been associated with metabolic syndrome, cardiovascular mortality, and disturbance in lipid metabolism. [12] Thyroid hormones have many effects on the cardiovascular system [13]. Their action results in changes in cardiac contractility, cardiac output, myocardial oxygen consumption, systemic vascular resistance, and blood pressure. [14] The relationship between abnormal thyroid functions and coronary heart disease (CHD) has been recognized for a long time, especially in hypothyroidism status due to the associated hypercholesterolemia and hypertension [15]. Even subclinical hypothyroidism and subclinical hyperthyroidism have been related to increased risk of CHD and mortality, although still controversial. [16]

MATERIALS AND METHODS

This study was carried out on Nursing Home Hospital in Baghdad Medical City during July to September 2015 .thirty hyperthyroidism and thirty hypothyroidism female patient were participated in this study by randomly chosen ,but nearly have the same condition like life style and activities. Detailed information on each patients age . blood pressure ,blood glucose ,lipid profile and duration of disease was recorded accordingly.The diagnosis of hyperthyroidism has been made on the basis on clinical examination, elevated circulating levels of T4 or T3 and suppressed TSH levels. The causes of hyperthyroidism are Graves ' disease in all patients.Thirty subjects includes control group apparently healthy after having been asked about their thyroid hormones level Venous blood was collected into plain tubes after an overnight at least 8 hours fasting , Thyroid gland functions TSH, T3 and T4 have been determined according to the manufacturing kit and reading by TOSO system in the lab of Nursing Home Hospital .the normal values of TSH (0.38-4.31 milil IU/ml), T3 (0.79-1.58 ng/ml) T4 (4.9-11 µIU/ml),Total cholesterol (TC), high density lipoprotein cholesterol (HDL), triglycerides (TGL) and liver functions test includes (amino transfers(AST), alanine amino transfers(ALT) ,alkaline phosphatase (ALP) and total serum bilirubin were determined by auto analyzer (COBAS 11) .The normal range of AST (30-42 U/L),ALT(20-42U/L), and ALP(30-85 U/L)Low-density lipoprotein (LDL), are calculated by the Friedewald formula:

$$\text{LDL mg/dL} = \text{C} - \text{HDL} - \text{TGS}/5.\ ^{17}$$

Index (BMI) was measured as follows:-

$$\text{Body Mass Index (BMI)} = \text{Weight in Kilograms/Square of height in meters}^{18}$$

Inclusion Criteria

Age range for all subjects are between 18–45 years and are without any chronic condition other than thyroid disorders that are included in this study.

Exclusion Criteria

The criteria which are excluded from this study including ;liver disease, , bone and muscle cardiac disease, pancreatic, hepatobiliary, diabetes,

,hypertension, malignancy, oral contraceptive pills (OCP), and pregnancy.

Statistical Analysis

Statistical Analysis System- SAS (2012) program is used to affect difference factors in study parameters. Least significant difference -LSD test is used to t compare, significantly, between means. The coloration of coefficiency between difference parameters,(*Duncan, D.B. 1955. Multiple Rang and Multiple F-test. Biometrics.) in this study is estimated.

RESULTS

Table 1
Comparison between age and BMI of hypo and Hyperthyroidism patients and controls

Groups	Mean ± SE	
	Age (year)	BMI (kg/m^2)
Control(n=30)	39.40 ± 1.88 a	27.03 ± 0.50 b
Hyperthyroidism Patients (n=30)	36.86 ± 1.79 a	28.58 ± 0.51 b
Hypothyroidism Patients (n=30)	36.10 ± 1.77 a	32.87 ± 0.74 a
LSD value	5.108 NS	1.685 **
P-value	0.409	0.0001

**** (P<0.01), NS: Non-significant**

***Note** : **a ,b ,ab Means having with the different letters in same column differed significantly.**

Table (1) shows the comparison between age, body mass index of hypo and hyperthyroidism patients, and the control group which show non-significant difference in age per year of patients and controls, a significant difference in body mass index between the patients and controls (p<0.01)is shown.

Table 2
Comparison between thyroid profiles of hypo and hyperthyroidism patients and controls

Groups	Mean ± SE		
	TSH (mIU/ml)	T4(µIU/ml)	T3(ng/ml)
Controls (n=30)	1.427 ± 0.20 b	7.00 ± 0.28 b	0.948 ± 0.04 ab
Hyperthyroidism patients (n=30)	0.822 ± 0.77 b	16.64 ± 0.48 a	1.447 ± 0.30 a
Hypothyroidism Patients (n=30)	25.38 ± 4.85 a	5.09 ± 0.44 c	0.904 ± 0.07 b
LSD value	7.983 **	1.163 **	0.520 *
P-value	0.0001	0.0001	0.0556

**** (P<0.05), ** (P<0.01).***

Table (2) shows thyroid hormones (T3, T4, TSH) levels for the study groups (hyper and hypothyroidism and control) which show significant differences between the study groups (p<0.05)(p<0.01).

Table 3
liver function enzymes (APL,AST,ALT and TSB) for hypo and hyperthyroidism and control groups

Groups	Mean ± SE			
	ALP(U/L)	AST(U/L)	ALT(U/L)	TSB(mg/dl)
Control(30)	52.53 ± 3.86 b	18.83 ± 1.41 b	16.73 ± 1.52 b	0.736 ± 0.03 b
Hyperthyroidism(30)	131.17 ± 8.96 a	53.73 ± 3.60 a	57.83 ± 2.08 a	1.006 ± 0.12 ab
Hypothyroidism(30)	148.46 ± 5.13 a	52.26 ± 2.30 a	52.06 ± 2.66 a	0.763 ± 0.08 ab
LSD value	17.902 **	7.316 **	7.064 **	0.247 *
P-value	0.0001	0.0001	0.0001	0.053

**** (P<0.05), ** (P<0.01).***

Note : a ,b ,ab Means having with the different letters in same column differed significantly.*

Table (3) shows the levels of liver enzymes (ALP, AST, ALT) and(TSB) for hypo and hyperthyroidism patients and controls which show significant difference between ALP of controls and both of hyper and hypothyroidism patients (p<0.01) , in addition there is a significant difference between AST and ALT levels of controls and hyperthyroidism, hypothyroidism patients (p<0.01). Also, there is a significant difference between TSB of the control group, hyperthyroidism, and hypothyroidism patients (p<0.05).

Table 4
Lipid Profile levels of the hypo and hyperthyroidism patients and the control group.

Groups	Mean ± SE			
	HDL(mg/dl)	LDL(mg/dl)	TG (mg/dl)	TC (mg/dl)
Controls (30)	**45.26 ± 1.11 c**	**117.93 ± 1.04 b**	**118.86 ± 5.39 c**	**171.60 ± 2.19a**
Hyperthyroidism patients(30)	33.96 ± 1.62 b	102.76 ± 2.74 c	167.93 ± 7.61 b	133.70 ± 7.22c
Hypothyroidism patients (30)	55.83 ± 1.94 a	163.03 ± 4.28 a	233.53 ± 7.53 a	227.76 ± 3.78a
LSD value	4.623 **	8.894 **	18.470 **	13.702 **
P-value	0.0001	0.0001	0.0001	0.0001

***** (P<0.01).***

***Note** : **a ,b ,ab Means having with the different letters in same column differed significantly**

Table(4) shows lipid profile levels for hypo and hyperthyroidism patients and the control group which show significant differences in all parameters of lipid profile of the study patients compared with the control group (p<0.01).

Table 5
Correlation between liver enzymes and thyroid hormone profile in hyperthyroidism patients

Thyroid Hormones	liver Enzymes			
	ALP(U/L)	AST(U/L)	ALT(U/L)	TSB(mg/dl)
TSH (mIU/ml)	0.23 NS	-0.02 NS	-0.17 NS	0.09 NS
T4(µIU/ml)	-0.28 *	-0.13 NS	0.33 *	-0.05 NS
T3(ng/ml)	0.25 NS	-0.33 *	-0.16 NS	-0.23 NS

**** (P<0.05) , NS: Non-significant..***

Table (5) shows the correlation between liver enzymes, TSB and thyroid hormones profile in hyperthyroidism patients which indicates no-significant correlation between TSH and liver enzymes levels. T4 shows significant correlation with ALP and ALT levels (P<0.05) and no-significant correlation with AST and TSB, also T3 show significant correlation with AST (p<0.05), and no-significant correlation with (ALP, ALT, TSB).

Table 6
Correlation between liver Enzymes,TSB and Thyroid Hormone Profile in Hypothyroidism patients

Thyroid Profile	Liver Enzymes			
	ALP(U/L)	AST(U/L)	ALT(U/L)	TSB(mg/dl)
TSH (mIU/ml)	0.14 NS	-0.06 NS	-0.07 NS	0.36 *
T4(µIU/ml)	-0.29 *	0.36 *	0.36 *	-0.23 NS
T3(ng/ml)	0.009 NS	-0.32 *	-0.33 *	-0.09 NS

**** (P<0.05) , NS: Non-significant..***

Table (6) shows the correlation between liver enzymes and thyroid hormone profile in hypothyroidism patients. TSH has no-significant correlation with liver enzymes while TSB shows a significant correlation (p<0.05). T4 shows significant correlation with all liver enzymes (p<0.05) ,and TSB shows no-significant correlation with T4. T3 shows significant correlation with AST and ALT (P<0.05) and no-significant with ALP, TSB.

Table 7
Correlation between thyroid hormone and lipid profile in hyperthyroidism

Thyroid Profile	Lipid Profile			
	HDL(mg/dl)	LDL(mg/dl)	TG(mg/dl)	TC(mg/dl)
TSH(mIU/ml)	0.01 NS	-0.11 NS	0.09 NS	-0.16 NS
T4(µIU/ml)	-0.50 **	0.11 NS	0.16 NS	-0.24 NS
T3(ng/ml)	-0.11 NS	0.005 NS	-0.06 NS	-0.07 NS

***** (P<0.01) , NS: Non-significant..***

Table (7) shows the correlation between thyroid hormones levels and lipid profile in hyperthyroidism patients which show no-significant correlation except T4 shows asignificant correlation with HDL (P<0.01)

Table 8
Correlation between thyroid hormones levels and lipid profile in Hypothyroidism patients

Thyroid Profile	Lipid Profile			
	HDL(mg/dl)	LDL(mg/dl)	TG(mg/dl)	TC(mg/dl)
TSH(mIU/ml)	0.21 NS	-0.05 NS	0.003 NS	-0.12 NS
T4(µIU/ml)	-0.07 NS	0.03 NS	-0.20 NS	0.11 NS
T3(ng/ml)	-0.31 *	0.12 NS	-0.44 **	0.29 *

**** (P<0.05), ** (P<0.01) , NS: No-significant..***

Table (8) shows the correlation between thyroid hormones levels and lipid profile in hypothyroidism patients which show no-significant difference except T3 shows a significant difference with HDL, TG and TC (P<0.01)(P<0.05) and not-significant with LDL.

DISCUSSION

Thyroid hormones (THs) are potent hormones modulating liver lipid homeostasis. The perturbation of lipid homeostasis is a hallmark of non-alcoholic fatty liver disease (NAFLD), which is a very common liver disorder. It was reported that NAFLD patients were associated with higher incidence of hypothyroidism. However, whether abnormal thyroid function contributes to the pathogenesis of NAFLD remains unclear.[19] Thyroid hormone (TH) is potent to influence multiple aspects of lipid, carbohydrate, protein, and mineral metabolism [20]. Through binding to nuclear TH receptors (TR), TH can modulate the expression of target genes [21]. Physiological inverse relationship between TH, such as thyroxine (T4) and triiodothyronine (T3), and thyroid stimulating hormone (TSH) , are maintained through a classic negative feedback loop mediated by the hypothalamic pituitary-thyroid axis. Overt hyperthyroidism is used to describe the situation when patients are found to have an undetectable TSH level and a high T4 or T3 level. In contrast, those who are diagnosed overt hypothyroidism show an elevated TSH level accompanied by a low free T4 level.Thyroid disease affects 6.6% of the general population. The liver is fundamental in metabolizing thyroid hormones, and hepatocytes are often affected in thyroid disease. Thyroid hormones modulate oxygen consumption rates, thermogenesis, the expression of the low-density lipoprotein (LDL) receptor, the strength and frequency of myocardial contraction [22], and bone turnover [23]. In addition, thyroid hormones have great importance in the physiology of the gastrointestinal tract: they are necessary for the maturation of its mucous membranes and influence gastrointestinal motility, glucose and fat uptake, and the composition of bile salts [24].Hypothyroidism directly affects the structure and function of hepatocytes, and is associated with cholestatic jaundice, which is attributed to reduced excretion of bilirubin and bile and reduced flow of bile [25] In addition, hypothyroidism is associated with obesity and dyslipidemia [26], which can induce steatogenesis and lead to nonalcoholic steatohepatitis. This association occurs because thyroid hormones increase the expression of LDL receptors in hepatocytes [27] and increase the activity of fat-reducing liver enzymes, leading to decreased levels of circulating LDL [28]. Hypothyroidism also leads to decreased intestinal motility that promotes increased intestinal absorption of enteric cholesterol. Indeed, increased serum levels of gamma-glutamyltransferase (GGT) and alanine aminotransferase (ALT) have been detected even in cases of minimal hypothyroidism. Moreover, liver damage can be detected in subclinical thyroid disease cases, with evidence of metabolic changes in liver-associated laboratory parameters [29]. An excess of thyroid hormone is also associated with liver injury. In thyrotoxicosis, hepatic afflictions are common and include hepatocellular injury, elevated liver enzymes (aspartate aminotransferase [AST] and ALT), cholestasis, and increased levels of alkaline phosphatase (ALP), GGT and bilirubin. It is believed that hepatitis caused by thyrotoxicosis is due to hypoxia in perivenular regions, reflecting an increased oxygen uptake by hepatocytes without a corresponding increase in blood flow [30] With respect to the parameters of age[31, 32,33], and etiology of thyroid disease [34, 35], the present study sample is consistent with previous studies of thyroid disease. The average age reported in individuals with thyroid disease is 41-50 years, and the prevalence of hypothyroidism increases with increasing of age in the studied populatio[36].Differential diagnosis on aminotransferases elevations may reflect liver diseases (alcoholic and nonalcoholic hepatic steatosis, liver injury induced by drugs, viral hepatitis, autoimmune hepatitis, hemochromatosis, etc.) or caused by pathologies affecting organs other than the liver such as thyroid disease, celiac disease, hemolysis, and muscle disorders, among others[37.] These results are in line with the descriptions in the medical literature indicating that both hyperthyroidism and hypothyroidism are associated with hepatic afflictions. (Kubota and Cols).[38]The present study confirms that abnormal LFTs are frequently observed in patients with newly diagnosed and untreated Gaucher's disease(GD), and most of the liver variable abnormalities in GD patients are mild. Compared with previous reports, [39, 40] several aspects contribute to hepatic dysfunction, including liver abnormalities due to hyperthyroidism alone, liver damage related to hyperthyroidism with associated complications (e.g. heart failure), and concomitant liver disease in the setting of hyperthyroidism. [41,42]In the present study the free-T3 and free-T4 levels are observed to be more elevated in patients with abnormal LFTs, which may be due to excess thyroid hormone causing hepatic tissue hypoxia via increased hepatic and splanchnic oxygen requirement. However, other studies have suggested that liver enzyme levels do not correlate with those of thyroid hormones[43,44,45] and even low FT4 concentrations are associated with hepatic steatosis. [46,47] This study shows relatively a large consecutive cohort which indicates that abnormal LFTs in patients with newly diagnosed and untreated GD are common and mild. Higher serum FT4 concentration(Kaliaperumal and Cols). [48] found that patients with untreated hypothyroidism had a means of cholesterol level (232.12 ± 5.12 mg/dL) which is significantly higher than the level of the control group (169.65 ± 2.59 mg/dL).The present study has some limitations to be mentioned. First, the number of patients is not significant considering the high prevalence of thyroid disorders in the general population. This is not a prospective study involving patients in the first outpatient evaluation. These results are in line with the descriptions in the medical literature indicating that both hyperthyroidism and hypothyroidism are associated with hepatic afflictions.

CONCLUSION

The result of our study and the comparison with other studies show that hypothyroidism and hyperthyroidism have a significant effect on liver that lead to increased level of specific enzymes like ALT,ALP,AST, but no

significant correlation between thyroid hormones and lipid profile excepted HDL .The increased level of specific enzymes in humans may be used in diagnosis tool with other valuable tests for predicting the hepatic dysfunction in thyroid disease .

CONFLICT OF INTEREST

Conflict of interest declared None.

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