Are there any changes in the coagulation parameters before and after the treatment in children with hypothyroidia?

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ABSTRACT

Objectives: Various coagulation and fibrinolysis disorders have been reported commonly in patients with thyroid dysfunction. Although it has been observed that bleeding time, protrombin time (PT), activated partial thromboplastin time (aPTT), platelet count, fibrinogen, D-dimer, Factor VIII, von Willebrand Factor have been investigated to examine the hemostatic profiles of patients with thyroid hormone disorders, studies on protein C, protein S, antithrombin 3 (ATIII), and homocysteine are rare.

Methods: The study included 25 healthy children without any hematological conditions and with normal renal and hepatic functions, as well as 25 children with hypothyroidism between the ages of 2 and 18 who were diagnosed in Pediatric Endocrinology outpatient clinics between March 2020 and June 2021, who had not yet received medical treatment, and whose TSH≥10 and fT4 levels were low for age (significant hypothyroidism), thyroid autoantibodies were negative. Complete blood counts, PT, aPTT, international normalized ratio (INR), fibrinogen, D-dimer, protein C, protein S, ATIII, homocysteine tests, and thyroid function tests were investigated. Age-appropriate L-thyroxine therapy was administered to hypothyroid patients for a period of 12 weeks. The differences between the coagulation parameters before and after treatment were compared once thyroid function tests had returned to normal ranges.

Results: Pretreatment PT, INR, D-dimer, hemoglobin, mean corpuscular volume (MCV) levels were found to be statistically similar between the control and study groups ($p > 0.05$). In hypothyroid patients, PTT, fibrinogen, protein C, protein S, ATIII levels were found to be statistically significantly lower than the control group before treatment ($p : 0.001$). While there was no significant change in D-dimer and INR levels of the patients in the study group before and after treatment ($p > 0.05$), there was a significant increase in PTT, fibrinogen, protein C, protein S, antithrombin 3, hemoglobin and MCV levels ($p : 0.001$). There was no statistically significant difference between the groups in terms of PT, INR, D-dimer, hemoglobin and MCV levels before treatment ($p > 0.05$).

Conclusions: There is a general decrease in anticoagulant proteins in children with hypothyroidism. It is important to closely monitor the coagulation system and especially the anticoagulant system. Thyroid hormones should be checked and hormone replacement

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therapy should be applied if necessary in patients who are followed up due to coagulation tendency.
Keywords: hypothyroidism, hemostasis, bleeding, thrombosis, childhood

Hypothyroidism is one of the most common endocrinopathies resulting from insufficiency or, rarely, ineffectiveness of thyroid hormone. It is seen in 2% of females and 0.2% of males. In children, it is seen at a rate of approximately 0.15%. Hypothyroidism can result from problems at any level of the hypothalamic-pituitary-thyroid axis. If hypothyroidism occurs in fetal life or birth, it is defined as 'congenital hypothyroidism', and if it presents in childhood and adolescence, it is defined as 'acquired hypothyroidism' [1].

In patients with thyroid dysfunction, changes are seen in both primary and secondary hemostasis and the fibrinolytic system. In individuals with hypothyroidism, prolonged activated partial thromboplastin time (aPTT) and prothrombin time (PT) as well as increased bleeding time and decreased factor VIII, von Willebrand Factor (vWF) and fibrinogen levels have been observed, but the mechanisms are still not fully clarified [2].

The most common coagulation disorder in hypothyroidism is primary hemostasis abnormalities due to vWF disease. Although the pathogenesis of acquired vWF disease due to hypothyroidism is still not fully elucidated, the most likely explanation for hypothyroidism is decreased vWF protein synthesis as a result of decreased thyroxine levels [3, 4].

There are also changes in secondary hemostasis. Studies have shown that the levels and activities of coagulation factors involved in secondary hemostasis in patients with overt hypothyroidism decreased, their fibrinolytic activities increased (low α-2 antiplasmin, TPA (tissue plasminogen activator), PAI-1 (plasminogen activator inhibitor), high D-dimer levels), and decreased fibrinolytic activity (high a-2 antiplasmin, TPA, PAI-1, low D-dimer levels) in patients with subclinical hypothyroidism [5, 6]. The common conclusion of the studies; In overt hypothyroidism, there is a bleeding tendency ranging from a mild mucocutaneous hemorrhage to bleeding after a serious trauma, depending on the decrease in coagulation [7].

Although various studies have reported that the coagulation and fibrinolytic system is impaired in patients with hypothyroidism, there are limited studies investigating protein C, protein S, homocysteine, antithrombin III (ATIII) and homocysteine levels in patients with hypothyroidism. For these reasons, our aim was to investigate the profile of coagulation/fibrinolytic activation parameters, including protein C, protein S, homocysteine, and AT III in children with hypothyroidism, in our prospective, case-control, cross-sectional study, and also to determine the changes that developed with treatment.

METHODS

This study is a prospective, cross-sectional, case-control study and was approved by the Ethics Committee of Health Sciences University Bursa Yüksek İhtisas Training and Research Hospital Clinical Research Ethics Committee dated 18.03.2020 and numbered 2011-KAEK-25.

Our study included twenty-five children and adolescent patients who applied to the Pediatric Endocrinology outpatient clinic between March 2020 and June 2021, had no additional hematological disease and a history of drug use, had normal renal and hepatic functions, had Tiroid stimülan hormon (TSH) ≥ 10 and low free T4 (fT4) levels for age (significant hypothyroidism), with negative thyroid autoantibodies and have not been treated yet. The physical examination (height, weight, body mass index, pubertal status, thyromegaly) data from the files of the patients were noted. Before the treatment, laboratory measurements of TSH, fT4, PT, INR, PTT, hemoglobin (Hgb), Mean corpuscular volume (MCV), fibrinogen, D-dimer, protein C, protein S, AT-III, homocysteine were performed.

Twenty-five healthy control groups of similar age, gender, and weight to patients with hypothyroidism were included in the study. Physical examination (height, weight, body mass index, pubertal status, thyromegaly) data of the control group were also noted. Laboratory measurements of serum TSH, fT4, PT, INR, PTT, Hgb, MCV, fibrinogen, D-dimer, protein C, protein S, AT-III, homocysteine were performed.

25 patients with hypothyroidism were given age-appropriate dose of L-thyroxine for 12 weeks. Changes in PT, INR, PTT, Hgb, MCV, fibrinogen, D-dimer, protein C, protein S, ATIII, homocysteine values were examined after thyroid function tests returned to normal values in patients who came for control after 12 weeks.

Thyroid function tests, complete blood counts and

PT, aPTT, INR, fibrinogen, D-dimer, protein C, protein S, AT-III, homocysteine tests were studied from 50 patients included in the study. Patients with hypothyroidism were given age-appropriate L-thyroxine therapy for 12 weeks. After thyroid function tests returned to normal values, changes in coagulation parameters before and after treatment were examined.

For TSH, T4, blood was collected in a vacuum gel tube with a yellow cap. After centrifuging at 3500 rpm for 15 minutes, measurements were made with the 'Architect plus I2000' device using the chemiluminescence method. For the hemogram, blood was taken into a purple capped tube with EDTA (ethylenediaminetetraacetic acid) and studied with the impedance method in the 'Mindray BC 6000' device without centrifugation. Blood is taken into a sodium citrate blue capped tube and centrifuged at 3000 rpm for 10 minutes, then PT, aPTT, fibrinogen by coagulometric method with 'Sysmex CS 5100' device, D-dimer by immunoassay method with 'Sysmex CS 5100' device, protein C, protein S, Measurements were made with the AT-III 'Sysmex CS 5100' chromogenic method. For homocysteine, the blood taken into heparinized green capped tube was centrifuged at 3000 rpm for 10 minutes and studied with the enzymatic method with the 'Roche Cobas c502' device.

Statistical analysis

IBM SPSS Statistics 22 program was used for statistical analysis. The suitability of the parameters to the normal distribution was evaluated by Kolmogorov-Smirnov and Shapiro Wilk tests. While evaluating the study data, in addition to descriptive statistical methods (mean, standard deviation, median, frequency), Student's t-test was used for the comparison of normally distributed parameters between two groups, and Mann Whitney U test was used for comparisons of non-normally distributed parameters between two groups. Paired Sample T test was used for in-group comparisons of normally distributed parameters, and Wilcoxon Sign Test was used for in-group comparisons of non-normally distributed parameters. Fisher's Exact Chi-Square test and Continuity (Yates) Correction were used to compare qualitative data. Significance was evaluated at the $p < 0.05$ level.

RESULTS

The median age of the patients was 13 (12.43 ± 3.56) years for the study group and 13.3 (13.11 ± 2.21) years for the control group. Eighteen (72%) of the study group were females, 7 (28%) were males, and 14 (56%) of the control group were females and 11 (44%) were males. There was no significant difference between the study and control groups in terms of age and gender ($p > 0.05$) (Table 1).

There was no statistically significant difference between the median body weights of the study and control groups (p : 0.403). There was no statistically significant difference between the standard deviation of body weights of the control and study groups (p : 0.823). There was no statistically significant difference between the mean height measurements of the control and study groups (p : 0.218). There was no statistically significant difference between the height

Table 1. Evaluation of groups in terms of demographic characteristics

	Hypothyroidism (n = 25)	Control (n = 25)	
	Mean ± SS (median)	Mean ± SS (median)	*p*
Age (years)	12.43 ± 3.56 (13)	13.11 ± 2.21 (13.3)	0.648
Weight (kg)	52.38 ±14.42 (53.2)	55.32 ± 7.51 (55)	0.403
Weight ss	0.97 ± 0.98 (1)	0.98 ± 0.92 (1.48)	0.823
Height (cm)	153.45 ± 15.72 (160)	157.33 ± 11.60 (162)	0.218
Height ss	0.57 ± 0.61 (0.59)	0.58 ± 0.52 (0.61)	0.861
BMI (kg/m$^{2)}$	20.16 ± 3.55 (19.7)	20.22 ± 2.63 (20)	0.943
BMI ss	0.27 ± 1.14 (0.5)	0.05 ± 0.73 (0.1)	0.421
Gender*			
Female	18 (%72)	14 (%56)	0.377
Male	7 (%28)	11 (%44)	
Thyromegaly n (%)	2 (%8)	0 (%0)	0.490

ss: standard deviation, BMI: Basal metabolic index * n(%)

Table 2. Evaluation of the groups in terms of study parameters before treatment

	Hypothyroidism	Control	
Before treatment	**Mean ± SS (median)**	**Mean ± SS (median)**	***p***
TSH (µIU/ml)	20.75 ± 16.93 (14.1)	2.93 ± 0.98 (2.9)	0.001
fT4 (ng/dl)	0.92 ± 0.15 (0.9)	1.1 ± 0.16 (1.1)	0.001
PT (sn)	12.04 ± 0.6 (11.9)	11.84 ± 0.64 (11.7)	0.280
aPTT (sn)	24.22 ± 1.68 (24)	25.88 ± 1.78 (26.1)	0.001
D-Dimer (mg/L)	0.25 ± 0.1 (0.2)	0.26 ± 0.11 (0.2)	0.418
Fibrinogen (mg/dl)	276.84 ± 57.69 (276)	368.96 ± 97.14 (355)	0.001
Hemoglobin (g/dl)	12.98 ± 0.8 (13)	13.35 ± 0.79 (13.3)	0.114
MCV (fL)	81.71 ± 2.48 (82.3)	82.56 ± 2.22 (82.3)	0.351
Protein C (%)	71.57 ± 14.42 (68.6)	116.6 ± 26.59 (111.7)	0.001
Protein S (%)	72.49 ± 11.86 (71)	125.65 ± 45.43 (116.1)	0.001
AT-III (%)	33.15 ± 2.16 (33.2)	37.19 ± 2.12 (37.2)	0.001

TSH: Thyroid stimulating hormone, fT4: Free T4, PT: Prothrombin time, aPTT: Active partial thromboplastin time,MCV: Mean corpuscular volume, AT-III: antithrombin III

standard deviation of the control and study groups (*p* : 0.861). There was no statistically significant difference between the body mass index of the study and control groups (*p*:0.943). There was no statistically significant difference between the body mass index standard deviation of the control and study groups (*p* : 0.421) (Table 1). There was no statistically significant difference between the groups in terms of the incidence of thyromegaly ($p > 0.490$). While thyromegaly was observed in two children (8%) in the hypothyroidism group, it was not observed in any of the children in the control group (Table 1).

The median TSH value of the hypothyroid group was 14.1 (20.75 ± 16.93) µIU/ml, and 2.9 (2.93 ± 0.98) µIU/ml in the control group. The TSH level of the hypothyroid group was found to be statistically significantly higher than the control group (*p* : 0.001) (Table 2). The median fT4 and aPTT levels of the hypothyroid group were found to be statistically significantly lower than the control group (*p* : 0.001) (Table 2). There was no statistically significant difference between the PT levels of the hypothyroid and control groups (*p* : 0.28) (Table 2). The median D-dimer value of the hypothyroid group was 0.2 (0.25 ± 0.1) mg/L, and 0.2 (0.26 ± 0.11) mg/L in the control group. There was no statistically significant difference in D-dimer levels of the two groups (*p* : 0.4) (Table 2). The median fibrinogen value of the hypothyroid group was 276 (276.84 ± 57.69) mg/dl, and 355 (368.96 ± 97.14) mg/dl in the control group. The fibrinogen level of the hypothyroid group was found to be statistically significantly lower than the control group (*p* : 0.001) (Table 2). The median protein C value in the hypothyroid group was 68.6% (71.57 ± 14.42), while it was 111.7% (116.6 ± 26.59) in the control group. When the levels of both groups were compared, it was found that the protein C level of the hypothyroid group was statistically significantly lower than the control group (*p* : 0.001) (Table 2). The median protein S value of the hypothyroid group was 71% (72.49 ± 11.86), while it was 116.1% (125.65 ± 45.43) in the control group. When the levels of both groups were compared, it was found that the protein S level of the hypothyroid group was statistically significantly lower than the control group (*p* : 0.001) (Table 2). The median ATIII value of the hypothyroid group was 33.2% (33.15 ± 2.16), while it was 37.2% (37.19 ± 2.12) for the control group. When the levels of both groups were compared, it was found that the ATIII level of the hypothyroid group was statistically significantly lower than the control group (*p* : 0.001) (Table 2). The median Hgb value of the hypothyroid group was 13 (12.98 ± 0.8) g/dl, while it was 13.3 (13.35 ± 0.79) g/dl for the control group. When the Hgb levels of both groups were compared, it was found that there was no statistically significant difference (*p* : 0.11) (Table 2). The median MCV value of the hypothyroid group was 82.3 (81.71 ± 2.48) fL, while it was 82.3 (82.56 ± 2.22) fL for the control group. When the MCV levels of both groups were compared, it was found that there was no statistically significant difference (p : 0.35) (Table 2).

The median TSH value of the patients was found to be 14.1 (20.75 ± 16.93) µIU/ml for pre-treatment and 2.5 (2.44 ± 1.15) µIU/ml for post-treatment. When

Table 3. Evaluation of post-treatment changes in hypothyroidism group compared to pre-treatment

	Hypothyroidism		
	Before treatment	After treatment	
	Mean ± SS (median)	Mean ± SS (median)	*p*
TSH (µIU/ml)	20.75 ± 16.93 (14.1)	2.44 ± 1.15 (2.5)	0.001
fT4 (ng/dl)	0.92 ± 0.15 (0.9)	1.1 ± 0.21 (1)	0.001
PT (sn)	12.04 ± 0.6 (11.9)	12.35 ± 0.69 (12.5)	0.022
aPTT (sn)	24.22 ± 1.68 (24)	25.07 ± 1.99 (25)	0.015
D-Dimer (mg/L)	0.25 ± 0.1 (0.2)	0.24 ± 0.09 (0.2)	0.704
Fibrinogen (mg/dl)	276.84 ± 57.69 (276)	312.6 ± 66.08 (310)	0.006
Hemoglobin (g/dl)	12.98 ± 0.8 (13)	13.44 ± 0.78 (13.5)	0.001
MCV (fL)	81.71 ± 2.48 (82.3)	83.53 ± 3.1 (84.3)	0.001
Homosistein(µmol/L)	8.59 ± 1.68 (8.5)	9.48 ± 1.91 (9.1)	0.001
Protein C (%)	71.57 ± 14.42 (68.6)	85.4 ± 12.96 (84.6)	0.001
Protein S (%)	72.49 ± 11.86 (71)	85.98 ± 14.53 (80)	0.001
AT-III (%)	33.15 ± 2.16 (33.2)	34.76 ± 2.08 (34.9)	0.001

TSH: Thyroid stimulating hormone, fT4: Free T4, PT: Prothrombin time, aPTT: Active partial thromboplastin time, MCV: mean corpuscular volume, AT-III: antithrombin III

the TSH levels of the patients were evaluated before and after the treatment, it was found that the TSH levels after L-thyroxine treatment were lower than before the treatment (*p* : 0.001) (Table 3). The median fT4 value of the patients was found to be 0.9 (0.92 ± 0.15) ng/dl for pre-treatment and 1 (1.1 ± 0.21) ng/dl for post-treatment. When the fT4 levels of the patients were evaluated before and after the treatment, it was found that the fT4 levels after L-thyroxine treatment were lower than before the treatment (*p* : 0.001) (Table 3). The median PT value of the patients was 11.9 (12.04 ± 0.6) seconds before treatment and 12.5 (12.35 ± 0.69) seconds after treatment. When the PT levels of the patients before and after the treatment were evaluated, it was found that the PT levels after L-thyroxine treatment were higher than before the treatment (*p* : 0.022) (Table 3). The median aPTT value of the patients was 24 (24.22 ± 1.68) seconds before treatment and 25 (25.07 ± 1.99) seconds after treatment. When the aPTT levels of the patients were evaluated before and after the treatment, it was found that the aPTT levels after L-thyroxine treatment were higher than the pretreatment period (*p* : 0.015) (Table 3). D-dimer median value of the patients was 0.2 (0.25 ± 0.1) mg/L for pre-treatment and 0.2 (0.24 ± 0.09) mg/L for post-treatment. When the D-dimer levels of the patients were evaluated before and after the treatment, no significant change was found in the D-dimer levels after L-thyroxine treatment (*p* : 0.07) (Table 3). The median fibrinogen value of the patients was found to be 276 (276.84 ± 57.69) mg/dl before treatment and 310 (312.6 ± 66.08) mg/dl after treatment. When the fibrinogen levels of the patients were evaluated before and after the treatment, it was found that the fibrinogen levels after L-thyroxine treatment were higher than before the treatment (p : 0.006) (Table 3). The median protein C value of the patients was determined as 68.6% (71.57±14.42) before treatment and 84.6% (85.4 ± 12.96) after treatment. When the protein C levels of the patients were evaluated before and after the treatment, it was found that the protein C levels after L-thyroxine treatment were higher than before the treatment (*p* : 0.001) (Table 3). The median protein S value of the patients was 71% (72.49 ± 11.86) before treatment and 80% (85.98 ± 14.53) after treatment. When the protein S levels of the patients were evaluated before and after the treatment, it was found that the protein S levels after L-thyroxine treatment were higher than before the treatment (*p* : 0.001) (Table 3). AT III median value of the patients was found as 33.2% (33.15 ± 2.16) for pre-treatment and 34.9% (34.76 ± 2.08) for post-treatment. When the AT III levels of the patients were evaluated before and after the treatment, it was found that the AT III levels after L-thyroxine treatment were higher than before the treatment (*p* : 0.001) (Table 3). The median Hgb value of the patients was found to be 13 (12.98 ± 0.8) g/dl before treatment and 13.5 (13.44 ± 0.78) g/

dl after treatment. When the Hgb levels of the patients were evaluated before and after the treatment, it was found that the Hgb levels after L-thyroxine treatment were higher than before the treatment (p : 0.001) (Table 3). The median MCV value of the patients was found to be 82.3 (81.71 ± 2.48) fL for pre-treatment and 84.3 (83.53 ± 3.1) fL for post-treatment. When the MCV levels of the patients were evaluated before and after the treatment, it was found that the MCV levels after L-thyroxine treatment were higher than before the treatment (p : 0.001) (Table 3). The median homocysteine value of the patients was 8.5 (8.59 ± 1.68) µmol/L for pre-treatment and 9.1 (9.48 ± 1.91) µmol/L for post-treatment. When the homocysteine levels of the patients were evaluated before and after the treatment, it was found that the homocysteine levels after L-thyroxine treatment were higher than before the treatment (p : 0.001) (Table 3).

DISCUSSION

Various coagulation and fibrinolysis disorders have been commonly reported in patients with thyroid dysfunction. However, what type of coagulation disorder the thyroid disorder causes, the type, and the mechanism behind these links are confusing and controversial.

The relationship between thyroid disorder and the hemostatic system was first described by Kaliebe in 1913 [8]. Kaliebe stated that cerebral thrombosis may be related in a patient with Graves' disease, and a later study by Squizzato *et al*. supported that there was a relationship between thyroid hormone and venous thrombosis [9]. Later studies focused on changes in the levels of coagulation factors in patients with thyroid disease, and it was shown that hyperthyroidism is mostly associated with prothrombotic changes. Although the exact mechanism is still unproven, the most recommended is increased vWF and FVIII levels [10, 11]. Bleeding tendencies with possible platelet dysfunction or autoimmune development have also been reported in hyperthyroidism [12, 13]. Individuals with reduced thyroxine levels had prolonged aPTT and PT, as well as increased bleeding time and decreased FVIII, vWF, and fibrinogen levels. However, reports from previous literature on hypothyroidism are still controversial.

Although there are many studies on bleeding time, PT, aPTT, platelet count, fibrinogen, D-dimer, FVIII, vWF to examine the hemostatic profiles of patients with thyroid hormone disorders, only a few studies have reported protein C, protein S, ATIII, and homocysteine. has been studied.

Gao *et al*. showed that aPTT, PT, and INR levels were prolonged in 53 adult patients with different degrees of hypothyroidism (14). Gullu *et al*. reported that PT and aPTT values were prolonged in their study in adult patients with overt hypothyroidism and low platelets [15]. It was observed that each of the above-mentioned parameters returned to normal values after levothyroxine treatment. Contrary to the studies mentioned, in our study, pre-treatment PT and aPTT levels of the hypothyroid group were found to be lower than those of the control group, while a significant increase was observed after the treatment. This can be explained by the fact that the platelet count was within the normal range in our patient group and only pediatric patients with overt hypothyroidism were included in the study.

Chadarevian *et al*. studied the fibrinolytic system in patients with overt hypothyroidism and observed a different fibrinolytic pattern depending on the severity of hypothyroidism [16, 17]. It was found that fibrinolytic activity was increased in patients with overt hypothyroidism (low α-2 antiplasmin, TPA, PAI-1, fibrinogen and high D-dimer levels), and decreased fibrinolytic activity in patients with subclinical hypothyroidism (high α-2 antiplasmin, TPA, PAI-1, low D-dimer levels) were observed. Ozcan *et al*. found that patients with various thyroid disorders, the fact that TFPI (tissue factor pathway inhibitor) level was found to be higher in patients with overt hypothyroidism compared to patients with subclinical hypothyroidism supports this study [18]. In overt hypothyroidism, mean fibrinogen levels were increased by 14.2% after treatment. They also confirmed that coagulation factor abnormalities were corrected upon levothyroxine replacement therapy.

In the study of Gürsoy *et al*. in patients with hypothyroidism, fibrinogen and D-dimer levels were found to be significantly higher than in controls, and the results after treatment were similar to those of patients with hypothyroidism [19]. Cantürk *et al*. were give LT4 treatment 35 patients with subclinical hypothyroidism for 6 months; it was determined that the fibrinogen levels of patients with subclinical hypothyroidism were higher than those of healthy individuals in the control group, but did not change despite LT4 treatment [20]. Çakal *et al*. reported that the fibrinogen levels of patients with overt hypothyroidism were higher than those in the control group [21]. In a study

by Erem C. it was reported that the fibrinogen levels of patients with subclinical hypothyroidism were not different from those in the control group [22]. In our study, after a 12-week follow-up with the overtly hypothyroid patients who received LT4 treatment, it was discovered that the pre-treatment fibrinogen level was statistically significantly lower than the control group (p : 0.001). However, the increase seen after the treatment compared to the pre-treatment fibrinogen level was statistically significant (p : 0.006). These findings also support studies conducted with other patients with overt hypothyroidism. However, there was no statistically significant change in D-dimer levels between the hypothyroid and control groups after treatment ($p > 0.05$). The common conclusion of these studies is that there is an increased bleeding tendency in overt hypothyroidism, while patients with subclinical hypothyroidism are predisposed to thrombosis.

Balci *et al*. located that MCV values were significantly higher in their study of patients with subclinical hypothyroidism when compared to the control group [23]. There was no statistically significant difference between the Hgb and MCV values of the hypothyroid patients and the control group in our study of patients with overt hypothyroidism. However, after treatment, the hypothyroid patient group's hemoglobin and MCV levels increased in a statistically significant way (p : 0.001).

Elevated homocysteine is a cause of thrombophilia that has been shown to cause both arterial and venous thrombosis [24]. High homocysteine levels can also be observed in cases where thyroid hormone levels are low [25]. However, the number of studies on the relationship between overt hypothyroidism and homocysteine is very limited. In 7 of 8 studies evaluating homocysteine levels in patients with subclinical hypothyroidism, it was found that homocysteine levels of patients with subclinical hypothyroidism were not different from the control groups. Sengul *et al*. found that homocysteine levels increased in patients with subclinical hypothyroidism and that existing homocysteine levels decreased with LT4 treatment [26].

Jackal *et al*. found that homocysteine levels in 20 patients with overt hypothyroidism were higher in 15 patients with subclinical hypothyroidism than in healthy individuals in the control group, and homocysteine levels decreased with LT4 treatment [21]. In our study, the increase in homocysteine levels of hypothyroid patients who were given LT4 treatment after 12 weeks of follow-up was found to be statistically significant (p : 0.001). Although our result is consistent with the results of the studies conducted by Şengül and Çakal, our patient group consists of individuals with overt hypothyroidism. The results of other studies show that individuals with subclinical hypothyroidism have a tendency to hypercoagulability, while the results of our study support the results of other studies in the literature showing the tendency of patients with overt hypothyroidism to bleed.

It is known that a decrease in the activity of anticoagulant proteins AT III, protein C, and protein S may lead to thromboembolic events. These proteins have been evaluated within the scope of the relationship between hypothyroidism and hemostasis in previous studies. Erem *et al*. found in their study on 20 hypothyroid patients that protein C and protein S activities were similar between the overt hypothyroid and control groups, whereas AT-III activity was higher in the patient group [22]. Müller *et al*. found that ATIII, protein C, and protein S activities were similar between the patient and control groups in another study they conducted with 42 female patients with subclinical hypothyroidism [27]. Kilic *et al*. found that ATIII, protein C, and protein S activities were lower in the hypothyroid patient group compared to the control group in their study with 54 overt hypothyroid patients and 55 healthy children [28]. In our study, ATIII, protein C, and protein S activities were lower than the healthy controls, and the increase in these values after treatment was statistically significant (p : 0.001). Although our study is consistent with the results of Kılıç *et al*., it supports other studies showing that patients with hypothyroidism have a high tendency to thrombosis.

Limitations of the Study

The small number of patients and the need for studies with larger series are one of the limiting factors of the study. In addition, the fact that we could not study parameters such as PAI and TFPI, which are more sensitive in terms of fibrinolytic system, is another limiting factor.

CONCLUSION

In conclusion, in the light of all these findings, it shows that there is a general decrease in anticoagulant proteins in children with hypothyroidism and the risk of thrombosis may be related to many factors. For this reason, we would like to emphasize that patients followed up with a diagnosis of hypothyroidism should be followed up for thrombosis. However, the

improvement of this condition with treatment reveals the importance of early diagnosis and treatment of hypothyroidism. In addition, thyroid hormones should be checked in patients followed up for thrombosis, and thyroid hormone replacement therapy should be administered if necessary. In addition, studies with larger series are needed to investigate the effects of hypothyroidism on the coagulation system.

Authors' Contribution

Study Conception: EGK,; Study Design: ÖK,; Supervision: HÇ,; Materials: ÖK,; Data Collection and/or Processing: HÇ,; Statistical Analysis and/or Data Interpretation: HÇ,; Literature Review: DG,; Manuscript Preparation: DG, HÇ and Critical Review: EGK.

Conflict of interest

The authors declare that they have no conflicts of interests.

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