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The Relationship Between Hypothyroidism and Obesity

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Keywords

Hypothyroidism, Obesity, Adipokines, Leptin, Lipid profile

Abstract

Clinical problems of obesity and hypothyroidism often co-occur. The significance of this correlation has increased against the background of a remarkable global increase in the incidence of obesity. Numerous studies show a link between thyroid issues and obesity. This research set out to assess, in relation to a control group, the impact of thyroid hormones on the levels of adipokine (leptin) and lipid profile in individuals with hypothyroidism. The current research included 60 healthy controls of the same age and 120 male Iraqi patients with hypothyroidism problems, ages ranging from 25 to 55. Serum samples were collected from the Tikrit Teaching Hospital between January 1st and March 29th, 2024. To measure thyroid hormones (TSH, T4, and T3), the ELFA method was used. The levels of leptin in the blood were measured using kits for the enzyme-linked immunosorbent assay (ELISA). A spectrophotometer was used to assess the lipid profile of serum samples. The findings showed that, in comparison to the control group, patients with hypothyroidism had significantly higher blood leptin levels. On the other hand, it was shown that in comparison to the control group, hypothyroid individuals had higher levels of triglycerides, LDL, and VLDL. In contrast to those with hypothyroidism, the control group had higher HDL values. According to Pearson's correlation analysis, leptin and T3 and T4 had significant negative correlations; TSH and leptin had a non-significant positive correlation; cholesterol, TG, VLDL, and LDL levels had negative correlations with T3 and T4 hormones, respectively; and HDL level had a positive correlation with T3 and T4 hormones. The current study reveals a complex relationship between thyroid hormones, adipokines—particularly leptin—and the lipid profile. It seems that leptin influences the thyroid hormones' negative feedback loop, which is the basis for the link between the hormone and the thyroid gland. Because TSH stimulates the TSH-receptor on adipocytes, it directly affects the release of leptin. However, the connection between hypothyroidism and storage fat cells may arise from its effects on metabolism. The new research provides evidence that blood levels of TSH and leptin, respectively, are related in males with hypothyroidism and in obese people.

1. Introduction:

Hypothyroidism and obesity are two common clinical conditions that have a strong relationship. In light of the remarkable rise in obesity cases worldwide, the link has become more and more relevant. Patients usually understand that their obesity is a result of thyroid dysfunction[4]. An innovative viewpoint indicates that changes in thyroid-stimulating hormone (TSH) may be related to obesity. Recent research has also shown a link between thyroid autoimmunity and obesity, with leptin, an adipocyte hormone, serving as the primary mediator between these two conditions [1].

The condition known as hypothyroidism is characterized by abnormally low thyroid hormone production. Hypothyroidism is a consequence of several conditions[2]. The thyroid gland may be impacted by several conditions either directly or indirectly. Inadequate thyroid hormone affects the body extensively since it affects many cellular processes, growth, and development. The focus of

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this information sheet will be adult hypothyroidism[3].

The thyroid gland produces thyroid hormones. This gland is located below the Adam's apple in the lower neck region. The gland resembles a butterfly in form, with two wings (lobes) linked by a central component (isthmus), and it encircles the windpipe (trachea). To produce thyroid hormones, the thyroid gland needs iodine, which is mostly obtained from food, particularly fish, bread, and salt[6]. Thyroxine (T4) and triiodothyronine (T3) are the two most important thyroid hormones; they make up 99% and 1% of the thyroid hormones found in blood, respectively. But T3 is the hormone having the greatest physiologic effect. A significant amount of T4 that is secreted into the blood by the thyroid gland is converted into T3, the hormone that is active and affects cell metabolism[5].

The pituitary gland, another organ in the brain, regulates the thyroid itself. The pituitary gland is in turn influenced by the hypothalamus, another gland located in the brain, as well as by thyroid hormone that is present in the blood and acts as a "feedback" effect on the pituitary gland[11].

Thyrotropin releasing hormone (TRH), which is produced by the hypothalamus, signals the pituitary to release thyroid stimulating hormone (TSH). TSH then instructs the thyroid to start producing thyroid hormones[12].

Hypothyroidism, or a thyroid hormone deficiency, may arise from a breakdown in thyroid hormone production at any one of these levels [7].

The pituitary gland controls the rate of thyroid hormone production. The pituitary gland releases TSH in an attempt to stimulate increased thyroid hormone synthesis when there is not enough thyroid hormone in the bloodstream to support normal bodily functions[20]. On the other hand, TSH levels decrease with excess of circulating thyroid hormone because the pituitary tries to suppress thyroid hormone production. Thyroid hormone levels in the blood are consistently low in hypothyroidism patients[18].

Hypothyroidism is a condition that occurs somewhat often. A third to five percent of people are thought to suffer from hypothyroidism. The illness is more common in women than in men, and it becomes more common as people age[14]. An explanation of these diseases is provided after a list of some of the common adult causes of hypothyroidism[9].

• Pituitary or hypothalamic issues; • Radiation-induced thyroid damage; • Hashimoto's thyroiditis; • Lymphocytic thyroiditis (which may develop after hyperthyroidism); • Medications; • Severe iodine deficiency[10]

2. Thyroid Function in Obese Subjects

TSH levels are positively correlated with BMI and are either slightly elevated or at the upper limit of the normal range in obese children, adolescents, and adults. Obese people have been shown to have low fT4 and slightly elevated T3 or free T3 (fT3) levels[15]. Increases in TSH and fT3 levels were linked to progressive fat formation, regardless of insulin sensitivity and metabolic characteristics. In obese patients, there is a positive association between the fT3 to fT4 ratio and both waist circumference and BMI. While the conventional perception of elevated TSH, decreased fT4, and elevated fT3 is widely held, several studies on adult obese individuals characterize thyroid hormone and TSH levels as either normal, elevated, or decreased[17].

Hyperthyrotropinemia is unquestionably the most common anomaly in children who are fat. Additionally, it has recently been shown that thyroid ultrasonography patterns in obese children patients are often highly suggestive of Hashimoto's thyroiditis. However, the development of thyroid autoantibodies is unrelated to these results[22].

It is unknown what causes these differences in thyroid function. One hypothesis suggests that a high rate of T4 to T3 conversion is the consequence of increased deiodinase activity. In obese people, this is thought to be a protective mechanism that increases energy expenditure in order to counterbalance the accumulation of fat[23].

The compensatory rise in TSH and fT3 production in an attempt to counteract decreased tissue responsiveness to circulating thyroid hormones due to decreased expression of thyroid hormones and TSH in obese people's adipocytes is another possible cause. Another likely reason is high levels of leptin, which are seen in obese patients[24]. Leptin's primary function is to centrally report fat

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content, which lowers appetite and food intake. Additionally, it has been shown that leptin centrally promotes the transcription of pro-thyrotropin-releasing hormone (TRH), and therefore, of TSH and TRH[25]. Additionally, leptin increases deiodinases' activity. Another explanation is that the generation of sodium/iodide symporter mRNA and iodide absorption activities are blocked by inflammatory cytokines generated from adipose tissue, such as tumor necrosis factor alpha, interleukin (IL)-1, and IL-6[30].

3. Leptin:

The name leptin comes from the Greek word leptons, which means thin. Adipose tissue produces the hormone leptin, proving that it is an endocrine gland rather than just a passive place to store fat as was previously believed[6]. Moreover, the brain uses leptin as an energy regulator to produce anorexic factors, suppress appetite factors, restrict intake, and increase energy expenditure. On the other hand, research indicates that although high leptin levels might increase energy intake and reduce appetite, low leptin levels may enhance meal absorption and limit energy expenditure[29]. About 25 years after leptin's discovery, one is reminded of the hormone's benefits and how it may be used to treat a variety of conditions, including leptin mimics like obesity and leptin-blockers like cancer. The most important topics including the relationship between leptin and pregnancy, cancer, and other conditions, as well as immunity, cortisone, and diabetes, are covered in this article[28].

Lack of leptin receptors or leptin itself causes an insatiable hunger, which ultimately results in obesity. Although high endogenous (and exogenous) leptins do not regulate the weight of obese persons, leptin concentrations are higher in hypertension patients. This suggests that leptin resistance may exist, as has been hypothesized internationally[39]. Additionally, in women with polycystic ovarian syndrome (PCOS) and hyperandrogenism, research has linked blood leptin levels to expression levels of testosterone, estradiol (E2), follicle-stimulating hormone (FSH), and aromatase (P450) [37]. There is yet no conclusive evidence in the human body supporting the negative correlation between thyroxine and leptin that has been shown in vitro. Growth hormone does not seem to directly affect leptin; rather, leptin serves as the basis for the physiological effects of growth hormone to be exerted[35].

4. Materials and Methods:

The Tikrit Teaching Hospital served as the site of this cross-sectional study from January 1 to March 29, 2024. 120 male hypothyroidism patients, ages 25 to 55, were enrolled in the study. Sixty samples of healthy men aged 25 to 55 were included, along with a random group selection (Table 1). The Enzyme Linked Fluorescent Assay (ELFA) technique was used to test the levels of thyroid hormones (TSH, T4, and T3). Kits for the enzyme-linked immunosorbent test (ELISA) were used to assess the blood levels of leptin. A spectrophotometer is used to determine the sample serum's lipid composition.

Table (1):- Distribution of Samples

Groups	No. of Samples	Age
Control (C)	60	**(25-55) years old**
Hypothyroidism (P)	120	

5. Statical Analysis:

The statistical analysis was done using the statistics application Minitab. One-way analysis of variance (ANOVA) was performed to compare the groups, and the test of Duncan multiple ranges was employed to estimate the arithmetic means for parameters in order to discover any significant differences, especially across groups.At ($P \leq 0.01$) and ($P \leq 0.05$), the statistical significance level was attained.

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6. Results And Discussion:

For hypothyroidism patients, the mean ± SD of T3, T4, and TSH levels were (0.812 ± 0.0308) ng/ml, (3.309 ± 0.903) µg/dl, and (27.06 ± 2.115) µIU/ml, respectively. Table (2) and Figures (1, 2, 3) show the mean ± SD of T3, T4, and TSH levels for the control group, which were (1.701 ± 0.208) ng/ml, (6.256± 2.176) µg/dl, and (2.130 ± 0.207) µIU/ml, respectively.

The mean ± SD of leptin levels for the hypothyroidism patients and control group were 201.12 ± 18.5) pg/ml and (152.19 ± 8.96) pg/ml, respectively, as shown in Table (2) and Figure (4).

The mean ± SD of the cholesterol levels for the hypothyroidism and control groups were 210.65 ± 37.98 mg/dl and 154.76 ± 33.28 mg/dl, respectively, as shown in Table (3) and Figure (5). The mean ± SD of the TG levels for the hypothyroidism and control groups were 194.65 ± 0.783) mg/dl and (119.65 ± 32.17) mg/dl, respectively, as shown in Table (3) and Figure (6). The hypothyroidism group's mean ± SD of HDL, LDL, and VLDL levels were (42.06 ± 5.815) mg/dl, (130.92 ± 5.91) mg/dl, and (40.06 ± 6.67) mg/dl, as shown by table (3) and figure (7,8,9); in comparison, the control group's mean ± SD was (48.13 ± 7.27) mg/dl, (84.99 ± 8.88) mg/dl, and (25.99 ± 6.99) mg/dl.

Table 2: Average range of thyroid hormones and leptin

Groups	T3 (ng/ml)	T4 (µg/ dl)	TSH (µIU/ml)	Leptin (pg/ml)
	Mean ± S.D	Mean ± S.D	Mean ± S.D	Mean ± S.D
P n=120	0.812 ± 0.0308	3.309 ± 0.903	27.06 ± 2.115	201.12 ± 18.5
C n=60	1.701 ± 0.208	6.256± 2.176	2.130 ± 0.207	152.19 ± 8.96

Table 3: Average range of Lipid Profile

Groups	Cholesterol (mg/dl)	Triglyceride (mg/ dl)	HDL (mg/ dl)	VLDL (mg/ dl)	LDL (mg/ dl)
	S.D ±Mean	S.D ±Mean	S.D ±Mean	S.D± Mean	S.D± Mean
P n=120	210.65 ± 37.98	194.65 ± 0.783	42.06 ± 5.815	40.06 ± 6.67	130.92 ± 5.91
C n=60	154.76 ± 33.28	119.65 ± 32.17	48.13 ± 7.27	25.99 ± 6.99	84.99 ± 8.88

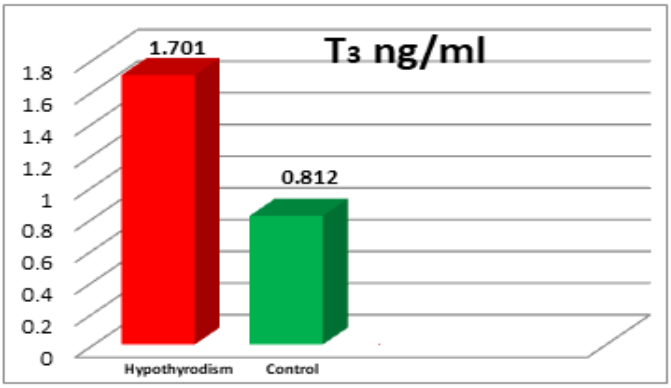

Figure (1): Levels of T_3 (ng/ml) in patients and control groups.

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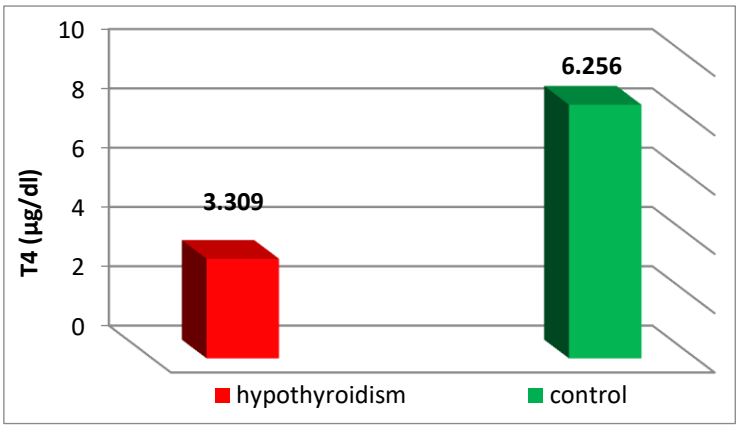

Figure (2): Levels of T4 (µg/dl) in patients and control groups.

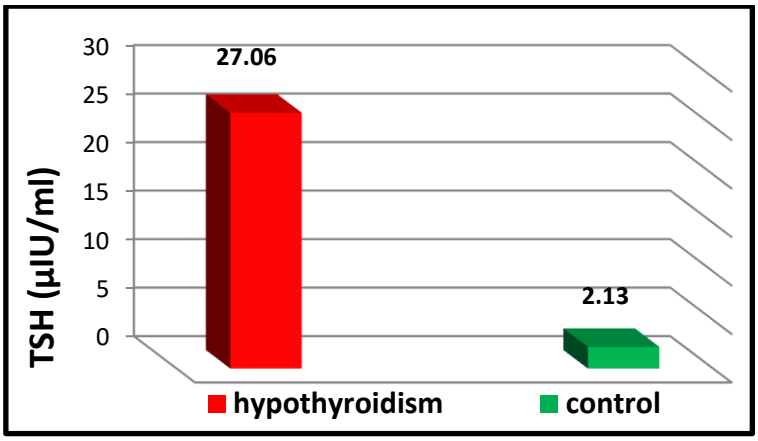

Figure (3): Levels of TSH (µIU/ml) in patients and control groups.

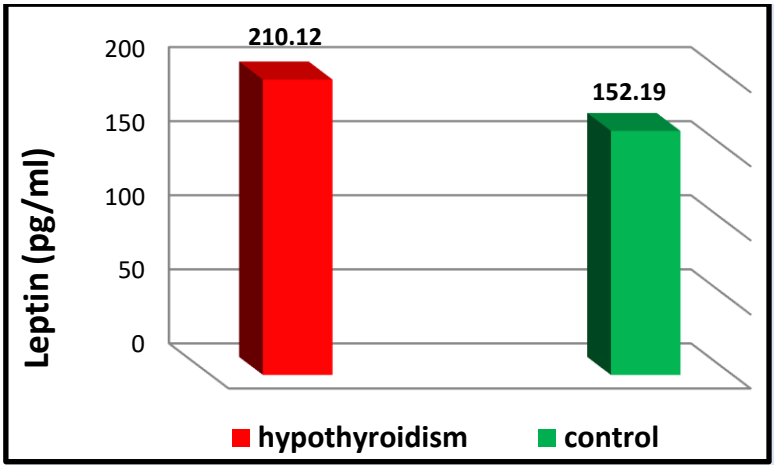

Figure (4): Leptin levels (pg/ml) in both the control and patient groups.

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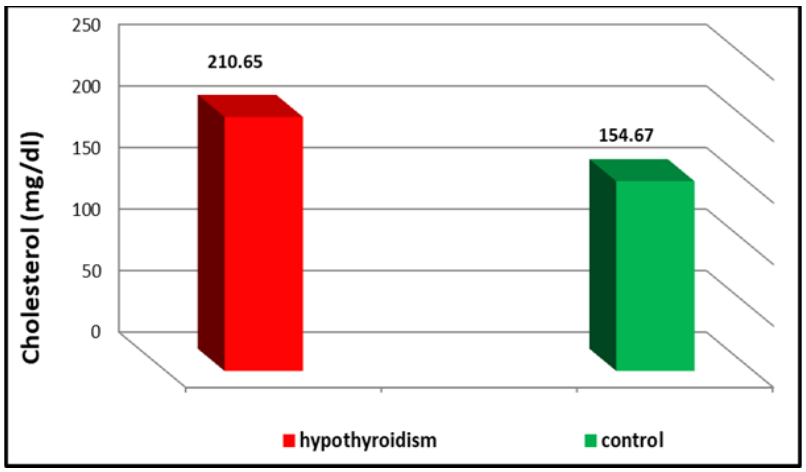

Figure (5): Cholesterol levels (mg/dl) in both the patient and control groups.

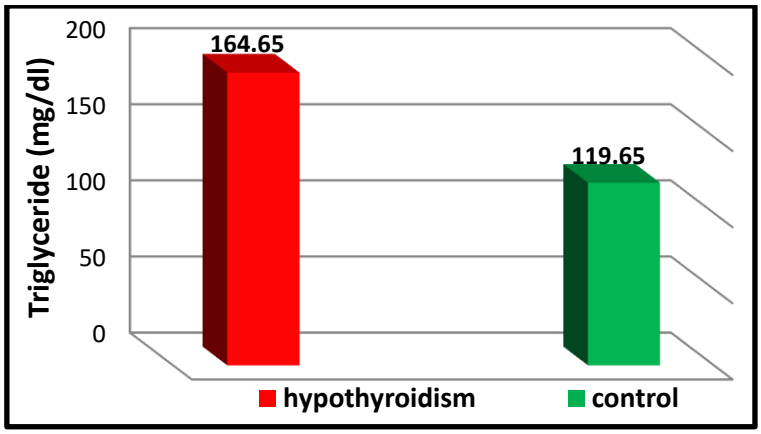

Figure (6): Levels of Triglyceride (mg/dl) in patients and control groups.

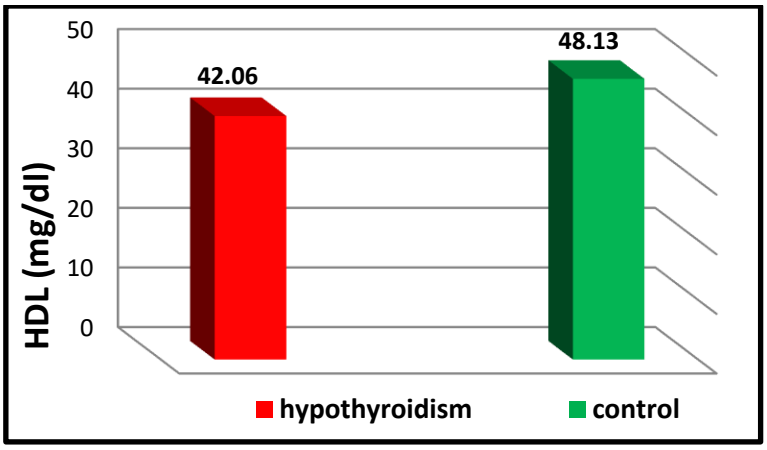

Figure (7): HDL (mg/dl) levels in both the patient and control groups.

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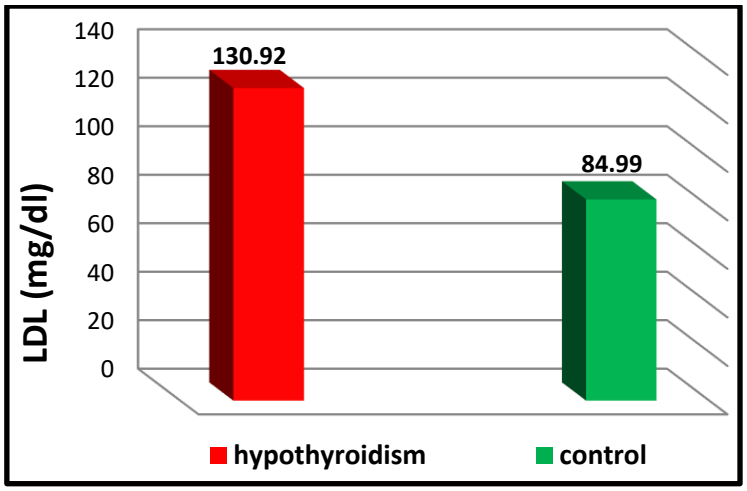

Figure (8): LDL concentrations (mg/dl) in both the patient and control groups.

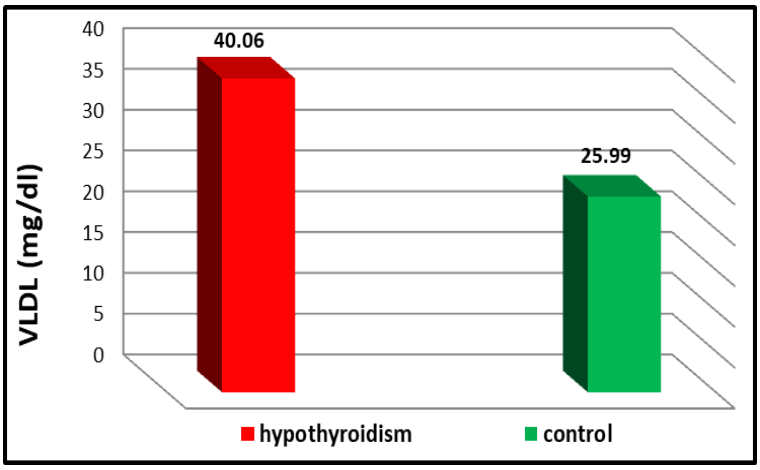

Figure (9): VLDL (mg/dl) levels in both the patient and control groups.

There was a significant difference (P≤0.01) between the P and C groups (T3, T4, TSH, respectively) in the present study. In people with hypothyroidism, TSH increased while T3 and T4 decreased. These findings were in agreement with those of Accorroni et al. (2016), Carle et al. (2013), and Ammar et al. (2018); however, no studies disagreed with them.

The Pearson's correlation results are shown in table (3). Interestingly, T3 levels showed a favorable correlation with T4 in all groups, in line with other previous study.In contrast, TSH levels in the patient group showed a negative correlation with T3 and T4. According to Chin and his colleagues' estimates, the hypothalamus attempts to achieve homeostasis in two cases: in hypothyroid patients, lowering TSH levels would be a compensatory response to inhibit the increase in thyroid hormones, and in hyperthyroid patients, raising TSH levels would be a compensatory response to counteract the decrease in TH levels [2].

Age and sex have the most effects on thyroid issue incidence and prevalence. Thyroid disorders are more common in women than in men, and in older adults than in younger ones [40]. The presence of different trace elements is necessary for the synthesis and metabolism of thyroid hormones (THs), which is the foundation of a healthy thyroid. The most important component of thyroid hormones is iodine [2]. De-iodinases (D), which regulate the synthesis and degradation of active T3, need selenium for proper thyroid hormone metabolism[44].

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Table 3 : correlation coefficient (R) in hypothyroid individuals between thyroid hormones and parameters.

parameters	Statistical variables	T3	T4	TSH	Leptin
T4	R	0.652	---	---	---
	P	0.000**	---	---	---
TSH	R	-0.400	-0.602	---	---
	P	0.053*	0.000**	---	---
Leptin	R	-0.526	-0.461	0.088	---
	P	0.000**	0.050*	0.620 ns	---
Cholesterol	R	-0.336	-0.393	0.547	-0.397
	P	0.407ns	0.047*	0.000**	0.050*
Tg	R	-0.390	-0.430	0.341	0.037
	P	0.020*	0.010**	0.048*	0.832 ns
LDL	R	0.106	0.060	-0.210	0.475
	P	0.545 ns	0.734 ns	0.233 ns	0.004 **
HDL	R	-0.290	-0.530	0.391	0.137
	P	0.025*	0.000 **	0.008 *	0.832 ns
VLDL	**R**	**-0.172**	**-0.113**	**0.458**	**-0.384**
	P	0.581 ns	0.119 ns	0.008* *	0.023*

Previous research addressing the connections between thyroid functions and adipokines are inconsistent owing to various patient features, autoimmune and probable dietary state. The present findings coincided with Chen, et al. (2016) and Maher, et al. (2016).This research demonstrated that serum leptin in hypothyroid individuals was considerably greater than in control group. On the other hand, Yaturu and his colleagues found that blood levels of leptin did not vary with change in the thyroid functional state [42].

The findings of Pearson's correlation displayed in table (3) found that there is negative association between leptin level with T3 and T4 levels in patients group which validated current result of increase leptin level in hypothyroidism patients compared with control group. There are contradictory data connected to the effects of thyroid hormones on leptin level with suppositions that thyroid hormones have repressive, stimulatory or no influence on leptin level [34] .

Hypothyroidism and diabetes are two most common medical disorders connected with higher levels of leptin and with other instance termed leptin resistance; the failure of elevated leptin levels to repress food and mediate weight reduction in general patterns of obesity[43].

One common problem in obese people with hypercholesterolemia is resistance to leptin-oriented hyperleptinemia. Even when there is sufficient leptin in the body, the response to it is reduced[32]. This resistance stems from the body misinterpreting a false signal that it is hungry, which causes a number of hormonal processes to increase fat storage in an attempt to reverse the acknowledged state of starvation. This is expected to increase the risk of weight gain or obesity even at modest calorie consumption. The downregulation of leptin receptors (LEPR-B), which results from an extended period of exposure to elevated leptin levels, may contribute to these processes[31]. Although absorption is decreased in

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individuals with elevated plasma leptin concentrations, leptin does arrive in the cerebrospinal fluid (CSF) in proportion to leptin levels. Therefore, it is possible that obese people with elevated plasma leptin concentrations have a saturable CSF-leptin transfer that results in detectable leptin resistance. It was believed that elevated levels of plasma leptin may affect the regulation of leptin transmission across the blood–brain barrier. Moreover, low resting energy expenditure (REE) is linked to elevated plasma leptin concentrations in obese men [23].

Significant findings in this study showed that the hypothyroid group had higher levels of LDL, VLDL, triglycerides, and cholesterol than the control group. However, the control group's HDL levels were higher than those of the hypothyroid people. These results concur with those of Biondi et al. (2022) and Fazaeli et al. (2022). These findings, however, go counter to those of Chen et al. (2016) and Duntas, who claimed that HDL levels in hypothyroidism were normal or even elevated. According to table (3)'s Pearson's correlation results, there is a negative link between the hormones T3 and T4, as well as cholesterol, TG, VLDL, and LDL levels, in people with hypothyroidism. These results might be explained by the fact that patients with hypothyroidism had higher levels of cholesterol, TG, VLDL, and LDL when compared to the control group, and that there was a positive correlation between HDL levels and T3 and T4 hormones. When compared to the control group, hypothyroidism patients may have lower HDL levels, which might account for these results.

Dyslipidemia, or abnormal lipid levels, is linked to endothelial problems, hypertension, and cardiovascular disease and may be brought on by thyroid dysfunction. Hyperlipidemia affects the way TH regulates antioxidant enzymes, reduces cholesterol clearance, and lacks an antioxidant system. A common cause of hyperlipidemia in both humans and animals is hypothyroidism. The most significant long-term lipid abnormality in hypothyroidism patients is hypercholesterolemia[44].

The body needs cholesterol for a variety of vital functions, including the maintenance of cell membranes, the synthesis of hormones, bile acids, and fat-soluble vitamins that aid in the digestion of fat. However, like with many positive things, having high cholesterol may also be dangerous or even deadly. Sterol regulatory element-binding protein-2 (SREBP-2) may regulate the levels of the LDL receptor (LDLR) via negative feedback regulation mediated by cellular cholesterol [34]. The main reason for hypercholesterolemia that makes sense is that decreased thyroid hormones lead to a reduction in LDL receptors on cell membranes, which in turn causes insufficient clearance of cholesterol and an increase in LDL, the nasty kind of cholesterol. Less thyroid hormone may also result in increased intestine absorption (intake) of cholesterol. Atherosclerosis develops when there is an accumulation of LDL particles in the bloodstream due to a lack of LDLR function[26]. There is a direct correlation between TSH and cholesterol levels. As previously mentioned, thyroid hormones (THs) have the ability to alter the expression of LDLR, which modifies LDL absorption and degradation inside cells. T3 reduces plasma cholesterol levels via increasing the liver's ability to absorb cholesterol, convert it to bile acids, and increase the production of bile acids from the feces[28].

Increased fatty acid esterification at the hepatic level causes triglycerides to increase. Moreover, low TH levels increase the activity of lipoprotein lipase (LPL), an enzyme required for the clearance of TG, leading to an increase in blood TG levels. Jiang and his colleagues discovered that TSH has a novel role in reducing the production of adipose triglyceride lipase (ATGL) in rat mature adipocytes. Based on these studies, basal lipolysis is impacted by TSH[33].

The present study also shown a significant reduction in HDL in patients with hypothyroidism. Many of HDL's atheroprotective properties include promoting inverse cholesterol transport, maintaining endothelial function, protecting LDL from oxidation, controlling hemostasis, and slowing down inflammatory responses associated with the vascular wall[21]. Lower HDL levels are usually associated with elevated TG levels. One possible explanation is that HDL associated with higher triglyceride levels may be more easily catabolized. The opposing relationship between TG and HDL levels is probably caused by the exchange

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via cholesteryl ester transfer protein CETP activity[19]. Particularly, the more VLDL buildup (higher TG levels) there is, the more CETP transfers cholesteryl ester CE from HDL to VLDL in exchange for TG. This results in small, dense HDL that is rich in TG, which is catabolized more quickly, lowering HDL levels[10]. Additionally, the anti-inflammatory and antioxidant properties of this small, dense HDL are decreased. As a result, the greater the increase in hepatic VLDL-TG, the lower the HDL concentration will be[34].

Reduced levels of lipoproteins in the bloodstream may also be attributed to lipoprotein lipase (LPL) activity brought on by measured TH levels. Moreover, THs decrease liver levels of Apo lipoprotein B (Apo B), which prevents the production of VLDL and LDL[22]. Thyroid hormones, in particular, increase the liver's key mechanisms for reducing steatosis—lipophagy, hepatic lipases, and mitochondrial oxidation of fatty acids[16].

7. Conclusion:

There is a connection between the thyroid gland and leptin, most likely because leptin affects thermogenesis and the negative feedback loop of thyroid hormones (THs). Thyroid function may be improved by decreasing weight and updating leptin problems. However, it is obvious that a sizable study team is needed to comprehend this relationship. TSH increases the TSH-receptor on adipocytes, which directly affects the release of leptin. Lipid issues associated with hypothyroidism include normal or slightly elevated total cholesterol, elevated LDL, and decreased HDL. In addition, endothelial dysfunction, aortic atherosclerosis, and myocardial infarction have all been linked to hypothyroidism. This study indicates a strong correlation between hypothyroidism and obesity, and it is plausible that this condition is the primary cause of the body's elevated adipokine and fat content due to dysregulated metabolism..

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