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Original Research Paper

A Study of Leptin & Thyroid Hormones in Pre and Post-Operative Patients with Thyrotoxicosis

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ABSTRACT:
Background: Hyperthyroidism is a thyroid hyperfunction. Treatment options include: Anti thyroid drugs, radioiodine therapy, and / or thyroid surgery. Leptin is a peptide hormone considered to play a role in the maintenance of energy balance and body weight by neuroendocrine mechanism. Thyroid hormones also take part in energy metabolism and have marked effects on adipose lipid metabolism. However it is not known whether adrenergic receptors or TSH receptors on adipocytes may play a role in regulating this hormone secretion from adipocytes. **Objective**: to look for the functional relationship between leptin, TSH and thyroid hormones in pre and post-operative patients with thyrotoxicosis. **Patients and Methods**: A total number of 78 samples divided into: Control group (n= 26) Pre-operative group (n= 26) Postoperative group (n= 26). For all studied Patients measurement of fasting serum leptin, thyroid hormones, (T3, T4, TSH) lipid profile and their BMI had been done. **Results**: Mean serum leptin level was significantly increased post-operatively Compared to pre-operative group ($p<0.05$) while the thyroid hormones (T3, T4, TSH) returned to normal levels post-operatively ($p<0.05$), lipid profile was significantly increased postoperatively ($p<0.05$) while BMI not significantly changed in two groups($p>0.05$). **Conclusions**: leptin has a strong functional relationship with thyroid hormones (T3, T4, TSH) in pre and post-operative patients with thyrotoxicosis while their lipid profile increased post-operatively irrespective to their BML.

Keywords: Leptin, Thyroid Hormones, Thyrotoxicosis

INTRODUCTION:

Hyperthyroidism is the medical term used for an overactive thyroid gland. In people with hyperthyroidism, the thyroid gland produces too much thyroid hormone which is critical determinant of brain and somatic development in infants and of metabolic activity in adults; it also affects the function of virtually every organ system (1).

It is the serum free T4 and T3 concentrations that determine the hormones' biological activity. The binding proteins serve to maintain the serum free T4 and T3 concentrations within narrow limits, yet ensure that 14 and T3 are immediately and continuously available to tissues. In the longer term, if thyroid secretion ceases, the T4 stored in serum serves to delay the onset of hypothyroidism (2). In contrast, the supply would be exhausted within hours if only free T4 were available. The binding proteins also protect tissues from sudden increases in thyroid secretion or extrathyroidal T3 production. Hyperthyroidism is more common in women than men (5:1 ratio), the overall prevalence of hyperthyroidism, which is approximately 1 percent, increases to 4 to 5 percent in older women, graves' disease is seen most often in younger women, while toxic nodular goiter is more common in older women (3). Leptin is produced primarily in fat cells, and also in the placenta and probably in the stomach and mammary epithelium. Large fat cells produce more leptin than small ones and serum leptin concentrations are highly correlated with body fat content in newborn infants, children, and adults Leptin mRNA and secretion by adipocytes declines rapidly during starvation (4). Features of leptin production in humans other than the correlation with body fat content include: Serum leptin concentrations increase with progressive obesity (5, 6)

The concentrations are higher in women than in men, for any measure of obesity (5, 6) and they decrease with age in both women and men (7). Pregnant women have higher serum leptin concentrations than nonpregnant women because it is produced by the placenta (8). Breastfeeding may reduce the risk of child obesity and leptin could possibly play a role, as it is produced in the breast and is present in milk because it is secreted by the mammary epithelium (9).

Aim of the Study:

This study was designed to measure serum leptin level in Iraqi patients with hyperthyroidism and comparing the results with matching postoperative euthyroid group and comparing them with matching controls. In addition, the lipid profile in all study subjects was studied with their BMI in order to elucidate the functional relationship between leptin, TSH, and thyroid hormones in pre and post operative patients with hyperthyroidism

Patients and Methods:

This study was conducted in AL-Khadimiya teaching hospital (department of general surgery) and AL-Khadimiya teaching hospital laboratories during the period from February 2022 to July 2022.

Twenty-six patients (20-40 years) were identified with newly diagnosed untreated thyrotoxicosis with goiter they are clinically and biochemically hyperthyroid patients.

Patients with diabetes mellitus, pregnancy, hypothalamic or pituitary disease were excluded. Body mass index (BMI) was the only anthropometric parameter specified, it was calculated by weight (in kilo gram) divided by the square of height (in meter), weight and height were measured by same scale for all patients.

BMI= weight (kg)/ squared height m^2.

Regarding the control group, twenty-six clinically and biochemically euthyroid healthy persons were selected from patients relatives attending the hospital. A total number of 78 samples (26 control ,26 preoperative patient, 26 postoperative patient), were chosen to participate in this study. Those patients who diagnosed as (toxic nodular goiter underwent subtotal or near total thyroidectomy returned back within (6-8week) to the hospital for checking their state, they were euthyroid postoperatively. Hemolyzed and lipemic samples were neglected, and some preoperative samples were neglected because those patients did not come back postoperatively.

Blood Samples Collection:

After an overnight fasting about five millimeters of venous blood was aspirated using disposable syringes and needles. Samples were collected between (09.00-12.00am) the blood was allowed to clot in plain tubes for (30 to 45) minutes at room temperature and serum was recovered by centrifugation at (3000 rpm) for (10 minutes) and transferred into plain plastic tubes and kept frozen at -20c until time of assay.

METHODS:

A measurement of leptin in serum: The leptin sandwich enzyme immunoassay kit provides materials for the quantitative determination of leptin in serum and plasma. This assay is intended for in vitro diagnostic use only. The leptin (sandwich) ELISA is a solid phase enzyme linked immunosorbent assay (ELISA) based on the sandwich principle the microtiter wells are coated with monoclonal (anti-leptin antibody). An aliquot of patient sample containing endogenous leptin is incubated in the coated well with a specific (rabbit anti-leptin antibody). As sandwich complex is formed. After incubation the unbound material is washed off and an antirabbit peroxidase conjugate is added for detection of the bound leptin having added the substrate solution, the intensity of color developed is proportional to the concentrate on leptin in the patients sample read at (450nm) with microtiter plate reader within (10minutes) after adding the stop solution.

Normal values: Female 7.36 + 3.73ng/ml
Male 3.84+ 1.79 ng/ml

Total Triiodo thyronine (T3) and total thyroxine (T4) (Competitive Enzyme immunoassay)
Thyrotropin (TSH) (Immunoenzymetric assay):

Lipid profile:

1. Measurement of triglyceride (TG):
2. measurement of total cholesterol TC
3. Measurement of high-density lipoprotein cholesterol HDL-C
4. Measurement of low-density lipoprotein cholesterol (LDL-C):

RESULTS:

Statistical Analysis of Preoperative Group:

There was a significant difference in mean BMI, Leptin, T3 ,T4, TSH, cholesterol, TG, HDL, LDL, VLDL, LDL/ HDL ratio between preoperative group and control group ($P<0.05$).

Table (1): Comparison of means between preoperative group and control group by t-Test

Parameters	Preoperative (n=26) mean±SD	Control (n=26) mean±SD	P value
BMI	23.03±2.12	26.27±5.81	0.0116
Leptin (ng/ml)	30.47±16.17	50.08±22.03	0.0006
T3 (0.49-2.02 ng/ml)	3.45±0.69	1.39±0.38	0.00001
T4 (45-116µg/dl))	138.73±9.95	74.58±13.56	0.00001
TSH (0.4-7.0 mIU/ml)	0.25±0.14	3.73±1.42	0.00001
Cholesterol	171.08±7.36	219.32±21.95	0.00001
TG	79.8±2.96	123.34±14.48	0.00001
HDL	40.6±0.73	41.8±0.44	0.00001
LDL	110.76±8.08	147±21.27	0.00001
VLDL	19.96±4.13	24.68±2.89	0.00001
LDL/HDL ratio	2.73±0.18	3.51±0.5	0.00001

Statistical Analysis of Postoperative Group:

There was no significant difference in mean leptin, T3, T4, TSH,(P>0.05) between postoperative and control groups, but there was a significant difference in mean BMI, cholesterol, TG, HDL, LDL VLDL, LDL/ HDL ratio P<0.05 between previous groups.

Table (2): Comparison of means between postoperative group and control group by t-Test

Parameters	Postoperative (n=26) mean±SD	Control (n=26) mean±SD	P value
BMI	23.15±1.98	26.27±5.81	0.0141
Leptin (ng/ml)	51.65±22.21	50.08±22.03	0.7992
T3 (0.49-2.02 ng/ml)	1.45±0.39	1.39±0.38	0.5927
T4 (45-116µg/dl))	71.96±11.92	74.58±13.56	0.4635
TSH (0.4-7.0 mIU/ml)	3.85±1.32	3.73±1.42	0.7476
Cholesterol	241.42±15.03	219.32±21.95	0.0001
TG	106.22±11.86	123.34±14.48	0.00001
HDL	44.4±0.46	41.8±0.44	0.00001
LDL	170.8±12.06	147±21.27	0.00001
VLDL	21.24±2.38	24.68±2.89	0.00001
LDL/HDL ratio	3.85±0.25	3.51±0.5	0.004

Statistical Analysis of Pre and Post-Operative Group:

There was a significant difference in mean leptin, T 3, T4, TSH, cholesterol TG, HDL, LDL, VLDL, LDL/ HDL ratio between pre and postoperative groups, but there is no significant difference in mean BMI between previous groups

Table (3): Comparison of means between preoperative group and postoperative group by t-Test

Parameters	Preoperative (n=26) mean±SD	Postoperative (n=26) mean±SD	P value
BMI	23.03±2.12	23.15±1.98	0.2464
Leptin (ng/ml)	30.47±16.17	51.65±22.21	0.0001
T3 (0.49-2.02 ng/ml)	3.45±0.69	1.45±0.39	0.00001
T4 (45-116µg/dl))	138.73±9.95	71.96±11.92	0.00001
TSH (0.4-7.0 mIU/ml)	0.25±0.14	3.85±1.32	0.00001
Cholesterol	171.08±7.36	241.42±15.03	0.00001
TG	79.8±2.96	106.22±11.86	0.00001
HDL	40.6±0.73	44.4±0.46	0.00001
LDL	110.76±8.08	170.8±12.06	0.00001
VLDL	19.96±4.13	21.24±2.38	0.0144
LDL/HDL ratio	2.73±0.18	3.85±0.25	0.00001

Table (4): Comparison of means between control, preoperative and postoperative groups by ANOVA

Parameters	Control (n=26) mean±SD	Preoperative (n=26) mean±SD	Postoperative (n=26) mean±SD	P value
BMI	26.27±5.81	23.03±2.12	23.15±1.98	0.0037
Leptin (ng/ml)	50.08±22.03	30.47±16.17	51.65±22.21	0.0004
T3 (0.49-2.02 ng/ml)	1.39±0.38	3.45±0.69	1.45±0.39	0.00001
T4 (45-116µg/dl))	74.58±13.56	138.73±9.95	71.96±11.92	0.00001
TSH (0.4-7.0 mIU/ml)	3.73±1.42	0.25±0.14	3.85±1.32	0.00001
Cholesterol	219.32±21.95	171.08±7.36	241.42±15.03	0.00001
TG	123.34±14.48	79.8±2.96	106.22±11.86	0.00001
HDL	41.8±0.44	40.6±0.73	44.4±0.46	0.00001
LDL	147±21.27	110.76±8.08	170.8±12.06	0.00001
VLDL	24.68±2.89	19.96±4.13	21.24±2.38	0.00001
LDL/HDL ratio	3.51±0.5	2.73±0.18	3.85±0.25	0.00001

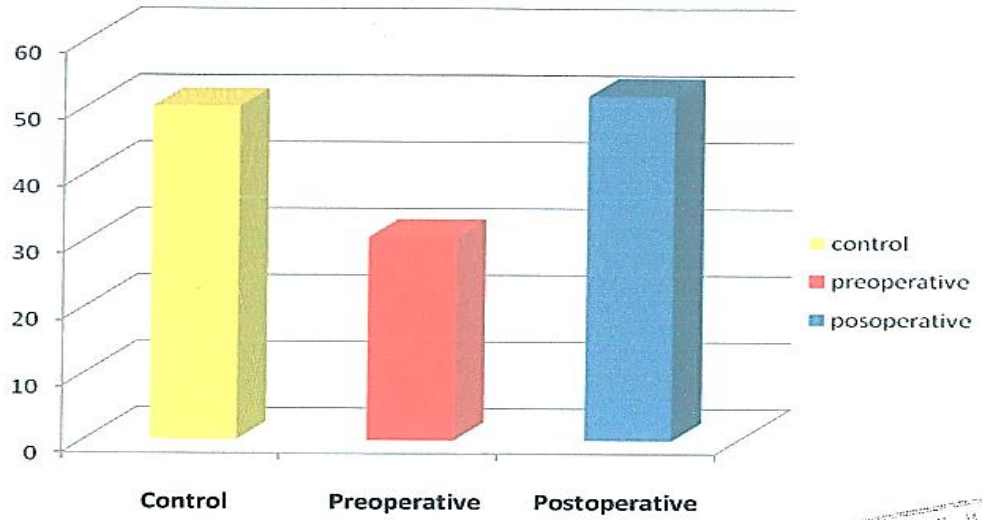

Fig 1: Comparison of serum leptin in three groups

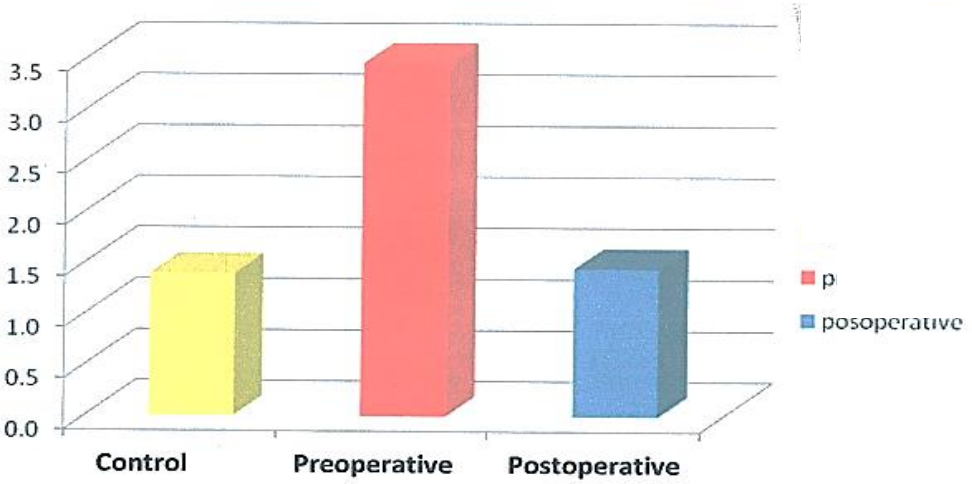

Fig.2. Comparison of T3 level in the three groups

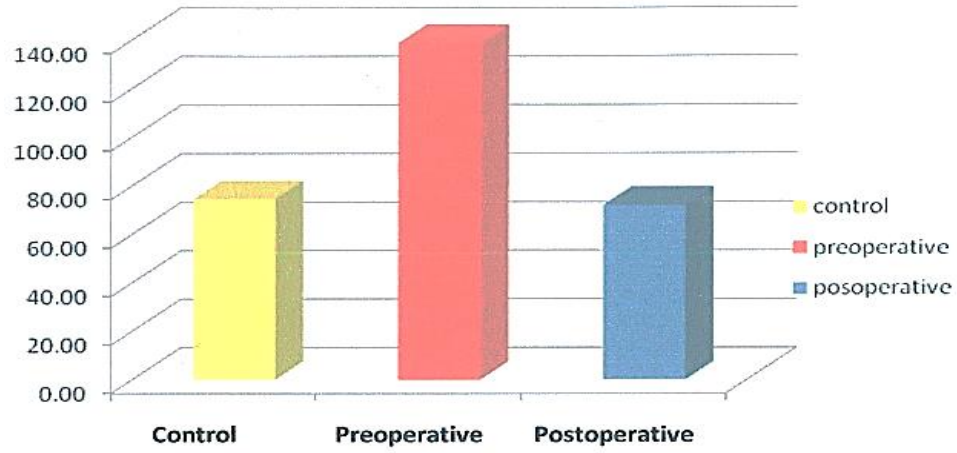

Fig.3. Comparison of T4 level in the three groups control

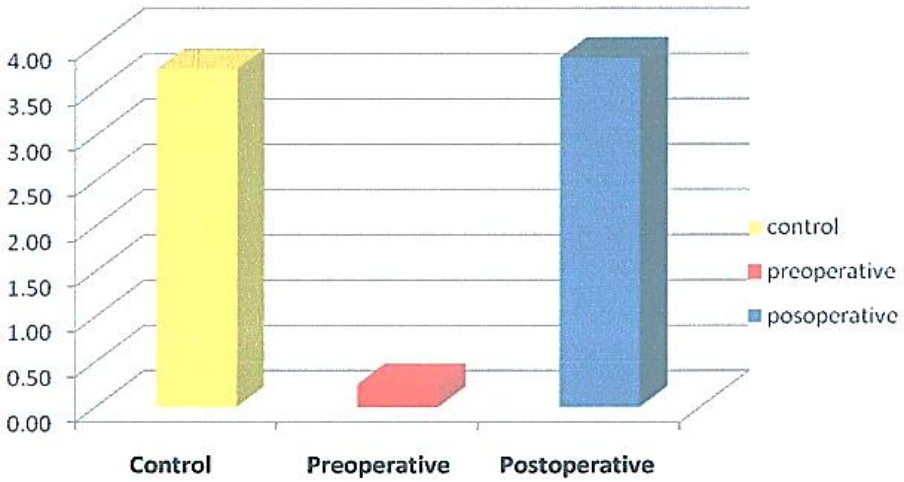

Fig.4. Comparison of TSH level in the three groups

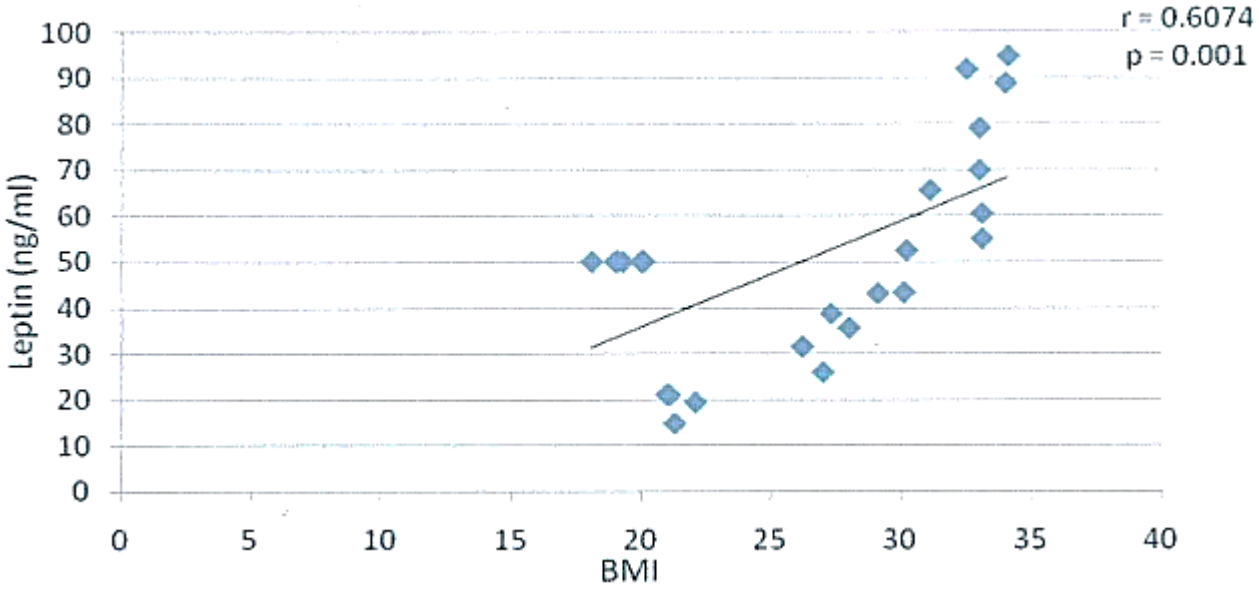

Fig.5. Correlation between leptin and BMI in control group

There is significant correlation between leptin and BMI in control group but there is no significant correlation between leptin and BMI in pre. and post op. group. No other significant correlations between other parameters were found.

Table 5: Correlations in control group

		BMI	leptin	T3	T4	TSH	Cholesterol	TG	HDL	LDL	VLDL	LDL/HDL
BMI	r	1.0000	0.6074	-0.0644	0.2409	0.2068	0.3517	0.2652	0.3063	0.2569	0.2645	0.2449
	p	0.0000	0.0010	0.7550	0.2360	0.3110	0.0780	0.1900	0.1280	0.2050	0.1920	0.2280
leptin	r		1.0000	0.1865	-0.0702	0.2264	0.0046	0.2004	0.1412	-0.0883	0.2004	-0.0989
	p		0.0000	0.3620	0.7330	0.2660	0.9820	0.3260	0.4910	0.6680	0.3260	0.6310
T3	r			1.0000	-0.1733	-0.2570	0.0360	0.0342	0.2358	-0.0094	0.0345	-0.0232
	p			0.0000	0.3970	0.2050	0.8610	0.8680	0.2460	0.9640	0.8670	0.9110
T4	r				1.0000	0.0250	0.3459	0.3378	0.2599	0.2575	0.3371	0.2506
	p				0.0000	0.9040	0.0840	0.0920	0.2000	0.2040	0.0920	0.2170
TSH	r					1.0000	-0.1779	0.2300	0.0437	-0.2678	0.2304	-0.2771
	p					0.0000	0.3850	0.2580	0.8320	0.1860	0.2570	0.1710
cholesterol	r						1.0000	0.4346	0.6908	0.9288	0.4332	0.9112
	p						0.0000	0.0270	0.0000	0.0000	0.0270	0.0000
TG	r							1.0000	0.8295	0.1078	1.0000	0.0669
	p							0.0000	0.0000	0.6000	0.0000	0.7450
HDL	r								1.0000	0.4154	0.8292	0.3714
	p								0.0000	0.0350	0.0000	0.0620
LDL	r									1.0000	0.1065	0.9988
	p									0.0000	0.6050	0.0000
VLDL	r										1.0000	0.0655
	p										0.0000	0.7500
LDL/HDL	r											1.0000
	p											0.0000

Table 6: Correlations in preoperative group

		BMI	leptin	T3	T4	TSH	Cholesterol	TG	HDL	LDL	VLDL	LDL/HDL
BMI	r	1.0000	0.3370	-0.2659	-0.0187	-0.2358	0.0367	-0.0376	0.0810	0.0363	-0.0218	0.0136
	p	0.0000	0.1000	0.1990	0.9290	0.2570	0.8620	0.8580	0.7000	0.8630	0.9180	0.9480
leptin	r		1.0000	-0.1370	-0.2152	0.0070	-0.0560	-0.0150	0.0744	-0.0457	-0.0218	-0.0707
	p		0.0000	0.5050	0.2910	0.9730	0.7860	0.9420	0.7180	0.8250	0.9160	0.7320
T3	r			1.0000	0.0180	0.1200	0.0235	-0.0185	0.0716	0.0312	-0.0300	0.0145
	p			0.0000	0.9280	0.5590	0.9090	0.9280	0.7280	0.8800	0.8840	0.9440
T4	r				1.0000	-0.0125	-0.0481	0.0395	-0.2778	-0.0371	0.0350	0.0403
	p				0.0000	0.9520	0.8150	0.8480	0.1690	0.8570	0.8650	0.8450
TSH	r					1.0000	-0.1491	0.1637	-0.1191	-0.1845	0.1225	-0.1737
	p					0.0000	0.4670	0.4240	0.5620	0.3670	0.5510	0.3960
cholesterol	r						1.0000	-0.3057	0.0300	0.0180	-0.0479	0.0710
	p						0.0000	0.1290	0.8840	0.9280	0.8160	0.7280
TG	r							1.0000	0.0180	0.0300	0.0710	0.0300
	p							0.0000	0.9280	0.8840	o.728	0.8840
HDL	r								1.0000	0.0560	0.0300	0.3033
	p								0.0000	0.7860	0.8840	0.1320
LDL	r									1.0000	0.0710	0.0180
	p									0.0000	0.7280	0.9280
VLDL	r										1.0000	0.0560
	p										0.0000	0.8840
LDL/HDL	r											1.0000
	p											0.0000

Table 7: Correlations in postoperative group

		BMI	leptin	T3	T4	TSH	Cholesterol	TG	HDL	LDL	VLDL	LDL/HDL
BMI	r	1.0000	0.2249	0.0046	-0.2547	0.1445	0.0270	0.0479	0.0896	0.0143	0.0477	-0.0073
	p	0.0000	0.2800	0.9820	0.2190	0.4910	0.8980	0.8200	0.6700	0.9460	0.8210	0.9720
leptin	r		1.0000	-0.0272	-0.2941	-0.3367	-0.0566	-0.2992	-0.0764	0.0533	-0.3027	0.0659
	p		0.0000	0.8950	0.1450	0.0930	0.7840	0.1380	0.7110	0.7960	0.1330	0.7490
T3	r			1.0000	0.0713	-0.0270	0.3576	0.3587	0.2364	0.2875	0.3578	0.2791
	p			0.0000	0.7290	0.8960	0.0730	0.0720	0.2450	0.1540	0.0730	0.1670
T4	r				1.0000	0.0300	0.2712	0.3823	-0.0132	0.1376	0.3830	0.1599
	p				0.0000	0.8840	0.1800	0.0540	0.9490	0.5030	0.0530	0.4350
TSH	r					1.0000	0.0744	0.1303	0.0359	0.0646	0.1327	0.0674
	p					0.0000	0.7180	0.5260	0.8620	0.7540	0.5180	0.7430
cholesterol	r						1.0000	0.0180	0.0300	0.0710	0.0560	0.3570
	p						0.0000	0.9280	0.8840	0.7280	0.7860	0.0730
TG	r							1.0000	0.2902	0.3805	0.0560	0.3822
	p							0.0000	0.1500	0.0550	0.7860	0.0540
HDL	r								1.0000	0.0560	0.2850	0.0180
	p								0.0000	0.7860	0.1580	0.9280
LDL	r									1.0000	0.3714	0.3570
	p									0.0000	0.0620	0.0730
VLDL	r										1.0000	0.3731
	p										0.0000	0.0600
LDL/HDL	r											1.0000
	p											0.0000

DISCUSSION:

Many investigators have described leptin alteration only in obese or over weight patients when serum leptin concentration is increased in obese subjects and is closely related to fat mass and BMI and declines with weight loss (5, 6). Leptin decreases appetite, increases thermogenesis and regulates body weight (10). Decreased body weight, increased appetite and increased thermogenesis are characteristic features in majority of hyperthyroid patients, therefore the role of leptin in thyroid disorders has been the point of interest since the mid of 1996 by many research workers. In this study we found that mean serum leptin was higher in postoperative group than its level in preoperative group while the levels of thyroid hormone returned to normal in postoperative group.

Results of this study agree with Escobar Morreale et al (11) who observed that thyroidectomized rats infused either with placebo or with high doses of thyroid hormones causing hyperthyroidism showed elevated leptin level in first group and suppressed leptin levels in second group. Those results also agree with Zimmermann Belsing et al (12), who observed that serum leptin level in thyrotoxic patients increased significantly after 12 months of treatment compared to both normal persons and their own baseline. Those results were also similar to the Findings of Pinkney et al (13) who observed relative hypo leptinemia in well characterized population of patients with clinically and biochemically confirmed hyperthyroidism.

Similarly, Al-Shoumer et al (14) also observed low leptin concentration in Arab women with hyperthyroidism also those results agree with Obermayer-Pitsch et al (15) who found that the base line leptin concentration were significantly decreased in all hyperthyroid patients as compared with control.

In an In Vitro study Fain et al (16) observed increased leptin mRNA expression in hypothyroid rats and a reduction in expression in response to T3 treatment. However, some studies didn't find this results in their study (17-19). Ca Ozata and Colleagues (20) found plasma leptin levels to be increased in hyperthyroidism and decreased in hypothyroidism.

In 1997, Mant Zoros et al (21) observed that short term hyperthyroidism induced by the administration of T3 has no effect on circulating leptin levels in healthy male volunteers. In 2000 Miyakawa et al (22) and Matsubara et al (23) found no change in serum leptin level in hyperthyroid female patient before and after treatment.

No differences in serum concentration of leptin were

observed by Wahren (24) et euthyroid controls.
The possible explanation of those results is that thyroid hormones produce over activity of sympathetic nervous system, resulting in the release of noradrenaline from sympathetic nerve endings in adipose tissue. The fat cells express adrenergic receptors that are stimulated by norepinephrine causing fatty acid hydrolysis and uncouple energy production from fat storage of hyperthyroid patient (25).
In experimental studies the administration of beta-adrenoceptors agonist led to the rapid disappearance of ob gene mRNA (26-28), and the, administration of the beta-antagonist propranolol partially reverses this effect (29).
It has been shown that infusion of isoprenaline (B-adrenoceptors agonist) in (30, 31) humans acutely suppress leptin concentration (30, 31), confirming the potential role for catecholamines in the. acute regulation of leptin. Therefore, the results of the present study may be interpreted in the context of adipocyte beta-adrenoceptor sensitivity.

Leptin in rodents and human has been shown to correlate highly significant with BMI or percentage of body fat (32-34) we have found that serum leptin level is related with BMI in normal control persons and significant decreased level is found in hyperthyroid patients, this suggested that the low serum leptin level in hyperthyroid patients is due to hyper adrenergic state found in these patients, so postoperatively when the level of adrenergic state become normal, the leptin level increased, in spite that their BMI level not increased significantly postoperatively.
A study showed that TSH releases leptin by a direct action at the adipocytes in human adipose tissue via the presence of TSH receptors in adipose tissue (11). Mant Zoros et al, (35) have shown in a systematically and mathematically validated analysis that TSH and leptin exhibit coordinated pulsatility.
Menedez et al (36) have shown in their study that TSH significantly stimulate leptin secretion by human adipose tissue In Vitro, suggesting a new mechanism in the inter relationship between the adipose organ and the thyroid axis.

Moreover, it was found in this study that mean plasma T4 and plasma total T3 are clearly high and TSH concentration is suppressed in clinically thyrotoxic patients of preoperative group. These hormonal levels return to their normal level in postoperative group after 6-8 weeks postoperative period. With regard to the lipid profile, we notice that mean total serum cholesterol is depressed in thyrotoxic preoperative group because of increase LDL clearance in thyrotoxic patient (37). The mean BMI in preoperative thyrotoxic group was decreased and there was no difference in BMI of the patients before and after the surgery, this may be related to the limited period of time to do this study so patients had no enough time to gain weight.
This agrees with Zimmerman-Belsing et al. (12) who showed that baseline thyrotoxic patients had a significantly low total fat mass which showed significant increase after 6-12 months of anti-thyroid treatment.

CONCLUSIONS:

Leptin has a strong functional relationship with thyroid hormones (T3, T4, TSH) in pre and postoperative patients with thyrotoxicosis while their lipid profile increased postoperatively irrespective to their BMI.

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