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Immunological and Metabolic changes in Iraqi Women Patient with Graves' disease

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ABSTRACT

Graves' disease, a common cause of hyperthyroidism, affects middle-aged individuals, affecting lipid metabolism. Risk factors include genetic, environmental, and immunological factors. The aim of the study was to examine the possible correlation between certain blood biomarkers in individuals with Graves' disease before and after undergoing therapy with radioactive iodine (RAI). Sixty grave's disease patients, 30 of them was received radioiodine therapy, in addition to 30 healthy people as control with age range from (25-60) years old were enrolled in this study through their presence at the AL-Amal National hospital for nuclear medicine in Baghdad. Blood samples were collected to evaluate the level lipid profile, C-reactive protein, complete blood count, sodium and calcium. Results showed highly significant ($P \leq 0.01$) decreased in lipid profile parameters and a significant increasing in C-reactive protein level in both groups, before and after treatment, but no relation were found between GD and sodium and calcium. Thyroid dysfunction had an obvious impact on lipid metabolism, Grave's disease decreases lipid levels and increases body metabolism. Also increase an inflammation in body leading to high CRP levels in patients. No relationship found between electrolyte elements.

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1. Introduction

The thyroid gland is an endocrine gland located on both sides of the trachea. The body's operations, such as metabolism, growth, internal temperature regulation, and several other processes, are under control of thyroid gland. The thyroid gland stores thyroid hormones, which the body releases when needed [1]. Thyroid hormones have a significant impact on all main metabolic pathways. In terms of lipid metabolism, they affect lipid synthesis, mobilization, and breakdown, with a greater effect on degradation than synthesis [2]. It has been also discovered that the T3 hormone exhibits more activity in the metabolism of the organism. Researchers also discovered an intimate correlation between the levels of iodine in meals and the [thyroid gland's functioning]. The thyroid gland plays a crucial role in several metabolic processes, such as brain function, lipid and energy metabolism, protein synthesis, tissue development, and cellular oxidation. [3] The pituitary gland produces thyroid-stimulating hormone (TSH), which is a significant growth factor. It plays a crucial role in regulating both T3 and T4 hormones.

Graves' disease (GD) is an autoimmune disease that may result in both inflammation and hyperthyroidism. The manifestations of Graves' illness, also known as toxic thyroid enlargement, often include dermatological issues, muscular debility, weight reduction, an accelerated heart rate, and ocular complications in the majority of those affected[4]. Hyperthyroidism is a significant public health issue, primarily because of its rising prevalence and its effect on death rates. Autoimmune hyperthyroidism is characterized by dysfunction of the thyroid gland[5]. which it charactered by low TSH level as shown in Abed et al (2023) study [6].

Graves' disease, which affects around 0.5% of the population, is the leading cause of hyperthyroidism, accounting for 50 to 80% of all cases. The gender distribution among persons with Graves' illness varies from a ratio of 5 females to 1 male to a ratio of 10 females to 1 male. The illness is most prevalent among adults in the age range of 40 to 60 years; however, it may occur at any age [7].

Radioactive iodine-131 (RAI) therapy has been used for almost 80 years as a cure for hyperthyroidism. In 1941, doctors provided the first therapeutic dose of radioiodine-131 (I-131) to a patient with Graves' disease (GD). Since then, RAI therapy has been administered to thousands of patients globally as a definitive treatment for hyperthyroidism caused by either autoimmune (such as Graves' disease) or non-autoimmune toxic (multi)-nodular goiter[8]. Radioactive iodine (RAI) therapy has been used as a substitute for surgery in the treatment of individuals with large non-toxic nodular goiters (NTG) to effectively reduce the size of the gland [9]. A high ablative dose RAI has a better outcome regarding hypothyroidism than a usual dose [10]. The purpose of the study was to investigate the potential association between certain blood biomarkers in persons diagnosed with Graves' disease, in pre and post treatment with radioactive iodine (RAI).

2. Materials and methods

The blood sample were withdrawn from 60 Iraqi female patients [suffer from] grave's disease (age ranging from 25 to 60 years) was attended hormonal department at the AL-Amal National hospital for nuclear medicine and private laboratory Specialized for Endocrinology in Baghdad during period between March to May 2024.

Patients' blood samples were divided into two groups, newly diagnosed (30) samples and treated patients (30) samples, in addition to 30 healthy [people as control].

Five ml of blood were collected from the vein using 5 ml disposable needles and syringes. The blood was dispensed in a gel tube and left to clot for 10 minutes at room temperature, after all the serum separation were done by centrifugation at 4000 rpm for 10-15 minute and well-preserved in deep freezer at -20 C before analysis. An automated quantitative hematology analyzer was done to evaluate the hematological parameters. The Mindray bc10 directly measures complete blood count.Measuring of C-reactive protein were done by Boditech Med CRP kit, using afias-6 device, 100 µL of serum were dispensed it into the sample well of the cartridge, using an Automated device that directly measure the factor level. As well as lipid profile were done by Roche kit, using Cobas C111 device, 200 µL of sample were added in a pipette and dispense it into the Hitachi cup of the cartridge, using an Automated device. The calcium and sodium level were measured by Roche Ca and Na kit.

Inclusion criteria

- Age from 25 to 60.
- Any case newly diagnosis with Graves' disease.
- Only female patients.

Exclusion criteria

- Male patients.
- as patients who received more than one pills of RAI.
- Any association with chronic diseases such as coronary artery disease, chronic hypertension, diabetes mellitus immunological disease.
- Patients that are more than 60 years old.

Ethical clearance

The ethical committee of the Department of Biology / College of Science / University of Bagdad, Baghdad, Iraq, gave their stamp of approval to this work. The authorization with the reference number CSEC/0424/0027.

Statistical Analysis:

The Statistical Analysis System- SAS (2018) program was used to detect the effect of difference Groups in study parameters. Least significant difference –LSD test (Analysis of Variation-ANOVA) was used to significant compare between means in this study.

3. Results and Discussion

Findings from Table 1 showed how cholesterol, triglycerides, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and very low-density lipoprotein (VLDL) were distributed among Iraqi female patients with Grave's disease. The cholesterol findings showed a very significant difference ($p = 0.0001$) ($P \leq 0.01$). The cholesterol levels among the GD groups before and after treatment were (114.60 ±4.79b) and (134.41 ±4.94a), respectively, whereas the control group had a level of (137.81 ±5.97a). A significant reduction was observed in patients with GD before treatment in compared to after therapy and the healthy control group.

There was a statistically significant difference (P≤0.01) (p = 0.0047) in HDL levels between the GD group before treatment compared to the GD group after treatment and the healthy control group. The pre- and post-treatment levels of GD patients were (33.53 ± 1.50b) and (38.17 ± 1.68a), respectively, whereas the healthy controls group were (41.18 ± 1.64a). There was a significant difference in VLDL level (P≤0.01) (p=0.0024), the mean of GD patient pre and post treatment was (21.09 ±0.76 b) (22.06 ±0.56 b), respectively, while the healthy control (24.35 ±0.63 a).

The p-value for triglyceride show significant difference (P≤0.05) (p = 0.0419) among studied group. The level of triglyceride before and after treatment were (116.12 ±5.78b) and (128.41 ±4.35ab), respectively, while the healthy control was (135.03 ±5.60a).

The LDL findings showed no significant difference between the studied group. The LDL levels for the GD patients without and with RAI treatment (108.05 ±3.62) and (116.07 ±3.18), respectively, and (118.15 ±3.66) for the control group, as shown in the table1.

Endocrine issues and hormone treatment may modify lipid metabolism and plasma lipid levels, thereby influencing the possibility of developing atherosclerotic cardio vascular disease [11].

The results in this study are in line with other study, which that revealed to significant decrease in VLDL as well as Triglyceride level in GD patient [12]. Also, other researcher indicate that Serum cholesterol and low density lipoprotein-cholesterol concentrations were increased in GD patient with RAI therapy in compared to other group[13]. Hyperthyroidism is characterized by an increase in lipid production and breakdown, mostly via catabolic pathways. As a result, hyperthyroid individuals have a decrease in their plasma cholesterol levels[14].

Hyperthyroid individuals experience a decrease in total and low-density lipoprotein (LDL) cholesterol levels due to increased breakdown of LDL, cholesterol elimination via bile, and decreased circulation of bile acids between the intestines and liver. This is due to the regulatory influence of thyroid hormone on a maim enzyme involved in lipoprotein metabolism. When thyroid hormones are released, they make Low cholesteryl ester transfer protein (CETP) work harder, facilitating the transfer of cholesteryl esters from HDL2 to VLDL and triglycerides in the opposite direction. Thyroid hormones also increase the production of lipoprotein lipase (LPL) and hepatic lipase (HL), enzymes that break down HDL2 into HDL3, making low-density lipoprotein (LDL) more likely to be oxidized. Studies by Largest et al., Kauusi et al., and Santamarina et al. also corroborate the idea of dyslipidemia [15, 16].

Additionally, these results are in line with current findings of the current study. A drop in HDL levels is also found in GD patients and increased hepatic triglyceride, lipase activity is thought to be the cause of this reduction [17].

Table 1: Comparison between difference groups in Lipid profile

Group	Mean ± SE (mg/dl)				
	Cholesterol	HDL	LDL	VLDL	Triglyceride
GD patients	114.60 ±4.79 b	33.53 ±1.50 b	108.05 ±3.62	21.09 ±0.76 b	116.12 ±5.78 b
GD patients with RAI treatment	134.41 ±4.94 a	38.17 ±1.68 a	116.07 ±3.18	22.06 ±0.56 b	128.41 ±4.35 ab
Healthy control	137.81 ±5.97 a	41.18 ±1.64 a	118.15 ±3.66	24.35 ±0.63 a	135.03 ±5.60 a
LSD value	14.789 **	4.535 **	10.832 NS	1.848 **	14.866 *
P-value	0.0001	0.0047	0.104	0.0024	0.0419
Means having with the different letters in same column differed significantly. * (P≤0.05), ** (P≤0.01).					

Table (2) presents the distribution of hematological parameters across the studied groups of patients with GD. The findings indicated that there was no statistically significant difference in white blood count (WBC) between the patient group and the healthy control group. This same outcome was observed for mixed cells (MID), granulocytes (GRAN) (GRAN%), lymphocytes present (LYM%), platelets (PLT), platelet distribution width (standard deviation) (PDWSD), platelet crit (PCT), and platelet-large cell ratio (PLCR).

There is a notable disparity in the lymphocyte (LYM) levels, with a statistical significance of (P≤0.01) (0.0001). The levels of LYM in patients with GD before and after therapy are lower compared to the levels seen in healthy individuals. Similar findings were seen in the percentages of mixed cells (MID%), and the variation in platelet distribution width (PDWCV).

The mean platelet volume (MPV) level exhibits a statistically significant difference (P≤0.01) (0.0003), with larger MPV levels seen in GD patients both before and after therapy compared to the healthy control group.

This study reveals a notable reduction in hemoglobin (HGB). This finding is consistent with another study that demonstrated a notable reduction in the levels of hemoglobin (Hgb) [18].

A study on a group of people with hyperthyroidism showed that the percentage of lymphocytes decreased while the percentage of granulocytes increased[19].

The results of this study reveal that patients with GD experience anemia, which is consistent with the findings of Gianoukakis et al. in 2009. The hematological indices are measurements and computations used to evaluate different elements of blood composition and function. The results indicate that 33% of the patients had anemia[20]. this is thought to be caused by alterations in iron metabolism, the degradation of red blood cells, and the existence of oxidative stress, resulting in heightened susceptibility of red blood cells to rupture and the oxidation of lipids, ultimately resulting in a decreased lifespan of red blood cells[21].
Also, People with Graves' disease (GD) and hyperthyroidism had significantly higher mean platelet volume (MPV) levels than people with autoimmune thyroid disorders (AITD). the difference was significant[22]. In addition, other study are in line with this study, it shows that PLT and LYM counts was decreased in patient with hyperthyroidism[19].

Table 2: Comparison between difference groups in CBC

CBC	Mean ± SE			LSD value	P-value
	GD patients	GD patients with RAI treatment	Healthy control		
WBC 10^9/L	6.52 ±0.38	6.65 ±0.46	7.04 ±0.30	1.094 NS	0.609
LYM 10^9/L	1.50 ±0.14 b	1.62 ±0.13 b	2.41 ±0.16 a	0.411 **	0.0001
MID 10^9/L	0.735 ±0.05	0.918 ±0.07	0.897 ±0.09	0.210 NS	0.172
GRAN 10^9/L	4.44 ±0.37	5.28 ±0.46	4.63 ±0.29	1.088 NS	0.277
LYM%	25.25 ±2.49	24.08 ±1.39	26.84 ±1.18	5.023 NS	0.552
MID%	9.88 ±0.51 b	11.17 ±0.43 a	11.13 ±0.39 ab	1.262 *	0.0474
GRAN%	64.27 ±2.81	65.07 ±2.41	61.27 ±1.12	6.288 NS	0.450
PLT 10^9/L	250.13 ±8.24	259.46 ±9.72	277.97 ±11.51	27.88 NS	0.136
MPV fL	10.26 ±0.23 b	11.01 ±0.31 a	9.57 ±0.16 c	0.670 **	0.0003
PDWCV %	14.69 ±0.17 b	14.30 ±0.21 b	15.82 ±0.15 a	0.494 **	0.0001
PDWSD fL	16.98 ±0.68	16.24 ±0.58	17.64 ±3.27	5.513 NS	0.881
PCT mL/L	2.39 ±0.13	2.52 ±0.13	2.28 ±0.08	0.334 NS	0.348
PLCR %	33.80 ±1.39	33.89 ±1.37	32.43 ±1.36	3.869 NS	0.702
Means having with the different letters in same row differed significantly. * (P≤0.05), ** (P≤0.01).					

Result of Na shows that there's no significant different among different group. The level of GD patient before and after treatment are (143.10 ±1.83) (142.97 ±1.34) respectively, while the healthy control is (140.93 ±1.21). Same result for calcium, the level of calcium shows no significant different among the groups, the mean level of GD patient pre and post treatment are (11.94 ±2.31) (9.68 ±0.21) respectively and the healthy control level is (9.31 ±0.13) as showed in table (3).

These results about NA and CA are in line with a study that involved patients with thyroid disorders, in addition to group of healthy people. Researchers measured the levels of NA and CA. The results show that subclinical hyperthyroidism did not show a significant difference between controls and patients ($p>0.05$), while in overt hyperthyroid patients, serum sodium was increased significantly ($p<0.05$). but the remaining results were not significant [23].

In this research, about only 10% of patient [suffer from] hypercalcemia, and this could be explained in Korytnaya et al (2011) Hypercalcemia may arise as a result of either hyperthyroidism or concomitant hyperparathyroidism. Up to 20% of hyperthyroidism patients have reported an asymptomatic blood calcium rise, which is associated with accelerated bone resorption. [24]. Thyrotoxicosis is characterized by impaired intestinal calcium absorption. Similarly, hypercalcemia results from decreased renal tubular calcium reabsorption, as shown in this case [25].

Table (3): Comparison between difference groups in Na and Ca concentration.

Group	Mean ± SE	
	Na (m mol/l)	Ca (mg/dl)
GD Patients	143.10 ±1.83	11.94 ±2.31
GD patient with RAI treatment	142.97 ±1.34	9.68 ±0.21
Healthy Control	140.93 ±1.21	9.31 ±0.13
LSD value	4.162 NS	3.739 NS
P-value	0.510	0.323
NS: Non-Significant.		

The result of CRP in this study shows that that there's no significant different (p≤0.01) (p=0.0006) in studied group. The level of CRP in pre and post treatment group were (5.25 ±0.37 mg/l b) and (8.92 ±61 mg/l a) respectively, but the healthy group was (2.841 ±0.27 mg/lb) as in table (4).

C-reactive protein (CRP) is a serum protein that is massively induced as part of the innate immune response to infection and tissue injury, As CRP has been noticed in damaged tissues and is known to activate complement [26]. C-reactive protein (CRP) levels have not been routinely used to diagnose thyroid disease, although many thyroid conditions involve inflammation, in this investigate the outcome result indicate that CRP level in a significant different in patients with GD in comparison with healthy control. According to tang (2021) he measures the CRP level in patient with thyroid disorder and found that serum level of CRP significantly higher than healthy control group [27] also according to Savas (2016) he measures CRP level in 156 patient [suffer from] thyroid disorder, including GD, serum level of CRP was significantly elevated in compared to healthy control people [28]

According to czarnywojtek et al (2014) Increased CRP might be due to that hyperthyroidism causes rapid metabolic activity, which may result in adrenergic nervous system hyperactivity, immune system stimulation and significantly increased peripheral blood flow. Thus, conditions which might result in an increase of CRP concentration. Also, Hyperthyroidism can lead to high metabolic activity, adrenergic nervous system hyperactivity, immune system stimulation, and increased peripheral blood flow. Conditions that may lead to elevated CRP levels[29]and[30].

Table (4): Comparison between difference groups in CRP concentration.

Group	Mean ± SE (mg/dl)
	CRP (mg/l)
GD	5.25 ±0.37 b
GD patient with RAI treatment	8.92 ±61 a
Healthy control	2.841 ±0.27 b
LSD value	2.094 **
P-value	0.0006
Means having with the different letters in same column differed significantly. * (P≤0.05), ** (P≤0.01).	

4. Conclusion

Thyroid dysfunction has a great impact on lipid metabolism. Grave's disease causes a drop in lipid levels in the blood and raises body metabolism. Also, this study revealed an increase in inflammation in the body, which explains the high CRP level in patients. Also, no relationship was found between Graves' disease electrolyte elements (Na, Ca).

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