

Effect of Levothyroxine on the Some Biological Variables in Women with Hypothyroidism

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Abstract: A recently discovered lipolytic adipokine called zinc- α 2-glycoprotein (ZAG) has been linked to the control of lipid and glucose metabolism in a variety of metabolic diseases. The present study aimed to evaluate level of ZAG, malondialdehyde MDA, iron, lipid profile, thyroid stimulating hormones TSH, thyroxine T4, and triiodothyronine T3 in hypothyroidism patients after and before treatment. The cross sectional study investigated 90 women (60 patients newly diagnosed with hypothyroidism and 30 controls), their ages between (16- >60) years. All women with hypothyroidism diagnosed before and after treatment with levothyroxine for 3 months. The patients were referred to private clinics in Samarra from September 2024 to December 2025. This study showed decrease ZAG and iron level in hypothyroidism women before treatment, while increase after treatment as compared with control, ZAG value were (98.68 \pm 8.30, 110.96 \pm 7.55, 159.06 \pm 19.11) μ g/ml respectively and iron value were (84.74 \pm 8.04, 109.63 \pm 13.95, 159.06 \pm 19.11) μ g/dL, at p-value P<0.001. MDA levels were significantly higher pre-treatment and elevated post-treatment compared to the control group(5.46 \pm 0.60, 2.59 \pm 0.44, 1.83 \pm 0.76) nmol/ml respectively, p-

value <0.001 . The lipid profile comprises total cholesterol, triglycerides, low-density lipoprotein (LDL), and high-density lipoprotein (HDL). A statistically significant difference (P-Value = 0.01) was noted, Value of Cholesterol were (223.10 ± 11.72 , 203.77 ± 9.09 , 175.53 ± 9.44) mg/dl, while (132.03 ± 36.58 , 121.05 ± 4.25 , 106.40 ± 8.93) mg/dl in triacylglycerol, (152.87 ± 13.79 , 128.57 ± 10.41 , 106.84 ± 10.46) mg/dl in LDL, (35.51 ± 1.90 , 50.55 ± 3.32 , 47.93 ± 2.80) mg/dl in HDL. Serum ZAG, iron, HDL, T3, and T4, decreased before treatment while treatment with levothyroxine for period 3 months improve level of these parameters. Furthermore increase TSH, MDA, total cholesterol, triacylglycerol, LDL, levels in hypothyroidism patients and with treatment decrease it.

Keywords: Hypothyroidism, Levothyroxine, Zinc- α 2-glycoprotein, Lipid Profile, MDA, Iron, Thyroid Hormones, TSH, Triiodothyronine, Thyroxine, Oxidative Stress, Body Mass Index, Malondialdehyde, Serum Iron, Lipid Metabolism, Adipokines, Oxidative Damage, Dyslipidemia, Treatment Effect, Lipid Peroxidation.

INTRODUCTION

Hypothyroidism happens when the hypothalamus or pituitary gland does not stimulate the thyroid gland enough, leading to insufficient production of thyroid hormone by the thyroid gland. Primary gland failure is one possible cause; others include iatrogenic factors, temporary factors, or central causes. Infrequently seen are central reasons, such as inadequate quantities of thyroid-stimulating hormone (TSH) and free thyroxine (FT4) [1]. People over the age of 65 have a greater incidence of clinical hypothyroidism than the overall population, which affects 0.3% of Americans [2]. Fifty percent of females and six percent of males experience it, making it seven times more common in girls than in males [3]. Several autoimmune diseases, Down syndrome, Turner syndrome, celiac disease, autoimmune gastric atrophy, type 1 diabetes mellitus, and numerous autoimmune endocrinopathies are additional risk factors [3]. Adipokines, such as zinc alpha 2 glycoprotein (ZAG), are primarily produced and released by adipose tissues and the liver. Semen, plasma, milk, perspiration, and CSF are among the many bodily fluids that contain ZAG [4, 5]. The soluble protein ZAG, which was initially isolated from human plasma, has a molecular weight of around 41 kilodaltons. ZAG can function in adipose tissue in a paracrine or autocrine fashion, or even in a mixed mode. ZAG regulates the secretion of other adipokines, promotes lipolysis, and inhibits lipogenesis [6]. Hence, it is frequently considered a crucial regulator of body composition, affecting both obesity and wasting [7]. Several factors influence the plasma concentration of ZAG, such as health state and body weight. Although ZAG has long

been thought to have many biological functions, its identified lipolytic effect and potential role in body weight management have recently piqued researchers' interests in the compound's function [8].

When reactive oxygen species (ROS) generation outpaces antioxidant defense systems, oxidative stress sets in. It disrupts intracellular signal transmission and physiological adaptation in addition to causing lipid peroxidation and oxidative DNA damage [9]. An increase in oxidative stress in hypothyroid participants was suggested by the greater levels of malondialdehyde (MDA), an end-product of lipid peroxidation, in treatment naive patients compared to controls [9]. In addition to being one of the most fundamental hormonal components in controlling the metabolic rate of vital organs including the brain, heart, kidneys, and liver, thyroid hormones are needed for proper development of the human body [10]. Hypothyroidism causes anemia by interrupting the hematopoietic process, which in turn reduces the oxygenation process [11, 12]. Thyroid hormone is involved in hemoglobin production in adults and in the maturation of haemoglobin in fetuses. Intracellular T3-receptor proteins primarily control transcription by binding to certain T3-response elements in functional genes, mediating the effects of triiodothyronine (T3), as is the case with steroid hormones [13, 14]. When the body's iron reserves run dry and different tissues start to receive less iron than they need, this is known as an iron deficiency [15]. It also causes a decrease in intracellular enzymes that are dependent on iron and are involved in several metabolic pathways [16]. Studies *in vivo* and *in vitro* indicate that thyroid hormones (THs) increase the production of ZAG in hepatocytes. Yet, there is little information on how TH might interact with ZAG in a human hypothyroidism model.

MATERIALS AND METHODS

Ninety people, including 60 hypothyroidism women and 30 healthy controls, were part of this research. Participants' ages ranged from sixteen to sixty-plus. All women with hypothyroidism diagnosed before and after treatment with levothyroxine for 3 months. From September 2024 to December 2025, patients were directed to private clinics in Samarra. Appendix I is the brief questionnaire that was used to gather clinical history data, as well as information about the patient's age, sex, weight, height, thyroid disease family history, chronic diseases, and treatment history. Patients with diabetes, chronic kidney disease, glucocorticoids, antiandrogens, antihypertensive, antidiabetic, antiobesity, smoking, hypertension, cancer, or other chronic conditions were not included.

Physical Examination

Weight (in kilograms) and height (in meters) were taken for the purpose of calculating the body mass index. This method was followed for both patient and control groups according to the following law [17]:

$$\text{Body Mass Index (BMI)} = \text{Weight (Kg)} / \text{Height (M}^2\text{)}$$

ZAG and MDA level by ELISA test

To measure the amounts in the serum, the ELISA method was used. Levels of ZAG and MDA were measured using the ELISA method in compliance. Human ZAG and MDA-specific antibodies were pre-coated onto the plate. We have added ZAG and MDA content to the sample. As color developed in the substrate solution, the concentration of human ZAG and MDA showed a positive connection. By adding an acidic stop solution and then measuring absorbance at 450 nm, the process can be effectively stopped.

Assessment of Iron Concentration Determination

The concentration of iron in the blood serum was estimated using the Colorimetric method, in which ready-made solutions from the French company BioLabo were used, which depends on separating the ferric ion from the protein carrying it, which is transferrin, in an acidic medium, and the ferric ion is reduced to the ferrous ion, after which the ferrous ion is complexed with

ferrin to give a color whose absorption intensity is measured at a wavelength of 600 nanometers, since the concentration of iron ions is directly related to the color intensity [18].

Assessment of lipid profile

The BIOLABO reagent kit was used to quantify serum cholesterol, triglyceride (TG), high density lipoprotein cholesterol (HDL), and low density lipoprotein cholesterol (LDL) in accordance with the method described by [19].

Statistical analysis

The data was statistically examined using SPSS software version 27 (SPSS, Inc.) and the Analysis of Variance (ANOVA) test. The goal was to find out how significant the differences were between the control group and the hypothyroidism patients.

RESULTS AND DISCUSSION

Ten patients with hypothyroidism and a body mass index (BMI) were found to be within the normal weight range (18.5-24.9), twenty patients were found to be overweight (25-29.9), and twenty-five patients were found to be obese (≥ 30).

TABLE 1: Relation the number of hypothyroidism patients with BMI.

BMI (Kg/m ²)		Study groups	
		hypothyroid groups	Control groups
(<18.5)	n	5	5
	%	%8	%17
Normal weight (18.5 – 24.9)	n	10	13
	%	%17	%43
Obesity (25 – 29.9)	n	20	10
	%	%33	%33
Overweight (≥ 30)	n	25	2
	%	%42	%7
Total	n	60	30

Chi-Square = 26.18 P-Value = 0.001

This study showed decrease ZAG level in hypothyroidism patients before treatment, while increase after treatment as compared with control, that were (98.68 \pm 8.30, 110.96 \pm 7.55, 159.06 \pm 19.11) μ g/ml respectively, at p-value P<0.001. As shown in Table (2)

TABLE 2: Comparison of the level of ZAG protein in the sera of patients with hypothyroidism after and before with the control groups

Study groups	No	zinc- α 2-glycoprotein(ZAG) P. value (μ g/ml) Mean \pm SD
Before treatment	60	98.68 \pm 8.30 P<0.001
After treatment	60	110.96 \pm 7.55 significant
Control groups	30	159.06 \pm 19.11

The iron level in hypothyroidism patients was shown to be lower before therapy and higher after treatment compared to the control group, with values of (84.74 \pm 8.04, 109.63 \pm 13.95, and 159.06 \pm 19.11) μ g/ml respectively, and a p-value of less than 0.001. Table (3).

TABLE 3: Comparison of the level of Iron in the sera of patients with hypothyroidism after and before with the control groups

Study groups	No.	Iron (μ g/dL) P. value Mean \pm SD
Before treatment	60	84.74 \pm 8.04 0.001 Highly
After treatment	60	109.63 \pm 13.95 significant
Control groups	30	159.06 \pm 19.11

In patients with hypothyroidism, MDA levels were significantly higher prior to therapy and elevated post-treatment compared to the control group, with respective values of (5.46 \pm 0.60, 2.59 \pm 0.44, 1.83 \pm 0.76) nmol/ml, and a p-value of less than 0.001. Table 4.

TABLE 4. Comparison of the level of MDA in the sera of patients with hypothyroidism after and before with the control groups.

Study groups	No	MDA nmol/ml
Before treatment	60	5.46 \pm 0.60
After treatment	60	2.59 \pm 0.44
Control groups	30	1.83 \pm 0.76
P. value		0.01

Measurements of blood serum lipid profiles were conducted pre- and post-treatment in healthy groups and compared with those of individuals with hypothyroidism. The lipid profile comprises total cholesterol, triglycerides, low-density lipoprotein (LDL), and high-density lipoprotein (HDL). A statistically significant difference (P-Value = 0.01) was noted, Value of Cholesterol were (223.10 \pm 11.72, 203.77 \pm 9.09, 175.53 \pm 9.44) mg/dl, while (132.03 \pm 36.58, 121.05 \pm 4.25, 106.40 \pm 8.93) mg/dl in

TG, (152.87 \pm 13.79, 128.57 \pm 10.41, 106.84 \pm 10.46) mg/dl in LDL, (35.51 \pm 1.90, 50.55 \pm 3.32, 47.93 \pm 2.80)mg/dl in HDL,with the results displayed in Table 5. The serum VLDL levels in hypothyroid patients, both pre- and post-therapy, did not exhibit a significant difference compared to the control groups (P= 0.06).

TABLE 5. Comparison of the level of lipid profile in the sera of patients with hypothyroidism after and before treatment with the control groups.

Study groups	No	Mean \pm SD				
			Cholesterol mg/dl	TG mg/dl	LDL mg/dl	VLDL mg/dl
Before treatment	60	223.10 \pm 11.72	132.03 \pm 36.58	152.87 \pm 13.79	26.40 \pm 7.31	35.51 \pm 1.90
After treatment	60	203.77 \pm 9.09	121.05 \pm 4.25	128.57 \pm 10.41	24.08 \pm 1.15	50.55 \pm 3.32
Control groups	30	175.53 \pm 9.44	106.40 \pm 8.93	106.84 \pm 10.46	21.28 \pm 1.78	47.93 \pm 2.80
P. value		0.01	0.01	0.01	0.06	0.01

Table (6) illustrates the mean serum levels of TSH, T3, and T4 in hypothyroidism before and after therapy, in comparison to the control group. The study results indicated elevated TSH hormone levels in women with hypothyroidism prior to treatment, in contrast to the hormone levels post-treatment and when compared to the control groups (15.66 \pm 3.66, 3.29 \pm 0.76, and 2.91 \pm 0.48 mU/L, respectively).

TABLE 6. Comparison of TSH, T4, and T3 in the sera of patients with hypothyroidism after and before treatment with the control groups.

Study groups	No	Mean \pm SD		
			TSH mU/L	T4 ng/dl
Before treatment	60	15.66 \pm 3.66	7.18 \pm 3.59	1.46 \pm 0.42
After treatment	60	3.29 \pm 0.76	11.80 \pm 2.05	3.18 \pm 0.77
Control groups	30	2.91 \pm 0.48	13.14 \pm 1.14	3.30 \pm 0.37
P. value		0.01	0.01	0.01

The current research confirms a link between fat and hypothyroidism. In contrast to their negative correlation with T3 and T4, the study by [20] found that TSH levels are positively correlated with both body weight and BMI. In a separate study, the researchers found that 44 percent of hypothyroidism patients were overweight.[21] When a person has hypothyroidism, their metabolism slows down due to a shortage of thyroid hormones (T3) and thyroid hormone (T4), which are important for basal metabolic rate (BMR) [22]. One of the most powerful regulators of thermogenesis is thyroid hormone. The activity of many enzymes involved in lipid metabolism is modulated, and they also control total and basal energy consumption [23]. Obesity and hypothyroidism often coexist, with different degrees of severity. Weight gain due to salt and water retention and an increase in mucin deposits in skin and other organs is a symptom of overt hypothyroidism. A measured decrease in resting energy expenditure and an increase in body weight are linked to an elevation in thyroid stimulating hormone (TSH [24].

The present study showed decrease ZAG level in both patients after and before treatment as compared with control. This result may suggest that ZAG level affected with obesity, which is an adipokine distinguished that is synthesized and excreted fundamentally by adipose tissues and liver its possible role in controlling the weight of body weight. Dysfunction of thyroid may affect adipokines excretion, which participates to lipid metabolic disorders its possible role in controlling the weight of body weight [25]. Hypothyroidism patients had decreased serum ZAG levels, which is consistent with previous research by Khorsheed, H. O., and Sarhat [26] and Abd et al. [27]. These findings ran counter to those of a prior study by Simó et al [28] which found higher ZAG levels in hypothyroidism patients compared to controls. ZAG, which is produced by the AZGP1 gene, causes a decrease in body fat in mice and promotes lipolysis in humans. One intriguing aspect of TH's lipolytic activity is that it enhances ZAG expression in hepatic cells [29]. Several endocrine metabolic disorders, such as obesity, polycystic ovary syndrome, type 2 diabetes mellitus, Cushing's syndrome, growth hormone deficiency, metabolic syndrome, nonalcoholic fatty liver disease, and changes in ZAG serum concentrations are strongly correlated with dyslipidemia, according to multiple studies [30, 31]. Patients with hypothyroidism had substantially reduced mean serum iron levels compared to healthy controls. According to the results of this study, anemia and a diminished bodily iron store are linked to changes in thyroid status, which in turn affect serum iron metabolism. The current study found that hypothyroidism patients had higher levels of malondialdehyde (MDA) before treatment and lower levels after levothyroxine medication. This is because hypothyroidism patients have increased lipid peroxidation, an end product. We can only guess as to the reasons, but we can say that proper treatment duration, tissue thyroid hormone levels, and TSH suppression were all satisfactory. There is a substantial positive association between MDA and TSH, and this finding is in agreement with [32], which also showed that levothyroxine decreased MDA levels. Increased oxidative damage can occur when reactive oxygen species (ROS) attack polyunsaturated fatty acid double bonds, leading to lipid peroxidation [33]. Lipid peroxidation products, like malondialdehyde, are formed when ROS-mediated oxidation of cell membrane lipids occurs [34]. The iron level was raised while using levothyroxine for three months. Consistent with [35], the current investigation found that hypothyroid individuals had lower iron levels. While hypothyroidism patients treated with levothyroxine improved their lipid profiles, this study found that TC, TG, and LDL levels increased while HDL levels decreased. This outcome is because thyroid hormones play a crucial role in lipid metabolism. Atherosclerotic disease risk factors include hyperlipidemia, which can be caused by any thyroid hormone deficit. In hypothyroidism, total cholesterol and low-density lipoprotein cholesterol levels are higher, as previously shown in this study. Other investigations, such the one conducted in Seoul, Korea, by [36], are supported by this finding. This is because thyroid hormones regulate LDL receptor expression. Experimental hypothyroid rats showed reduced hepatic expression of lipoprotein receptors as shown by ligand binding analysis in a study conducted by [37]. The process of dyslipidemia in hypothyroidism was elucidated in a separate study by [38]. Both total and LDL cholesterol levels rise in hypothyroidism because the liver's LDL receptor count drops. Additionally, we noted that triglyceride levels were higher in cases of obvious hypothyroidism. A lack of adequate endogenous and exogenous triglyceride clearance from the bloodstream is the reason for this in hypothyroidism [39]. Hypothyroid patients had higher HDL levels compared to controls. In hypothyroid situations, lower activities of hepatic lipase and Cholesterol Ester Transfer protein (CETP) generate normal or higher levels of HDL [38]. Cholesteryl esters are less efficiently transported from HDL-2 to VLDL and IDL as a result of this mechanism [40]. This study show increase TSH in hypothyroidism patients while decrease T3 and T4. This result agree with [41, 42] that show increase TSH, while decrease T4 hypothyroidism patients. The study conducted by Mohamed corroborated these findings, revealing significantly elevated TSH levels ($p=0.046$) in patients, alongside a notable drop in T3 ($p=0.040$) and T4 ($p=0.029$) levels compared to the control group [43].

Thyroid hormones are essential for regulating metabolism, defined as the pace at which the body utilizes energy, by stimulating diverse metabolic processes in most tissues and elevating the basal metabolic rate, which subsequently leads to increased heat production in the body[44]. The thyroid gland exerts a significant biological influence on various bodily functions, including growth, reproduction, and metabolic regulation. Thermogenesis induced by thyroid hormone results from an elevated demand for ATP due to heightened cellular activity and diminished ATP synthesis efficiency. Consequently, individuals with hypothyroidism exhibit a reduction and stagnation in metabolic activity, frequently resulting in an elevation of BMI, in contrast to the manifestations observed in patients with hyperthyroidism. [45-47].

CONCLUSION

Serum ZAG, iron, Total, high density lipoprotein cholesterol (HDL), T3, and T4, while decrease level OF TSH, MDA, total cholesterol(TC), triacylglycerol(TG), low density lipoprotein cholesterol (LDL), levels in hypothyroidism patients.

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