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The Impact of Hemostatic Alterations in Manifest and Subclinical Hypothyroidism on Endothelial Dysfunction

Nazokat Bekchanova[1,*], Shaira Babadjanova[2]

[1]PhD Student, Department of Hematology, Transfusiology and Laboratory Work, Tashkent State Medical University, Uzbekistan
[2]DSc., Professor, Department of Hematology, Transfusiology and Laboratory Work, Tashkent State Medical University, Uzbekistan

Abstract Autoimmune thyroiditis (AIT) with progression to hypothyroidism is frequently accompanied by systemic vascular and hemostatic abnormalities that contribute to increased cardiovascular risk. This study aimed to explore the relationship between endothelial dysfunction and hemostasis alterations in patients with subclinical and manifest hypothyroidism. A total of 87 participants were enrolled, including 20 healthy controls, 38 with subclinical hypothyroidism, and 29 with manifest hypothyroidism. Laboratory assessment comprised classical coagulation markers such as prothrombin index (PTI), activated partial thromboplastin time (APTT), fibrinogen, platelet count, and D-dimer, along with endothelial indicators including von Willebrand factor (vWF), endothelin-1 (ET-1), and soluble intercellular adhesion molecule-1 (sICAM-1). The results revealed progressive endothelial dysfunction in hypothyroid groups, manifested by a decline in vWF levels and significant elevation of ET-1 and sICAM-1. Concurrently, hemostatic imbalance was evident, with prolonged APTT, increased fibrinogen concentration, and higher D-dimer values compared with controls. Correlation analysis demonstrated strong positive associations between endothelial and coagulation parameters, most notably between ET-1 and sICAM-1 ($r = 0.81$, $p < 0.001$). These findings indicate that both subclinical and manifest hypothyroidism are characterized by distinct but interconnected vascular and coagulation disturbances. Importantly, alterations emerge even at the subclinical stage, underscoring the need for early identification and monitoring to reduce thrombotic risk in autoimmune thyroid disease.

Keywords Autoimmune thyroiditis, Hypothyroidism, Subclinical hypothyroidism, Endothelial dysfunction, Hemostatic abnormalities, von Willebrand factor (vWF), Endothelin-1 (ET-1), Soluble intercellular adhesion molecule-1 (sICAM-1), Thrombotic risk, Cardiovascular complications

1. Introduction

Autoimmune thyroiditis (AIT) constitutes one of the most prevalent organ-specific autoimmune disorders and is recognized as the primary etiology of hypothyroidism within iodine-sufficient populations [9,20]. In addition to the traditional consequence of compromised thyroid hormone production, AIT has increasingly been acknowledged as a systemic disorder exerting significant influence on vascular biology and hemostatic processes [14,17].

The presence of hypothyroidism, whether manifest or subclinical, exhibits a strong correlation with cardiovascular complications, wherein endothelial dysfunction (ED) and hemostatic irregularities function as pivotal mediators of vascular risk [6,8]. The vascular endothelium operates as a fundamental regulatory interface, preserving a delicate balance between vasodilation and vasoconstriction, antithrombotic and prothrombotic signaling pathways, as well as inflammatory and anti-inflammatory responses [7,12].

Disruption of this intricate equilibrium leads to impaired release of vasoactive mediators, altered expression of adhesion molecules, and abnormalities in endothelial biomarkers such as von Willebrand factor (vWF), endothelin-1 (ET-1), and soluble intercellular adhesion molecule-1 (sICAM-1) [7,11,14]. Concurrently, hypothyroid states have been associated with disturbances in the coagulation cascade, characterized by reduced prothrombin activity, prolonged activated partial thromboplastin time (APTT), hyperfibrinogenemia, and increased D-dimer generation, collectively contributing to a prothrombotic or hemorrhagic tendency depending on disease severity [2,4,5,6,13].

Despite the proposed pathophysiological association between thyroid dysfunction, endothelial injury, and coagulation abnormalities, the extent and stage-dependent nature of these alterations remain insufficiently clarified [8,16]. Most previous investigations have focused primarily on overt hypothyroidism or on patients with advanced cardiovascular comorbidities [4,5,6]. In contrast, only a limited number of studies have examined endothelial and hemostatic interactions during the early, subclinical phase of

* Corresponding author:
bekchanovanazokat55@gmail.com (Nazokat Bekchanova)
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autoimmune hypothyroidism, a stage in which vascular impairment may already be developing but remains clinically silent [1,6,14].

This gap in knowledge is of particular importance, as early endothelial and coagulation abnormalities may precede overt cardiovascular disease and provide an opportunity for timely risk stratification and preventive intervention [8,12]. Therefore, the present study was undertaken to comprehensively evaluate endothelial function alongside key coagulation parameters in patients with both subclinical and manifest autoimmune hypothyroidism.

By assessing classical hemostatic indices—including prothrombin index (PTI), APTT, fibrinogen concentration, platelet count, and D-dimer levels—together with endothelial markers (vWF, ET-1, and sICAM-1), this investigation aims to generate novel insights into the interrelated vascular and hemostatic disturbances associated with autoimmune hypothyroidism [1,6,8,14]. Understanding these early alterations is essential for improving cardiovascular risk assessment and may contribute to more informed clinical decision-making in patients with autoimmune thyroid disease.

2. Materials and Methods

This observational cross-sectional study was designed to evaluate endothelial dysfunction and hemostatic alterations in patients with different thyroid functional states. A total of 107 participants were enrolled and stratified into three groups according to thyroid hormone status. The control group consisted of 30 euthyroid individuals with normal thyroid function tests. The subclinical hypothyroidism group included 53 patients characterized by elevated thyroid-stimulating hormone (TSH) levels with normal free thyroid hormone concentrations, while the manifest hypothyroidism group comprised 54 patients with increased TSH and reduced free thyroid hormone levels.

Endothelial function was assessed by measuring circulating biomarkers associated with endothelial activation and dysfunction, including vWF, ET-1 and sICAM-1.

In addition, a comprehensive evaluation of the hemostatic system was performed. This included assessment of the prothrombin index (PI), APTT, plasma fibrinogen concentration, platelet count, and D-dimer levels, providing insight into both coagulation and fibrinolytic activity.

Statistical analysis was conducted using appropriate parametric methods. Differences between the study groups were analyzed using one-way analysis of variance (ANOVA). Pearson's correlation coefficient (r) was applied to determine the strength and direction of associations between thyroid function parameters and endothelial or hemostatic biomarkers. Statistical significance was defined as a p-value of less than 0.05.

3. Result and Discussion

Endothelial dysfunction markers showed significant differences among the study groups (Table 1). In the control group vWF levels were within normal range, averaging 85.3 ± 2.36%, whereas a marked reduction was observed in both the subclinical and manifest hypothyroidism groups, with values of 61.3 ± 2.52% and 59.1 ± 3.01%, respectively. This decrease was statistically significant compared to controls ($p<0.05$), indicating impaired endothelial hemostatic function in hypothyroid states.

Table 1. Endothelial Marker Comparison

Group	vWF (%)	ET-1 (pg/mL)	sICAM-1 (pg/mL)
Control	85.3 ± 2.36	2,1+0,07	6,1+0,29
Subclinical	61.3 ± 2.52	4,9+0,51	8,9+0,49
Manifest	59.1 ± 3.01	5,9+0,40	9,7+0,36

Conversely, ET-1, a potent vasoconstrictor and marker of endothelial activation, demonstrated a progressive increase across the groups. Mean ET-1 levels were lowest in euthyroid individuals (2.1 ± 0.07 pg/mL), significantly higher in subclinical hypothyroidism (4.9 ± 0.51 pg/mL), and reached the highest values in manifest hypothyroidism (5.9 ± 0.40 pg/mL). A similar trend was observed for sICAM-1, which increased from 6.1 ± 0.29 pg/mL in controls to 8.9 ± 0.49 pg/mL and 9.7 ± 0.36 pg/mL in subclinical and manifest hypothyroidism, respectively.

These findings reflect progressive endothelial inflammation and activation with worsening thyroid dysfunction.

Hemostatic parameters demonstrated distinct alterations across the study groups (Table 2). The prothrombin index (PI) was highest in the control group, with a mean value of 103.5 ± 3.4%, while a gradual reduction was observed in patients with subclinical hypothyroidism (92.8 ± 4.9%) and manifest hypothyroidism (90.2 ± 5.6%). This downward trend indicates a relative decrease in coagulation capacity associated with thyroid hormone deficiency.

Table 2. Hemostatic Marker Changes

Parameter	Control	Subclinical	Manifest
Prothrombin Index (%)	103.5 ± 3.4	92.8 ± 4.9	90.2 ± 5.6
APTT (sec)	26.0 ± 1.1	26.3 ± 1.3	29.9 ± 1.9
Fibrinogen (g/L)	3.4 ± 0.4	2.4 ± 0.5	2.2 ± 0.6
Platelets ($\times 10^9$/L)	249.6 ± 17.3	213.6 ± 18.1	207.5 ± 19.4

Activated partial thromboplastin time (APTT) showed a slight but progressive prolongation across the groups. In euthyroid individuals, the mean APTT was 26.0 ± 1.1 seconds, whereas it increased marginally in subclinical hypothyroidism (26.3 ± 1.3 seconds) and more noticeably in manifest hypothyroidism (29.9 ± 1.9 seconds). These findings suggest a tendency toward delayed intrinsic pathway activation in patients with more advanced thyroid dysfunction.

In contrast to coagulation times, plasma fibrinogen levels exhibited a significant decrease in hypothyroid patients. The highest fibrinogen concentration was recorded in the control group (3.4 ± 0.4 g/L), followed by lower levels in subclinical hypothyroidism (2.4 ± 0.5 g/L) and manifest hypothyroidism

(2.2 ± 0.6 g/L). This reduction may reflect impaired hepatic synthesis or altered inflammatory response associated with hypothyroidism.

Platelet counts also demonstrated a declining trend with worsening thyroid function. Mean platelet levels decreased from 249.6 ± 17.3 $\times 10^9$/L in the control group to 213.6 ± 18.1 $\times 10^9$/L in subclinical hypothyroidism and further to 207.5 ± 19.4 $\times 10^9$/L in manifest hypothyroidism. Although remaining within reference ranges, this pattern suggests a potential suppressive effect of thyroid hormone deficiency on thrombopoiesis.

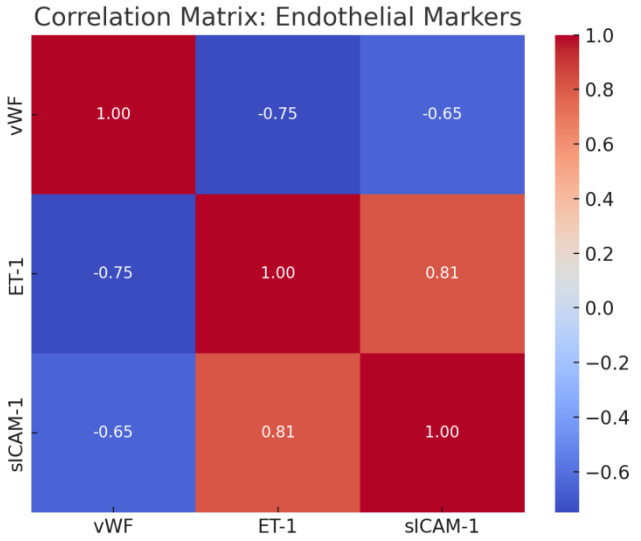

Figure 1. Correlation matrix: vWF, ET-1, sICAM-1

The correlation matrix presented highlights significant interrelationships between three key endothelial markers: von Willebrand factor (vWF), endothelin-1 (ET-1), and soluble intercellular adhesion molecule-1 (sICAM-1). These markers are commonly used to assess endothelial function and inflammation, both of which play pivotal roles in vascular health and disease. The findings from this matrix reveal several important insights into the dynamics of these markers in endothelial dysfunction.

1. *Negative Correlation Between vWF and ET-1:* The observed strong negative correlation between vWF and ET-1 (-0.75) suggests an inverse relationship between these two markers. vWF is a glycoprotein released by endothelial cells and platelets, typically in response to endothelial injury. ET-1, on the other hand, is a potent vasoconstrictor involved in regulating vascular tone and blood pressure. The inverse relationship between these markers may reflect a compensatory mechanism in response to endothelial damage or dysfunction. Increased vWF may indicate endothelial cell damage or activation, which could reduce ET-1 expression or vice versa. This inverse association could be explored further in the context of vascular diseases where endothelial activation and damage are prevalent.
2. *Negative Correlation Between vWF and sICAM-1:* A moderate negative correlation (-0.65) between vWF and sICAM-1 suggests that higher levels of vWF are associated with lower levels of sICAM-1. ICAM-1 is a cell adhesion molecule expressed on endothelial cells during inflammatory responses, facilitating leukocyte adhesion and migration. The negative correlation observed here could imply that in some conditions, increased vWF, as a marker of endothelial activation, might suppress or alter the expression of sICAM-1. This relationship warrants further investigation, as it may provide insights into how endothelial cell injury and inflammatory responses are coordinated in vascular pathophysiology.
3. *Positive Correlation Between ET-1 and sICAM-1:* A strong positive correlation (0.81) between ET-1 and sICAM-1 points to a potential concurrent activation of both pathways in endothelial dysfunction. Both ET-1 and sICAM-1 are involved in inflammatory and vascular remodeling processes. Elevated ET-1 levels lead to vasoconstriction and increased vascular resistance, while sICAM-1 facilitates leukocyte adhesion to the endothelium, a key step in inflammation. This positive correlation suggests that ET-1 might play a role in promoting inflammation, either directly or indirectly, through the upregulation of adhesion molecules like sICAM-1. Understanding the relationship between these two markers could provide insights into mechanisms of endothelial inflammation in diseases such as atherosclerosis or hypertension.

4. Conclusions

The present study demonstrates that autoimmune thyroiditis complicated by both subclinical and manifest hypothyroidism is accompanied by pronounced and interrelated disturbances in endothelial function and hemostatic balance. Our findings provide compelling evidence that endothelial dysfunction develops early in the course of autoimmune hypothyroidism and progressively worsens with increasing thyroid hormone deficiency.

A consistent reduction in von Willebrand factor levels alongside a marked elevation of endothelin-1 and sICAM-1 reflects a shift toward endothelial inflammation, vasoconstriction, and impaired endothelial hemostatic capacity. These endothelial alterations are paralleled by significant changes in the coagulation system, including a decrease in prothrombin index, prolongation of activated partial thromboplastin time, reduced fibrinogen concentration, and a decline in platelet count, indicating a complex dysregulation of both primary and secondary hemostasis.

Importantly, correlation analysis revealed strong and biologically meaningful associations between endothelial and coagulation markers, particularly the robust positive relationship between endothelin-1 and sICAM-1, underscoring the central role of endothelial activation and inflammation in

the pathogenesis of hemostatic disturbances in autoimmune hypothyroidism. The inverse correlations involving von Willebrand factor further suggest that endothelial injury and inflammatory activation occur through interconnected but partially divergent regulatory pathways.

Notably, similar directional changes were observed already at the subclinical stage of hypothyroidism, highlighting that vascular and hemostatic abnormalities precede overt clinical manifestations. This emphasizes the necessity for early identification of endothelial and coagulation dysfunction in patients with autoimmune thyroiditis, even before the development of manifest hypothyroidism.

In conclusion, autoimmune hypothyroidism should be regarded as a systemic disorder characterized by early endothelial dysfunction and hemostatic imbalance. Integrated assessment of endothelial markers and coagulation parameters may enhance cardiovascular risk stratification and support timely preventive strategies aimed at reducing thrombotic and vascular complications in patients with autoimmune thyroid disease.

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