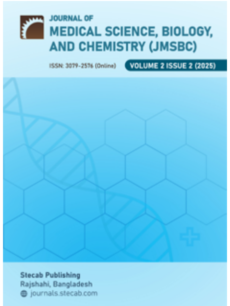

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Research Article

Immunological and Physiological Interactions Between Autoimmune Thyroid Dysfunction and Cardiovascular Dysregulation

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About Article

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ABSTRACT

A complex immunological and metabolic mechanism, so thyroid dysregulation worsens the condition of the heart. In addition, combination of lipid-controlling hormones, inflammatory cytokines, and the autoantibodies destroys the physiology of the heart and the vascular homeostasis. The study involved the change in the cytokines and thyroid autoantibodies, lipid regulators, also cardiac damage due to determine the correlation between immunological and physiological biomarkers among autoimmune thyroid dysfunction patients as an outcome of the cardiovascular disease (CVD). Eighty participants comprised of thirty healthy controls and fifty CVD patients who had autoimmune thyroid dysfunction. Measures of leptin, adiponectin, LDL, troponin, carotid intima-media thickness (IMT), also, endothelin-1, interleukin-1- beta/IL-1-B, and the interleukin-1-10/IL-1-10 were made together with the serum levels of thyroid peroxidase antibody (TPO-Ab), anti-thyroglobulin antibody (Tg-Ab) in addition TSH receptor antibody (TR-Ab). Furthermore, the insulin resistance was measured by HOMA-IR. Otherwise, the statistical study, Pearson correlation and t-test were used. TPO-Ab, Tg-Ab, TR-Ab, leptin, LDL, troponin, carotid IMT, endothelin-1, IL-1 -, and HOMA-IR were found significantly higher in CVD patients than in controls, in contrast adiponectin and IL-10 were significantly lower ($p < 0.001$). Also, there were positive relationships between troponin and leptin ($r = 0.484$, $p = 0.001$) and TR-Ab and adiponectin ($p = 0.024$). In addition, the correlation between IL-10 and carotid IMT and LDL was found negative ($p = 0.011$ and 0.001, respectively) having an anti-atherogenic effect. While the rest of the associations were not significant. According to the results, immunological dysregulation characterized by an increase of pro-inflammatory cytokines and thyroid autoantibodies in combination with metabolic disequilibrium plays a significant role in cardiovascular pathology of patients with autoimmune thyroid dysfunction. Furthermore, monitoring of therapy and risk assessment would be improved by the evaluation of these interconnected biomarkers.

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1. INTRODUCTION

Thyroid hormones are considered to be the essential modulators of cardiovascular and metabolic equilibrium. Their surplus or deficiency carries substantial systemic implications on the cardiac contractility, vascular tone and also lipid metabolism (Brent, 2012). Autoimmune autoimmune thyroid dysfunction is increase the risk of the cardiovascular disease due to modifying lipid profiles, instigating inflammation, and also dysfunction of endothelium (Klein & Danzi, 2016). Meanwhile, clinical and immunophysiological overlap is huge in case of the thyroid disorders and cardiovascular disease (CVD) co-occurrence. Antibodies such as thyroid peroxidase antibody (TPO-Ab), anti-thyroglobulin antibody (Tg-Ab) in addition TSH receptor antibody (TR-Ab), are all signs of autoimmune thyroid disease, thus is a chronic autoimmune activation that extends beyond the thyroid gland (Ferrari *et al.*, 2020). These antibodies are associated with oxidative stress and vascular inflammation that expose patients to the risk of endothelial injury and atherosclerosis (Hu *et al.*, 2020).

2. LITERATURE REVIEW

The inflammatory cytokines such as interleukin-10 (IL-10) and interleukin-1 -1 (IL-1) regulate the balance between pro and anti-inflammatory responses in the cardiovascular system (Han *et al.*, 2022). Also, recent data suggest that thyroid-related immunological dysregulation may affect adipokine signaling, in particular, leptin and adiponectin signaling, which that control lipid metabolism and insulin sensitivity (Latek & Tutuncu, 2025). The high level of leptin and low level of adiponectin form a metabolic-inflammatory axis between autoimmune thyroid dysfunction and cardiovascular disease and also are the cause of insulin resistance (HOMA-IR), dyslipidemia, in addition a pro-atherogenic environment (Soetedjo *et al.*, 2024). The severity of this immune-metabolic disturbance can be measured by the levels of troponin, endothelin-1, the endothelial markers as well as the carotid intima-media thickness (IMT) (Zhang, 2022). There is limited research that has examined immunological and physiological interaction between thyroid autoimmunity, cytokine imbalance, also, adipokine changes, and cardiac biomarkers in one model although much has been done in either the thyroid or the cardiovascular pathology (Liu *et al.*, 2025). To explain the potential immune-metabolic pathways involved in the development of cardiovascular problems, also, to determine the connection between the immunological and physiological biomarkers in patients with autoimmune thyroid dysfunction and cardiovascular disease, the current study was developed.

3. METHODOLOGY

3.1. Study Design and Population

This case-control study was aimed at determining the interaction between immunological and physiological indicators in people with autoimmune thyroid dysfunction and cardiovascular disease (CVD). These were 80 individuals in total, 30 of whom appeared healthy and would serve as the controls in accordance to age and sex, and the other 50 CVD patients with the thyroid disorder. The outpatient cardiology and endocrinology clinics of the Al-Zahraa Teaching Hospital in Wasit, Iraq, were the recruitment sites of the patients between January 2025 and June 2025. The diagnosis of the CVD was validated by clinical, electrocardiographic, and biochemical evidence and TSH, free T3, and free T4 levels of serum were used to diagnose the autoimmune thyroid dysfunction.

3.2. Inclusion and Exclusion Criteria

The inclusion criteria were adult patients that aged between 37 years to 70 years who already had established cardiovascular disease and had lab-confirmed autoimmune autoimmune thyroid dysfunction. Furthermore, the exclusion criteria included diabetes mellitus, acute infections, chronic renal or hepatic diseases, and also other. In addition, unhealthy individuals with no history of heart or endocrine conditions were used in this study as controls.

3.3. Sample Collection

After an overnight fast, so five milliliters of venous blood had been taken out of each subject. After that the serum was separated by centrifugation followed by storage at -20 o C until the analysis.

3.4. Biochemical and Immunological Assays

• *Thyroid autoantibodies:* TPO-Ab, anti-thyroglobulin antibody (Tg-Ab), and also TSH receptor antibody (TR-Ab) levels were measured by using the enzyme-linked immunosorbent assay (ELISA) kits (MyBioSource, USA).

• *Cytokines:* Interleukin-1β (IL-1β) and interleukin-10 (IL-10) in serum were measured by ELISA (Thermo fisher Scientific, USA) as the recommended by the manufacturer.

• *Adipokines and metabolic markers:* Leptin and adiponectin were also measured with Sandwich ELISA in addition the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) was calculated with the use of insulin and fasting glucose by the following formula:

\text{HOMA-IR} = \frac{\text{Fasting insulin (μU/mL)} \times \text{Fasting glucose (mmol/L)}}{22.5}

• *Lipid profile:* Lipids density (LDL) cholesterol was also quantified through an enzymatic colorimetric test.

• *Cardiac injury biomarkers:* Troponin I, carotid intima -media thickness (IMT) and endothelin-1 were assessed to assess cardiac and vascular activity. Carotid IMT was measured by using high-resolution B-mode ultrasonography (Philips iE33, USA).

3.5. Statistical Analysis

The data were analyzed with the help of SPSS version 26.0 (IBM Corp, USA). Also, the results were reported in the mean +-SD. Intergroup comparisons were analyzed with the independent samples t -test, and Pearson coefficients of correlation (r) were calculated to measure relationships between these biomarkers. P-values of below 0.05 were considered to be significant. Furthermore, the graphs and figures were drawn in Graphpad Prism 9.0.

3.6. Ethical approval

The ethical committee of the College of Science of the University of Wasit approved the protocol of the study (Approval No. BIO-2025-012).

4. RESULTS AND DISCUSSION

A summary of the demographic information of the groups under this study is presented in (Table 1). It was not found that the mean age of the control group (55.76 ± 8.98 years) and the mean age of CVD patients with autoimmune thyroid dysfunction (57.48 ± 7.05 years) differ significantly (p = 0.346). Similar to the controls, there was no significant difference in sex of patients 36% male and 64% female (p = 0.515). also, there was also no perceivable difference in the residency (rural vs. urban) (p = 0.148). These results confirm the matching of the two groups in terms of demography.

Table 1. The demographic information of the healthy control volunteers and patient with CVD

Characteristic	CVD Patients n = 50	Healthy control n = 30	P
Age (years)			
Mean ±SD	57.48 ± 7.05	55.76 ± 8.98	0.346 † NS
Range	39–69 years	37– 70 years	
< 50 years, n (%)	5 (10.0)	6 (20.0%)	0.436 ¥ NS
50-59 years, n (%)	26 (52.0%)	13 (43.3%)	
≥ 60 years, n (%)	19 (38.0%)	11 (36.7%)	
Sex			
Male, n (%)	18 (36.0 %)	13 (43.3 %)	.515 ¥ NS
Female, n (%)	32 (64.0%)	17 (56.7%)	
Residency			
Urban, n (%)	20 (40.0%)	17 (56.7%)	0.148 ¥ NS
Rural, n (%)	30 (60.0%)	13 (43.3%)	

n: number of cases; †: independent samples t-test; ¥: Chi-square test; NS: not significant at P > 0.05.

In Table 2 showed a significant increase in the levels of thyroid autoantibodies in patients with CVD. The blood concentration of TPO-Ab and Tg-Ab was 263.30 ± 12.41 and 243.88 ± 8.71 IU/mL, respectively, also the controls were 28.88 ± 2.04 and 28.01 ± 1.05, respectively (p = 0.001). Furthermore, the TR-Ab increased significantly (16.18 1.21 vs. 0.71 0.06 IU/mL, p = 0.001). These gains are due to autoimmune activation which is linked to vascular stress and autoimmune thyroid dysfunction.

Table 2. Diagnosis of autoimmune thyroid dysfunction in patients of CVD and healthy management

Parameters	CVD Patients n = 50	Healthy control n = 30	P
Thyroid Peroxidase Antibodies (TPO-Ab) IU/mL			
Mean ± SE	263.30 ± 12.41	28.88 ± 2.04	0.001 † S
Range	160.90 –467.40	17.90 –37.70	
Anti-thyroglobulin antibody (Tg-Ab) IU/mL			
Mean ± SE	243.88 ± 8.71	28.01 ± 1.05	0.001 † S
Range	157.90 –399.70	17.00 –35.00	
TSH receptor antibodies (TR-Ab) IU/mL			
Mean ± SE	16.18 ± 1.21	0.71 ± 0.06	0.001 † S
Range	5.70 –26.70	0.20 –1.70	

n: number of cases; †: independent samples t-test; S: significant at P > 0.05.

In Table (3) the mean value HOMA-IR level was significantly higher in patients (5.72 ± 0.91) as compared to controls (1.67 ± 0.29, p = 0.001). Also, this implies a reduction of insulin sensitivity, which is in line with a metabolic-inflammatory relation between cardiovascular disease and autoimmune thyroid dysfunction.

Table 3. HOMO-IR results in the patients and the healthy controls

Groups		HOMO-IR
CVD patients	Mean ± SD	5.72 ± 0.91
	Range	4.10-7.10
Control	Mean ± SD	1.67 ± 0.29
	Range	1.10-2.10
p-value		0.001 S

n: number of cases; SD: standard deviation; †: independent samples t-test; S: significant at P ≤ 0.05.

In Table 4 shows the relationship between the insulin resistance (HOMA-IR) and thyroid autoantibodies in patients with CVD with autoimmune thyroid dysfunction. So TPO-Ab and HOMA -IR were weakly correlated (r = 0.174, p = 0.228), while this was not statistically significant. Furthermore, non-significant correlations between the Tg-Ab (r = 0.005, p = 0.971) and TR-Ab (r = 0.068, p = 0.641) were established.

Also, such findings indicate that the effect of insulin resistance in such persons is more influenced by metabolic and inflammatory mediators such as increased IL-1 β, reduced adiponectin and also elevated leptin than direct immunogenic burden of thyroid antibodies. In addition the absence of strong correlation implies that instead of having a direct effect of alteration in the insulin sensitivity, thyroid autoimmunity also can lead to metabolic impairment through the indirect mechanism of low-grade systemic inflammation.

Table 4. A correlation with the levels of HOMO-IR in patients with CVD with other variables

Characteristic	HOMO-IR	
	r	P
TPO-Ab (IU/mL)	0.174	0.228
Tg-Ab (IU/mL)	0.005	0.971
TR-Ab (IU/mL)	0.068	0.641

r: correlation coefficient.

Table 5 shows that the patients have a large adipokine imbalance and dyslipidemia. Despite of adiponectin levels significantly declined (3.15 66 vs. 8.42 11μg/mL, p = 0.001), also, the levels of leptin rose significantly (21.42 3.77 ng/mL) when compared with control groups (5.30 1.33 ng/mL, p = 0.001). On the other hand, the LDL cholesterol increased (198.54 ± 19.20 vs. 91.76 ± 11.31 mg/dL, p = 0.001).

Table 5. Results of specific lipid profiles (LDL), leptin, and adiponectin of healthy controls and patients

Groups		Leptin ng/ml	Adiponectin	LDL mg/dL
CVD patients	Mean ± SD	21.42 ± 3.77	3.15 ± 0.66	198.54 ± 19.20
	Range	15.70-29.70	2.00-4.10	165.00-220.00
Control	Mean ± SD	5.30 ± 1.33	8.42 ± 1.11	91.76 ± 11.31
	Range	2.80-7.90	6.40-10.10	70.00-118.00
p-value		0.001 S	0.001 S	0.001 S

n: number of cases; SD: standard deviation; S: significant at P ≤ 0.05.

In Table 6 Leptin exhibited a minor positive relationship with the troponin (r = 0.484, p = 0.001) and also, TR-Ab correlated with adiponectin (p = 0.024), which demonstrates an inflammatory effect on the cardiac tissue and a compensatory immunometabolic response, respectively.

Table 6. Correlations between serum adiponectin, leptin, and lipid profiles (LDL) with other factors in CVD patients

Characteristic	Leptin		Adiponectin		LDL	
	r	P	r	P	r	P
Leptin ng/ml	1					
Adiponectin	-0.087	0.548	1			
LDL mg/dL	0.218	0.129	-0.034	0.814	1	
Homo-IR	0.204	0.155	-0.147	0.310	0.211	0.141
TPO-Ab(IU/mL)	0.180	0.211	-0.205	0.154	0.124	0.390
Tg-Ab(IU/mL)	0.053	0.712	0.001	0.995	0.023	0.874
TR-Ab(IU/mL)	0.234	0.102	-0.318	0.024*	0.053	0.714

r: correlation coefficient.

Furthermore, the heart stress markers are highly increased in the CVD patients (Table 7). Also, Troponin I rose to 6.71 ±1.59 ng/L as compared to 0.27 ± 0.03 ng/L in the control (p < 0.001). In addition, Carotid IMT was almost doubled (1.39 ± 0.18 mm vs. 0.66 ± 0.05 mm, p = 0.001), and the level of endothelin-1 almost increased sixfold (6.58 ± 0.85 vs. 1.00 ± 0.32 pg/mL, p < 0.001). However, these statistics validate augmented endothelial dysfunction and subclinical atherosclerosis in patients.

Table 7. The Heart attack profile (troponin, carotid IMT and endothelin-1) results in the patients and the healthy controls

Groups		Troponin-1 (ng/L)	Carotid IMT (mm)	Endothelin-1(pg/Ml)
CVD patients	Mean ± SD	6.71 ± 1.59	1.39 ± 0.18	6.58 ± 0.85
	Range	1.70-9.90	1.00-1.69	5.20-7.90
Control	Mean ± SD	0.27 ± 0.03	0.66 ± 0.05	1.00 ± 0.32
	Range	0.1-0.4	0.57-0.75	0.50-1.50
p-value		0.001 S	0.001 S	0.001 S

n: number of cases; SD: standard deviation; S: significant at P ≤ 0.05.

In Table 8 There was a significant difference between patients (18.64 ± 4.46 pg/mL) and controls (2.85 ± 0.68 pg/mL, p < 0.001) in the pro-inflammatory cytokine IL-1 β. On the other hand, anti-inflammatory IL-10 was much smaller (3.22 ± 0.91 vs. 7.83 ± 0.94 pg/mL, p < 0.001). The cytokine diagnostic performance study indicated that IL-1β and IL-10 would be perfect in the discrimination of CVD patients and healthy controls.

Table 8. The IL-10 and IL-1 β levels were analyzed in the patients and healthy controls

Groups		IL-1β pg/mL level	IL-10 pg/mL level
CVD patients	Mean ± SD	18.64 ± 4.46	3.22 ± 0.91
	Range	11.60-27.30	1.50-4.90
Healthy control	Mean ± SD	2.85 ± 0.68	7.83 ± 0.94
	Range	0.60-5.00	6.40-9.90
p-value		< 0.001 † HS	< 0.001 † HS

n: number of cases; SD: standard deviation; †: independent samples t-test; HS: highly significant at P ≤ 0.001.

The correlation in Table 9 revealed that IL-10 had a negative relationship with carotid IMT (r = -0.358, p = 0.011*) and also LDL (r = -0.451, p = 0.001), which indicated carotid IMT and LDL protection by interleukin IL-10. While, the IL-1 β had positive but not significant relationship with LDL and TPO-Ab indicating that there is an inflammatory-autoimmune relationship between them.

Table 9. The Association of IL-1B and IL-10 concentrations with other variables in CVD patients

Characteristic	IL-1β (pg/mL)		IL-10 (pg/mL)	
	r	P	r	P
IL-1β(pg/mL)	1			
IL-10(pg/mL)	-0.142	0.326	1	
Troponin (ng/L)	0.041	0.780	-0.085	0.557
Carotid IMT(mm)	0.191	0.183	-0.358	0.011*
Endothelin-1 (pg/Ml)	-0.045	0.756	0.157	0.276
Leptin (ng/ml)	0.223	0.119	-0.147	0.307
Adiponectin	0.073	0.614	0.056	0.702
LDL (mg/dL)	0.242	0.090	-0.451	0.001*
Homo-IR	0.037	0.797	-0.056	0.702
TPO-Ab(IU/mL)	0.270	0.059	-0.005	0.974
Tg-Ab (IU/mL)	0.120	0.406	0.029	0.839
TR-Ab(IU/mL)	0.069	0.634	-0.200	0.164

r: correlation coefficient.

4.1. Discussion

In this study, the immuno-metabolic pattern in the patients with autoimmune thyroid dysfunction in connection with the cardiovascular disease (CVD) was peculiar. Also, increased levels of thyroid autoantibodies, pro-inflammatory cytokine (IL-1), and leptin, reduced levels of the adiponectin and IL-10 indicators of chronic low-grade inflammation, as well as the metabolic disruption. In addition, these findings support the hypothesis that thyroid and cardiac disorders have common pathophysiological pathways, and indicate a mutual interaction between the immune activation and the endothelial damage (Duntas & Brenta, 2012). Compared to the normal conditions, patients were found to have significantly elevated levels of thyroid autoantibodies with TPO-Ab and also Tg-Ab being the predominant which is an evidence of autoimmune reactivity as a sign of the autoimmune thyroid dysfunction. So the main antigen of these antibodies is the thyroid tissue, the sustained circulation of these antibodies can result in the inflammation of endothelium through the complement and cytokine activity which also encourages atherogenesis (Yan *et al.*, 2015). Furthermore, these antibodies were not directly correlated with insulin resistance in our study, and so, most probably, autoimmunity indirectly induces metabolic impairment by disrupting insulin signalment due to inflammatory mediators (Krishnamurthy *et al.*, 2025). In the recent findings, it is evidenced that a substantial imbalance in the homeostasis of the adipokine is observed in the elevated levels of leptin and reduced levels of adiponectin in the patients. Also, leptin is an immunomodulator and metabolic hormone that activates the release of the inflammatory cytokines and T-cell activation (Procaccini *et al.*, 2017).

In addition, endothelial dysfunction and myocardial stress have been confirmed to be linked with higher levels of leptin, which is higher in relation to the higher levels of troponin and carotid intima-media thickness (Liu *et al.*, 2025). Meanwhile, adiponectin reduces oxidative stress and also enhances nitric oxide production; so that, its depletion facilitates the destruction of the vascular system and insulin resistance (Lei *et al.*, 2023). Furthermore the cytokine profile of this study is also another evidence of the inflammatory relationship. The sharp increase in IL-10 and the sharp decrease in IL-10 propose an imbalance in inflammatory and also regulatory immune responses. In addition, the IL-1B accelerates atherosclerosis in autoimmune thyroid dysfunction by stimulating endothelial and the smooth muscle proliferation (Papadopoulou *et al.*, 2020). On the other hand, IL-10 suppresses the macrophage activation process and also reduces LDL oxidation, which makes it have anti-atherogenic properties, which is confirmed by the correlation between its decrease and the high carotid IMT and LDL (Caligiuri *et al.*, 2003). Morever, the results are in line with previous studies that have established that the lack of IL-10 increases vascular inflammation in autoimmune thyroid and cardiovascular diseases (Mikoś *et al.*, 2014). So Endothelin-1, Troponin, and carotid IMT have a very high correlation, and this highlights the fact that vascular endothelium is also influenced by immunological and metabolic disorders. Also, the increase in the levels of endothelin-1 is an evidence of the endothelial dysfunction caused by the action of oxidative stress and also long-term exposure to cytokines (Taddei *et al.*, 2001). In addition, the high troponin of the present cohort indicates subclinical myocardial infarction that could be attributed to either metabolic stress and also autoimmune vascular inflammation. It is interesting to observe that not every immunological feature is directly linked to the cardiac indicators however in cases of a combination of thyroid autoimmunity and also cytokine dysregulation. Thus, this indicates a multifaceted mechanism where all adipokines, thyroid hormones and immunological mediators interact to alter heart and the vascular physiology. Therefore, the thyroid ailment and the heart danger can be connected through one path, immune-endocrine axis (Khan *et al.*, 2020). Clinically, simultaneous measurement of cytokines (IL-1 β, IL-10), adipokines (leptin, adiponectin), and cardiac (troponin, endothelin-1, IMT) provide a more comprehensive assessment of the disease progression as well as relying on the concentration of thyroid hormones. In addition, these biomarkers can be used as add-ons to the concept of the immune-metabolic risk stratification as they can be used as early warning of the cardiovascular issues in the thyroid patients (Xing *et al.*, 2024).

5. CONCLUSION

This paper highlights the complex interplay between the physiological and immunological dysregulation in people with autoimmune thyroid dysfunction and cardiovascular disease. Meanwhile, this is a chronic immune-metabolic imbalance evidenced by increased thyroid autoantibodies, pro-inflammatory cytokines (IL-1 β), and also leptin, and reduced adiponectin and IL-10.As soon as subclinical myocardial damage, endothelial dysfunction, and insulin resistance are all enhanced by these aberrations. Furthermore, there is no significant association between thyroid autoantibodies and insulin resistance, and also instead inflammatory cytokines and adipokines or other factors are directly responsible. In addition, the negative correlation between IL-10 and carotid and LDL IMT illustrates the protective effect of the cytokine on the vascular and the potential of the cytokine as a prognostic factor.

Cumulating the findings shows that a more precise image of the cardiovascular risk among thyroid patients may be achieved through the assessment of the physiological (leptin, adiponectin, HOMA-IR, troponin, endothelin-1, and IMT) and also immunological (IL-1 2, IL-10, and thyroid autoantibodies) indicators. Moreover, the timely diagnosis of this immune-metabolic condition can augment the risk assessment and inform specialized treatment patterns that are supposed to the modify metabolic and the inflammatory events.

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