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The pathophysiological role of Adiponectin, Insulin Growth Factor-1 (IGF-1) and Growth Factor Binding Protien-3 (IGFBP-3) in thyrotoxicosis patients

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ABSTRACT:

Background: Adiponectin, insulin-like growth factor-1 (IGF-1), and insulin-like growth factor-binding protein-3 (IGFBP-3) play vital roles in endocrine regulation, energy homeostasis, growth, and metabolism, and have been shown to interfere with thyroid hormones.

Aim: This study seeks to detect the pathophysiological roles of adiponectin, IGF-1, and IGFBP-3 and to assess their relationships with thyroid hormone levels in patients with thyrotoxicosis.

Material and Methods: A case-control study was conducted, involving 56 patients diagnosed with thyrotoxicosis and 30 healthy controls matched for age and gender. Serum levels of triiodothyronine (T3), thyroxine (T4), and thyroid-stimulating hormone (TSH) were measured by an automated chemiluminescence immunoassay (CLIA) system, and adiponectin, IGF-1, and IGFBP-3 were measured using human enzyme-linked immunosorbent assay (ELISA) kits.

Results: Patients with thyrotoxicosis exhibited significantly higher serum T3 and T4 levels and significantly lower TSH levels compared with healthy controls ($p<0.0001$). Serum adiponectin, IGF-1, and IGFBP-3 concentrations were significantly elevated in the patient group ($p=0.004$, $p<0.0001$, and $p<0.0001$, respectively). Patients with a positive family history demonstrated significantly higher adiponectin and IGF-1 levels, whereas IGFBP-3 levels were significantly higher among those without a family history. Correlation analysis revealed significant positive correlations between serum adiponectin and T3 ($r=0.229$, $p=0.032$) and T4 ($r=0.240$, $p=0.049$). while other correlations among the studied biomarkers were weak and non-significant.

Conclusions: Thyrotoxicosis is associated with significant increases in serum adiponectin, IGF-1, and IGFBP-3 levels, suggesting that these biomarkers may contribute to the metabolic and endocrine adaptations associated with excess thyroid hormone. Family history appears to influence adiponectin and IGF-1 concentrations, highlighting a potential genetic contribution to metabolic alterations in thyrotoxicosis. These findings

support a role for adiponectin, IGF-1, and IGFBP-3 in the pathophysiology of thyrotoxicosis and warrant further investigation into their clinical significance

INTRODUCTION:

Thyrotoxicosis is a clinical syndrome identified by extreme thyroid hormone secretion and activity, including triiodothyronine (T3) and thyroxine (T4). Thyrotoxicosis involves several circumstances, including Graves' disease (GD), thyroiditis, toxic nodules, and hormonal treatment [1]. Hyperthyroidism, a subset of thyrotoxicosis, refers specifically to excess thyroid hormone synthesis and secretion by the thyroid gland [2].

Adiponectin is primarily derived from adipose tissue and is a widely available adipokine that circulates at high concentrations in human plasma, due to its inverse correlation with adipose tissue abundance. Adiponectin is a plasma collagen-like protein that is associated with the progression of insulin resistance [3]; it has anti-inflammatory, anti-proliferative, pro-apoptotic, and insulin-sensitizing properties [4,5]. Studies suggest that serum adiponectin levels are changed in thyroid disorders, in which circulating adiponectin can influence thyroid hormone production, mainly free T4 (FT4), through the carboxyl-terminal globular structure of adiponectin via the gC1q receptor on thyroid mitochondria. While both adiponectin and thyroid hormone play important roles in energy homeostasis, their functions and interactions in metabolic regulation are yet unclear, with conflicting results [6]. Thyrotoxicosis is accompanied by decreased body lipid and muscle mass and loss of fat stores. Hence, higher levels of adiponectin could epitomize a compensatory response to insulin resistance observed in hyperthyroidism [7].

Insulin-like growth factor 1 (IGF-1) is a protein mainly produced by the liver and is primarily regulated by growth hormone (GH) and nutritional status. IGF-1 may influence energy metabolism and has an important role in the endocrine system, metabolism, and growth [8]. Many cytokines, growth factors, and hormones share pathways with the IGF pathway. Additionally, thyroid hormones and thyrotropin (TSH) may affect the biological actions of GH and IGF-I on target tissues. Many metabolic and immunologic processes are impaired as a result of this two-way interaction. In particular, IGF-I supports the normal function of the thyroid gland and thyroid hormone production [9].

One of the key components of the IGF family is Insulin-like Growth Factor Binding Protein-3 (IGFBP-3). Acts to adjust the biological activity of IGF via its binding with it, and to maintain the stability between growth factors and insulin [10]. Thyroid hormones regulate the expression of IGF-1 and IGFBP-3, and both IGF-1 and IGFBP-3 have been shown to be related to thyroid function and growth [11].

This study aimed to evaluate serum levels of adiponectin, IGF-1, and IGFBP-3 in patients with thyrotoxicosis and to investigate their associations with thyroid hormone status and some clinical parameters. The study was also designed to elucidate the possible involvement of these biomarkers in the pathogenesis of thyrotoxicosis.

MATERIALS AND METHODS:

Study design: Observational case-control study

Study Population

This case-control study involved a total of 86 participants. Sixty-five (65) patients were included in the patient group diagnosed as having thyrotoxicosis at the National Center for Endocrine Disease and Diabetes in Baghdad city between May/ August 2022. The age of participants ranged from 20 to 65 years. Thirty (30) apparently healthy subjects were selected for the control group; their ages ranged from 20 to 54 years, matching the patient group in age and gender. Demographic and clinical data for each participant were obtained using a specially designed case sheet that included age at follow-up, sex, family history of disease, disease duration, treatment use, smoking habits, and other diseases. A few exclusion criteria were applied, such as chronic systemic diseases; autoimmune disorders; pregnant and lactating women; smoking persons; and individuals receiving medications.

Sample Size

Considering the 95% confidence level and 80% power, the sample size n = 86 was calculated for two groups using the G*Power program 3.1.9.7 (Franz Faul software). Thus, a total of 86 participants were included in the study, comprising 56 patients with

thyrotoxicosis and 30 apparently healthy controls. The sample size was deemed sufficient to statistically detect differences between the study groups.

Ethical Approval

The Ethics Committee of the College of Dentistry at the University of Baghdad approved the research under reference number 362821 on 6/7/2021. All participants received complete information about the current study's objectives and procedures.

Sample Collection

Venous blood was drawn from an aseptic site in each case, with an average volume of 4mL. Blood samples were placed in clot activator tubes and left to clot at room temperature. Later, samples were centrifuged for 5 minutes at 3000 rpm to get serum. The separated serum was transferred into Eppendorf tubes and frozen at −20°C for biochemical measurements.

Biochemical Analysis

The automated chemiluminescence immunoassay (CLIA) analysis system was used to measure serum levels of thyroid hormones (thyroxine [T4], triiodothyronine [T3] and thyroid-stimulating hormone [TSH]) to confirm the diagnosis. The serum levels of adiponectin, IGF-1, and IGFBP-3 were analyzed using commercially available human enzyme-linked immunosorbent assay (ELISA) kits, following the manufacturer's instructions: adiponectin (Cat: DEE009), Insulin-like growth factor 1 (IGF-1 Cat: DE4140), and insulin-like growth factor–binding protein-3 (IGFBP-3 Cat: DEE003A).

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) software, version 26.0, was used to analyze the data. Continuous variables were expressed as mean ± standard deviation (SD), while categorical variables were presented as frequencies and percentages. Comparisons between two groups were performed using the independent-samples t-test for quantitative variables and the Chi-square test for categorical variables. Pearson's correlation coefficient was used to assess correlations among biomarkers. P-values less than 0.05 were considered statistically significant, and those less than 0.01 were considered highly significant.

RESULTS

This study included the analysis of two groups. The thyrotoxicosis group (56 patients) and the healthy control group (30 subjects). The results of the current study, presented in Table 1, compare demographic characteristics between the study groups and show no significant differences in gender ($p>0.05$) between 56 patients (49 female, 7 male) and 30 controls (26 female, 4 male). Besides showing no significant differences ($p>0.05$) in mean age (20-65 years: 40.87±11.03 years) compared with the control range (20-54 years: 42.23±9.06 years). This analysis shows that females are more likely to develop thyrotoxicosis (87.5%) than males (12.5%), and that the age range with the highest incidence is 35-45 (39%). Additionally, the analysis showed that the majority of patients with thyrotoxicosis had significant differences in their family history of disease (60.7%, $p= 0.032$), and (39.3%) had a negative family history.

Table (1): Age, gender, and family history of disease distribution of study groups

Gender and Age	Study groups				P-value
	Thyrotoxicosis group		Healthy control group		
	N	%	N	%	
Gender					0.912^{NS}
Female	49	87.5	26	86.6	
Male	7	12.5	4	13.4	
Total	56	100.0	30	100.0	
Age group (years)					0.282^{NS}
<35	15	26.1	6	20.0	

35-45	22	39.0	8	26.6	
45+	19	34.9	16	53.4	
Total	56	100.0	30	100.0	
Range	(20 - 65)		(20 - 54)		
Mean ± SD	40.87± 11.03		42.23± 9.06		
Family history of disease	**Thyrotoxicosis patients' group**				
	N		%		
Positive	36		64.3%		0.032*
Negative	20		35.7%		
Total	56		100.0		

The t- test in Table 2 demonstrates that patients with thyrotoxicosis had significantly higher serum levels ($p<0.0001$) of T3 (3.72±1.55 ng/mL) than the levels in the control (1.70±0.51 ng/mL). The mean level of T4 increased significantly ($p<0.0001$) in the patient group (129.31±30.73 ng/mL) compared with the control group (82.38±14.69 ng/mL). Conversely, serum TSH levels were markedly lower ($p<0.0001$) in the patient group (0.81±1.13 µIU/mL) than in the control group (2.92±1.23 µIU/mL).

However, the mean level of adiponectin was significantly elevated ($p<0.004$) in the patient group (30.77±20.59 ng/mL) than the level in the control group (19.64±12.91 ng/mL). The mean levels of serum IGF-1 and serum IGFBP-3 were significantly elevated ($p<0.0001$) in the patient group (158.69±48.93, 24.39±3.65 ng/mL) compared with the control group (100.27±34.27, 18.27±3.79 ng/mL), respectively.

Table (2): Case-control difference in serum biomarker levels in study groups

Measured Variable	Thyrotoxicosis patients' group (N=56)	Healthy control Group (N=30)	Significance (P-value)
T3 (ng/mL)	3.72±1.55	1.70±0.51	<0.0001**
T4 (ng/mL)	129.31±30.73	82.38±14.69	<0.0001**
TSH (µIU/mL)	0.81±1.13	2.92±1.23	<0.0001**
Serum Adiponectin (ng/mL)	30.77±20.59	19.64±12.91	<0.004**
Serum IGF-1 (ng/mL)	158.69±48.93	100.27±34.27	<0.0001**
Serum IGFBP-3 (ng/mL)	24.39±3.65	18.27±3.79	<0.0001**
The data expressed in mean ± standard deviation (Mean ± S.D); significant p-value < 0.001**, highly significant (HS)			

Table 3 reveals that thyrotoxicosis patients with a positive family history had significantly higher ($p= 0.006$) mean serum adiponectin (36.14±22.36) than those with a negative family history (22.48±14.35), and the level of IGF-1 increased significantly ($p= 0.044$) in patients with a positive family history (167.66±52.54) compared to those with a negative family history (144.83±40.03). Interestingly, patients with a negative family history showed significantly higher ($p= 0.020$) IGFBP-3 levels (25.62±3.58) than those with a positive family history (23.59±3.52). No significant differences ($p>0.05$) were observed in serum T3, T4, or TSH concentrations by family history.

Table (3): Comparison of biomarker levels according to family history in the patient group.

Biomarkers	Thyrotoxicosis patients' group		P-value
	Family history		
	Positive N=34	Negative N=22	
T3 (ng/mL)	3.86±1.58	3.50±1.50	0.200^{NS}
T4 (ng/mL)	129.22±29.88	129.45±32.70	0.489^{NS}
TSH (µIU/mL)	0.75±1.06	0.91±1.26	0.306^{NS}
Serum Adiponectin (ng/mL)	36.14±22.36	22.48±14.35	0.006**
Serum IGF-1 (ng/mL)	167.66±52.54	144.83±40.03	0.044*
Serum IGFBP-3 (ng/mL)	23.59±3.52	25.62±3.58	0.020*
The data expressed in mean ± standard deviation (Mean ± S.D); significant p-value < 0.001**, highly significant (HS)			

Pearson correlation illustrates correlations among biomarkers in patients with thyrotoxicosis. A significant positive correlation was found between serum adiponectin and T3 (r=0.229, p=0.032) and T4 (r=0.240, p=0.049). All other correlations were weak and non-significant, including the relationship between adiponectin and IGF-1 (r=0.081, p=0.552), adiponectin and IGFBP-3 (r=-0.040, p=0.769), and IGF-1 and IGFBP-3 (r=-0.066, p=0.628), as demonstrated in Table 4.

Table (4): Correlation between biomarkers in thyrotoxicosis Patients group.

	Adiponectin		IGF-1		IGFBP-3	
Biomarkers	r	p	r	p	r	p
T3	0.229	0.032*	0.200	0.139	0.016	0.906
T4	0.240	0.049*	0.006	0.960	0.085	0.529
TSH	-0.168	0.215	-0.176	0.194	-0.136	0.317
Adiponectin	1	--	0.081	0.552	-0.040	0.769
IGF-1	0.081	0.552	1	--	-0.066	0.628
IGFBP-3	-0.040	0.769	-0.066	0.628	1	--

DISCUSSION

Thyrotoxicosis is a clinical syndrome caused by excessive circulating thyroid hormones, leading to a hypermetabolic state [12]. The predominance of females among patients with thyrotoxicosis observed in the current study is consistent with findings reported by Mammen & Cappola (2021) and Usama et al. (2026), which indicate that females are more likely to develop thyroid disorders [13,14]. This may be attributed to the autoimmune nature of most hyperthyroid disorders, particularly GD, which occurs more frequently in women due to hormonal and immunological differences [15]. Several studies agree with the current findings, which describe that thyrotoxicosis occurs predominantly in females and commonly affects middle-aged adults [16,17,18]. It has been suggested that estrogen boosts humoral immune responses and predisposes to autoimmune thyroid diseases [18]. In addition, females may be more susceptible to infections due to genes associated with the X chromosome that

may be involved in regulating the immune system [15]. However, Taylor et al. (2018) found a relatively younger age distribution among thyrotoxic patients, which could be due to differences in ethnicity, environmental factors, iodine intake, or differences in access to health services and diagnostic practices [19].

The present study revealed that 64.3% of patients had a positive family history of thyroid disease; this is similar to the results found by Thomsen et al. (2020), who found that people who have a family history of thyroid disease are at a much higher risk of developing thyrotoxicosis [20]. But Ahmed et al. (2026) and Taylor et al. (2018) reported lower rates of positive family history possibly owing to population heterogeneity, small sample sizes, or different diagnostic criteria, which may result in a constant imbalance in metabolism and progressive endocrine dysfunction [17,19]. Autoimmune thyroid disease has been associated with several susceptibility genes such as HLA-related genes and immune-regulatory polymorphisms. Family clustering could also be due to common environmental factors, including dietary iodine intake, stress, and habits in life [21].

The results of this study confirmed the diagnosis of thyrotoxicosis (hyperthyroidism). The clinical features of the patient cohort in these results, however, were again typical of other observations – low TSH and high T4 and T3, supporting the diagnosis of disease [2,22,23]. In fact, the mechanism of thyroid hormone excess in thyrotoxicosis is continual stimulation of the thyroid follicular cells by thyroid-stimulating antibodies or by an autonomous thyroid nodule. This stimulation increases uptake of iodine, production of thyroglobulin, and release of thyroid hormones. Increased TH levels then stimulate mitochondrial function and energy expenditure, and inhibit pituitary TSH secretion by negative feedback. All these endocrine changes are responsible for the typical biochemical profile found in thyrotoxicosis [24].

In the case of the adiponectin results in the current study, the results are in accordance with Ismaiel (2023), who found that patients with GD had higher levels of adiponectin than healthy controls and also proposed that high levels of thyroid hormone and autoimmune activity can lead to higher metabolism of adipocytes and production of adiponectin by those cells [25]. Other studies have reported increased adiponectin in hyperthyroid patients compared to controls, with a positive correlation with FT3 and FT4, consistent with the current results [26,27,28]. Both thyroid hormones and adiponectin have important roles in metabolic regulation, affecting energy homeostasis, body temperature, and basal metabolic rate.

On the other hand, Ho and his assistants (2022) found that adiponectin levels decreased in hyperthyroid patients compared with euthyroid patients. Circulating adiponectin levels were significantly increased following treatment [29].

Yu et al. (2006) found that insulin levels increased significantly in hyperthyroid patients, and insulin has been reported to stimulate adiponectin secretion. Thus, increased insulin levels stimulate adiponectin secretion [27]. Chu et al. (2011) suggested that in the case of thyrotoxicosis, even though adiponectin levels are related to insulin resistance in general, the associated insulin resistance is not necessarily changed by the elevated adiponectin secretion. Adiponectin levels in hyperthyroid patients may be affected by multiple conflicting factors [30]. Petito et al. (2023) explain that the most plausible mechanism is that the hyperthyroid state activates the adrenergic receptor system and lipolysis, thereby increasing adiponectin secretion from adipocytes; thus, thyrotoxicosis may stimulate the development of small fat cells that release adiponectin [26]. The high levels of adiponectin observed in patients with a positive family history may suggest the involvement of inherited metabolic and immunological factors in the pathogenesis of thyrotoxicosis [31]. Gao et al. (2026) found that inherited factors may influence adipocyte function, inflammatory responses, and endocrine metabolism, thereby altering adiponectin secretion [32].

The results of the present study about IGF-1 and IGFBP-3 agree with the results by Inukai et al. (1999), which demonstrate that the IGF-I and IGFBP-3 concentrations were increased more notably in GD patients than in control subjects, and concluded that in patients with autoimmune thyroid diseases, thyroid hormone modulates the synthesis and/or the secretion of IGF-I and IGFBP-3 [33]. Zimmermann-Belsing and colleagues (2004) found that in patients with autoimmune thyrotoxicosis, IGF-I and IGFBP-3 levels were higher than in the control group. There was a positive correlation between IGF-I and IGFBP-3, indicating that the IGF system was intact in these patients. Nevertheless, all IGF-related peptides decreased from baseline during thyroid disease treatment, except for free IGF-I levels [34].

The results of Asaad and Kakey (2025) demonstrated a significant elevation in IGF-I levels in hyperthyroid patients compared to hypothyroid and control subjects, and showed that IGF-I correlate negatively with TSH, and positively with T3 and T4, suggesting that there might be a regulatory balance between the IGF-I system and thyroid hormone axis, and IGF-I could serve as an appreciated adjunct biomarker for evaluating thyroid disorders and could be included in routine thyroid estimation to improve early detection [8]. Similarly, Smith (2025) has reported that IGF-I levels were altered by the effect of thyroid hormones independently of growth hormone; they noticed that changes in IGF-1 levels by the effect of autoimmune thyroid

disease were raised in hyperthyroidism and lowest in hypothyroidism, but IGF-1 may contribute to the progression of diverse thyroid diseases [9].

Conversely, Akin et al. (2009) stated that IGF-I levels in hyperthyroid patients and the control group were similar, and that serum IGFBP-3 levels were slightly lower in the hyperthyroid group, but the difference was not statistically significant [35].

A proper explanation of the complex interaction between IGF-I and thyroid hormones is essential to elucidating the causal mechanisms of thyroid disorders. Vargas-Ortega et al., 2021, reported that IGF-I receptors are expressed in the thyroid gland, and there is a synergistic effect of IGF-I and TSH on thyroid cell growth and proliferation [36]. Also, IGFBP-3 expression might be independent of thyroid hormones and induced by cytokines, growth factors, and hepatic metabolic activity [37]. Thyroid hormone levels are largely controlled by a feedback system involving the hypothalamus-pituitary-thyroid axis and may not differ widely among hereditary groups after the onset of thyrotoxicosis [38].

Regarding the family history of thyroid disease and its relationship to marker levels in the present study, increased adiponectin levels in patients with a positive family history could indicate the role of inherited metabolic and immunological factors in the pathogenesis of thyrotoxicosis [31]. In fact, Simmonds and Gough (2004) studied autoimmune thyroid disorders, particularly GD, and determined that genetic susceptibility, through polymorphisms in HLA genes, CTLA-4, and immune-regulatory pathways, plays a significant role in their development [39].

The present study has also shown a significantly higher level of IGF-1 in those with a positive family history. This may show that inherited endocrine and growth-regulatory mechanisms contribute to the activation of the growth hormone–IGF axis in thyrotoxicosis [40]. According to a previous study by Møller and Jørgensen (2009), thyroid hormones stimulate hepatic IGF-1 synthesis by enhancing growth hormone sensitivity and anabolic metabolic pathways [41].

Ranke (2015) found that increased IGFBP-3 levels in patients without a family history may represent a compensatory regulatory mechanism to control excessive IGF-1 bioactivity and maintain endocrine balance. Variations in genetic background, disease duration, treatment status, nutritional status, and individual endocrine responsiveness may contribute to differences in IGFBP-3 concentrations among patients. Additionally, IGFBP-3 expression may be influenced independently by cytokines, growth factors, and hepatic metabolic activity, rather than exclusively by thyroid hormones [37].

The present study also demonstrated weak, non-significant correlations among adiponectin, IGF-1, and IGFBP-3. The findings of the present study indicate that such markers are independently affected by thyroid dysfunction but might be controlled by relatively independent metabolic pathways in thyrotoxicosis [42].

The current study results suggest that no significant correlation exists between IGF-1 and adiponectin, as had also been observed by Hsieh and Wang [6] in hyperthyroid patients. Thus, the results by Chen et al. [43] showed that adiponectin was also altered in hyperthyroidism and showed no strong associations with other adipokines and growth-related markers.

The lack of association between IGF-1 and IGFBP-3 in the current study may suggest that regulation of the growth hormone/IGF axis in thyrotoxicosis is complex and influenced by factors such as hepatic function, nutritional status, and disease severity [41]. While IGFBP-3 is responsible for the major circulating pool of IGF-1, IGF-1 and IGFBP-3 can respond differently to the excess thyroid hormone, depending on the metabolic demands and endocrine adaptation [44]. These findings are consistent with those of Iglesias and Díez [42], who demonstrated that thyroid dysfunction affects both IGF-1 and IGFBP-3 concentrations; however, their relationship may vary with hormonal status.

Regarding the significant correlation between adiponectin and thyroid hormones, studies have observed positive correlations between adiponectin levels and both FT3 and FT4 in patients with hyperthyroidism. This suggests that excessive thyroid hormone levels may increase serum adiponectin levels by regulating lipid metabolism, as serum total cholesterol levels may influence adiponectin [26-29].

CONCLUSION

Increased serum adiponectin, IGF-1, and IGFBP-3 concentrations in patients with thyrotoxicosis suggest that excess thyroid hormone may influence adipose tissue function and the growth hormone–IGF axis. Family history was associated with higher adiponectin and IGF-1 levels, suggesting a possible genetic influence on metabolic responses to thyrotoxicosis. In summary, adiponectin, IGF-1, and IGFBP-3 may serve as valuable parameters for assessing endocrine and metabolic activity in patients with thyrotoxicosis.

Contribution of the study: This study contributes to understanding the modifications in metabolic and endocrine parameters associated with thyrotoxicosis through assessing serum adiponectin, IGF-1, and IGFBP-3 in Iraqi patients. To the best of our knowledge, no studies in Iraq have included these biomarkers in patients with toxic thyroid disease. Furthermore, no previous studies have examined these three biomarkers together to assess their relationships with thyroid hormone status and family history of thyroid disease, suggesting a possible link between excess thyroid hormone and endocrine activity in adipose tissue. The findings provide additional evidence that adiponectin and the IGF system may participate in the metabolic adaptations associated with thyrotoxicosis.

Recommendation: To better determine the clinical and prognostic roles of adiponectin, IGF-1, and IGFBP-3, and their implications in the pathogenesis of thyrotoxicosis, further studies with larger sample sizes and longitudinal follow-up to evaluate changes in their levels over time are recommended. Investigate these biomarkers and their relation to body mass index (BMI), lipid profile, insulin, and glucose metabolism. Examine the genetic and familial factors and their potential effect on adiponectin, IGF-1, and IGFBP-3 levels.

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