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# A relationship between subclinical hypothyroidism and hematologic parameters in patients with Down Syndrome



Down Sendromlu hastalarda subklinik hipotiroidizm ve hematolojik parametreler arasındaki ilişki

ID Abdullah Yazar<sup>a</sup>, ID Alaaddin Yorulmaz<sup>b</sup>, ID Esra Ture<sup>a</sup>, ID Fatih Akin<sup>a</sup>, ID Ahmet Sert<sup>b</sup><sup>a</sup> Necmettin Erbakan University, School of Medicine, Department of Pediatrics, Konya, Turkey<sup>b</sup> Selcuk University, School of Medicine, Department of Pediatrics, Konya, Turkey**ABSTRACT**

**Introduction:** Down syndrome (DS) which is defined as trisomy 21 is the most common chromosomal defect characterized by mental retardation, hypotonia, dysmorphic facial features, and other distinctive phenotypic characteristics. The prevalence of thyroid disorders in DS is 3% and is significantly higher than in the normal population. In this study we aimed to investigate hematologic parameters of children with DS who had and hadn't subclinical hypothyroidism and compare them with healthy controls.

**Methods:** This study included 184 patients who were followed up with genetically diagnosed DS. Complete blood count, levels of serum electrolytes, glucose, urea, liver function tests, thyroid function tests were reviewed.

**Results:** 102 (55.4%) of the patients with DS were male and 82 (44.6%) were female. Mean age was  $6.2 \pm 4.0$  years. Control group was constituted of outpatient healthy children. White blood cell count, hemoglobin, hematocrit, and neutrophil counts were found to be significantly lower in patients with DS. Platelet count and plateletcrit levels were found to be higher and platelet distribution width was lower in patients with DS than in the control group.

**Conclusion:** We found significant differences among hematological parameters in patients with DS. Subclinical hypothyroidism influences red blood cell distribution width, platelet count and MPV. Knowing the incidence and severity of hematologic abnormalities in patients with DS will be beneficial during follow-up in clinical practice.

**Keywords:** child, down syndrome, hematological parameters, hypothyroidism

**ÖZ**

**Giriş:** Trizomi 21 olarak tanımlanan Down sendromu (DS) mental retardasyon, hipotoni, dismorfik yüz özellikleri ve diğer ayırt edici fenotipik özellikleri ile karakterize en sık görülen kromozomal defektir. DS'de görülen tiroid bozukluğu prevalansı % 3'dür ve normal popülasyona göre anlamlı derecede yüksektir. Bu çalışmada, subklinik hipotiroidisi olan ve olmayan DS'li çocukların hematolojik parametrelerini araştırmayı ve bunları sağlıklı kontrollerle karşılaştırmayı amaçladık.

**Yöntem:** Çalışmaya genetik olarak tanısı konan ve takip edilen DS'li 184 hasta dahil edildi. Hastaların tam kan sayımı, serum elektrolit seviyeleri, glikoz, üre, karaciğer fonksiyon testleri ve tiroid fonksiyon testleri gözden geçirildi.

**Bulgular:** DS'li hastaların 102'si (% 55,4) erkek, 82'si (% 44,6) kadındı. Yaş ortalaması  $6,2 \pm 4$  yıl idi. Kontrol grubu, polikliniğimize başvuran sağlıklı çocuklardan oluşturuldu. DS'li hastalarda kan sayımı, hemoglobin, hematokrit ve nötrofil sayıları anlamlı olarak düşük bulundu. Yine DS'li hastalarda kontrol grubuna göre trombosit sayısı ve trombosit düzeyleri daha yüksek bulunurken trombosit dağılım genişliği daha düşük bulundu.

**Sonuç:** DS'li hastalarda hematolojik parametreler arasında anlamlı farklar bulduk. Subklinik hipotiroidizm, eritrosit dağılım genişliğini, trombosit sayısını ve MPV'yi etkiler. DS'li hastalarda hematolojik anormalliklerin sıklığını ve şiddetini bilmek, klinik uygulamada takip sırasında yararlı olacaktır.

**Anahtar Kelimeler:** Çocuk, Down sendromu, hematolojik parametreler, hipotiroidizm

**Submission:** May 09, 2018**Acceptance:** Aug 17, 2018**E-mail:** [drabdullahyazar@hotmail.com](mailto:drabdullahyazar@hotmail.com)

**Correspondence:** Abdullah Yazar, MD. Necmettin Erbakan University, School of Medicine, Department of Pediatrics, 42080 Konya-TURKEY

## Introduction

Down syndrome (DS) which is defined as trisomy 21 is the most common chromosomal defect characterized by mental retardation, hypotonia, dysmorphic facial features, and other distinctive phenotypic characteristics. The incidence of DS is approximately 1 in every 733 live births. While 95% of the cases have 3 copies of chromosome 21, 4% have translocation at chromosome 21 and 1% are mosaics. Advanced age (>35) of mother is attributed as the major cause of trisomy 21 [1].

Hematological disorders are frequently seen in DS. It is known that various abnormalities are observed in all three hematopoietic cell lines. Leukemia-like transient proliferative disorder, increased leukemia incidence, neutrophilia, thrombocytopenia, polycythemia, thrombocytosis and anemia are common haematological abnormalities seen in the course of DS [2].

The prevalence of thyroid disorders in DS is 3% and is significantly higher than the normal population. The most common thyroid disease in this syndrome is subclinical hypothyroidism (SCH). The biochemical condition of elevated TSH and normal triiodothyronine (T3) and thyroxine (T4) levels is defined as SCH. Hypothyroidism or thyroid dysfunction can be congenital or acquired in patients with DS. Therefore, patients with DS should be followed up periodically for thyroid functions since birth [3-5].

While thyroid hormones regulate the metabolism and proliferation of blood cells, they have an important role in hematopoiesis. Hypothyroidism is one of the most common diseases of the endocrine system that affects all systems including the hematopoietic system. It has been shown that three main components of hematopoiesis; erythropoiesis, lymphopoiesis and myelopoiesis, are affected by hypothyroidism [6].

To the best of our knowledge there is no study investigating the association of thyroid disorders and hematologic parameters in patients with DS. In this study we aimed to investigate hematologic parameters of children with DS who had and hadn't subclinical hypothyroidism (SCH) and compare them with healthy controls.

## Methods

This study included 184 patients who were followed up with genetically diagnosed DS and SCH in pediatrics departments of Necmettin Erbakan University Meram Medical Faculty and Selcuk University Medical Faculty between January 2011 and July 2017. Ethical approval of the study was taken from the ethics committee of Meram Medical Faculty of Necmettin Erbakan University. Patients' data were reviewed retrospectively and demographic characteristics recorded. Complete blood count, levels of serum electrolytes, glucose, urea, liver function tests, thyroid function tests were reviewed. The white blood cell count (WBC), absolute neutrophil count (ANC), absolute lymphocyte count (ALC), neutrophil to lymphocyte ratio (NLR), red blood cell distribution width (RDW), platelet count and MPV, Platelet distribution width (PDW) and Plateletcrit (PCT) values were obtained from the hemogram results. Patients who had high TSH (TSH > 4 IU / L) and normal free T4 levels were diagnosed as SCH.

The study population was classified into three groups; Group 1: DS patients without SCH; Group 2: DS patients with SCH; Group 3: control group. Patients with gastrointestinal system, cardiovascular system involvement or who had other diseases (i.e. diabetes mellitus, epilepsy, asthma, hypertension and immunodeficiency) and patients using any drug were not included in the study. Control group was constituted of outpatient healthy children with normal physical examination, who did not have any chronic illness or sign of any infection and undergone blood analyses for other reasons (i.e. routine check-up, poor appetite, abdominal pain).

## Statistical analysis

Statistical methods of descriptive data were shown as mean±standard deviation. The Kolmogorov-Smirnov and Shapiro-Wilk tests were applied to check the distribution of parameters. While parametric data were analyzed using student's t-test, nonparametric were analyzed with chi-square and Mann-Whitney U test. Kruskal-Wallis test was used to compare groups. Spearman correlation test was applied for the correlation analysis of the parameters. Results were considered as significant if  $p < 0.05$ . SPSS 21.0 (SPSS Inc., Chicago, IL, USA) packet computer program was used for statistical analysis of data.

## Results

102 (55.4%) of the patients were male and 82 (44.6%) were female and the mean age was  $6.2 \pm 4.0$  years. The control group was consisted of 36 males (43.9%) and 46 females (56.1%) with a mean age of  $6.9 \pm 3.5$  years. Demographic and laboratory characteristics of patients are given in Table 1. When patients with DS were compared with control group; WBC, ANC, hemoglobin and hematocrit were found to be significantly lower in patients with Down syndrome ( $p$  values: 0.039, 0.004, 0.042, 0.014, respectively). However, no statistically significant difference was found between the two groups in terms of NLR, RDW and ALC. The comparison of platelet indices revealed that platelet count and PCT levels were found to be higher and PDW ratio was lower in patients with DS than in the control group, and these differences were statistically significant. However, there was no statistically significant difference in terms of MPV values.

**Table 1.** Demographic and laboratory characteristics of patients and the control group

	Patients with DS (n=184)	Control group (n=82)	P value
Female/male	82/102	36/46	>0.05
Mean age (year)	6.28±4.02	6.98±3.56	>0.05
WBC (/mm <sup>3</sup> )	7113±1973	7601±1669	<b>0.039</b>
ANC (/mm <sup>3</sup> )	3277±1739	3628±1287	<b>0.004</b>
ALC (/mm <sup>3</sup> )	3048±1205	3130±1060	>0.05
NLR	1.39±1.37	1.32±0.73	>0.05
Hb (gr/dl)	12.51±1.97	13.06±0.90	<b>0.042</b>
Hct (%)	37.11±5.31	38.70±2.41	<b>0.014</b>
RDW (%)	15.09±3.04	14.70±1.06	>0.05
<b>Platelet indices</b>			
PLT (x10 <sup>3</sup> /uL)	355±133	305±640	<b>0.001</b>
MPV (fL)	8.20±1.88	8.24±0.76	>0.05
PCT (%)	0.83±1.22	0.23±0.09	<b>0.001</b>
PDW (%)	15.97±9.29	16.41±2.30	<b>0.001</b>

Data as means± SD, DS: Down Syndrom, WBC: White blood cell count, ALC: Absolute lymphocyte count, ANC: Absolute neutrophil count, Hb: Hemoglobin, MPV: Mean platelet volume, NLR: Neutrophil-to-lymphocyte ratio, RDW: Red cell distribution width, PLT: Thrombocyte count PCT: Plateletcrit PDW: Platelet distribution width, p value: p value of comparison between controls and DS

**Table 2.** Comparison of demographic and laboratory characteristics of patients according to study groups

	DS patients with SCH (n=57)	DS patients without SCH (n=127)	Control group (n=82)	P <sup>1</sup> value	P <sup>2</sup> value	P <sup>3</sup> value
Female/male	29/28	53/74	36/46	>0.05	>0.05	>0.05
Mean age (year)	7.04±3.52	5.93±4.20	6.98±3.56	>0.05	>0.05	>0.05
WBC (/mm <sup>3</sup> )	7021±1702	7154±2088	7601±1669	>0.05	>0.05	>0.05
ANC (/mm <sup>3</sup> )	3175±1526	3323±1831	3628±1287	>0.05	<b>0.016</b>	<b>0.01</b>
ALC (/mm <sup>3</sup> )	3061±1116	3042±1247	3130±1060	>0.05	>0.05	>0.05
NLR	1.34±1.45	1.41±1.37	1.32±0.73	>0.05	>0.05	>0.05
Hb (gr/dl)	12.93±1.61	12.33±2.09	13.06±0.90	>0.05	>0.05	<b>0.008</b>
Hct (%)	38.33±4.31	36.56±5.64	38.70±2.41	>0.05	>0.05	<b>0.001</b>
RDW (%)	14.37±2.32	15.42±3.27	14.70±1.06	<b>0.034</b>	>0.05	>0.05
<b>Platelet indices</b>						
PLT(x10 <sup>3</sup> /uL)	387±159	340±117	305±64	<b>0.034</b>	<b>0.001</b>	<b>0.017</b>
MPV (fL)	7.67±2.09	8.44±1.74	8.24±0.76	<b>0.009</b>	>0.05	>0.05
PCT (%)	0.82±1.42	0.84±1.12	0.23±0.09	>0.05	<b>0.003</b>	<b>0.001</b>
PDW (%)	16.77±9.98	15.61±8.98	16.41±2.30	>0.05	>0.05	>0.05

Data as means± SD, DS: Down Syndrom, SCH: Subclinical hypothyroidism, WBC: White blood cell count, ALC: Absolute lymphocyte count, ANC: Absolute neutrophil count, Hb: Hemoglobin, MPV: Mean platelet volume, NLR: Neutrophil-to-lymphocyte ratio, RDW: Red cell distribution width, PLT: Thrombocyte count, PCT: Plateletcrit, PDW: Platelet distribution width, P<sup>1</sup>: p value comparison between DS patients with SCH and DS patients without SCH, P<sup>2</sup>: p value comparison between DS patients with SCH and controls, P<sup>3</sup>: p value comparison between DS patients without SCH and controls.

There was no statistically significant difference between three groups in terms of gender. Comparison of demographic and laboratory characteristics of the three groups are given in Table 2. WBC, ALC and NLR levels showed no statistically significant difference when 3 groups were compared. ANC was statistically lower in both groups of DS than in the control group, however, no statistically significant difference was found between DS patients with SCH and without. When three groups were compared for PDW, hemoglobin and hematocrit levels, these were significantly lower in DS patients without SCH than both other groups. While RDW levels were significantly lower in DS patients with SCH than other groups, platelet count was significantly higher DS with SCH. There was a statistically significant difference between all the three groups when MPV levels were compared. PCT levels were significantly lower in the control group than others.

**Discussion**

In this study, we showed that hematological parameters were significantly affected in patients with DS when compared with control group. While WBC, PDW, hemoglobin, hematocrit, and neutrophil counts were found to be significantly lower in patients with DS, PLT and PCT levels were higher when compared with the control group. We found that ANC and PLT levels were affected more excessively in DS patients with SCH.

Thyroid hormones regulate the metabolism of all the cells in the human body, thus they play a major role in the metabolism of blood cells. Thyroid gland has important effects on erythropoiesis by the induction of erythropoietin secretion and the proliferation of erythroid progenitors at the same time [7]. Additionally hypothyroidism causes hypoplasia of all myeloid cell roots including anemia with different severity, thrombocytopenia, leukopenia, and even rare cases of pancytopenia [8]. Hypothyroidism also has negative effects on other blood indices including mean corpuscular volume (MCV), mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, hemoglobine, RDW, MPV. All these dysfunctions usually return to normal after treatment of the thyroid disorder [9]. The difference of hematological parameters between DS patients on thyroid hormone therapy and the groups suggests that this difference may be due to other mechanisms besides hypothyroidism.

The incidence of various hematologic abnormalities associated with DS has not been clearly defined. In the study of Miller et al. [10] which evaluated 81 infants with DS, hematological evaluation was done in 61 infants, and 33 had a normal hematological status, and 28 (46%) had at least one abnormality, including hematocrit, white cell count, or platelet count. Hord et al. reported that 66% of 25 newborns with DS had thrombocytopenia in their study [11].

The largest study evaluating hematologic abnormalities in newborns with DS in the United States involved 158 cases and neutrophilia (80%), thrombocytopenia (66%) and polycythemia (34%) were reported to be the most common hematological abnormalities. Thrombocytosis, anemia and neutropenia were rarely seen [3]. In the study performed by DW Kim et al, thrombocytopenia (35.1%) was the most common hematological abnormality in East Asian Newborns. Other common haematological abnormalities were neutropenia (16.2%), leukocytosis (10.8%) and polycythemia (10.8%). They showed that hematological findings recovered spontaneously in those patients [12]. In our study WBC levels was found to be lower in DS patients than in the control group. Leukocytosis was present in 22 and leukopenia in 5 patients. We think that SCH influences blood WBC levels. Also in our study, thrombocytosis was found in 20.6%, neutropenia in 10.32%, thrombocytopenia in 4.34% and neutrophilia in 2.17% of our patients. No patient had polycythemia. The first fact that our rates differ from other studies is that our patients were older and might have recovered spontaneously. The second, some of our patients had SCH, suggesting that SCH has an effect on hematological parameters. We think that the low ANC in our study are due to the suppressive effect of SCH on the bone marrow.

Weinberger and Oleinick reported that 15% of newborns with DS had polycythemia [13]. In subsequent studies, the prevalence of polycythemia in patients with DS was reported to be between 8% and 64% [10,11,14]. Widness and colleagues found that newborns with DS had elevated concentrations of erythropoietin in the umbilical cord blood and suggested that this caused polycythemia [15]. In our study, hemoglobin and hematocrit levels were found to be lower in patients with DS than in the control group. Hemoglobin and hematocrit levels were found to be lower in DS patients without SCH than in DS patients with SCH and the control group. Polycythemia was not detected in any of our patients.

RDW is part of a standard full blood count that measures the change in size and volume of the RBC. RDW is used in conjunction with MCV to determine the cause of anemia [16] There are no studies about RDW in patients with DS. Additionally, there are rare studies on the relationship between RDW and hypothyroidism. In a study of patients with thyroid dysfunction, Yu HM et al. showed that SCH and RDW were associated significantly when patients with SCH and the control group were compared [17]. RDW and serum TSH levels were reported to be associated significantly in another study [18]. In our study, we found that RDW was significantly higher in patients with DS compared to the control group. However, DS patients without SCH were found to have a higher incidence than DS patients with SCH. This suggests that DS has an impact on RDW.

In a large case series study, thrombocytopenia was identified as one of the most common hematologic abnormalities in about two thirds of infants with DS during the first week of life [12]. The etiology of thrombocytopenia seen in DS is not fully understood. In a study evaluating thrombopoietin and platelet counts in newborn infants with DS, thrombocytopenia rate was 58% and the average TPO levels were reported to be not different from the control group of newborns without DS [18]. However, in the study of Kivivuori et al. that thrombocyte counts of neonates with DS were prospectively monitored, indicated that thrombocytopenia was usually short-term and then displaced by thrombocytosis [19]. In a study conducted by Kater et al. In 28 of 49 patients with congenital cardiac defects had DS. Thrombocyte counts of patients with DS reached to 100,000 / mm<sup>3</sup> on postoperative 6th day, whereas patients without DS reached on same day of cardiac surgery. It was hypothesed that the cause of thrombocytopenia seen in patients with DS may be due to a short-term decrease of thrombopoietin synthesis after cardiac surgery [20]. In our study, we found that the mean platelet count of DS patients was higher than the control group. DS patients with SCH had higher platelet count than DS patients without SCH and the control group. We have also found that SCH causes an increase in platelet levels in patients with DS. While thrombocytopenia (<150000 / mm<sup>3</sup>) was detected in 8 patients and 38 patients had thrombocytosis (> 450000 / mm<sup>3</sup>).

Platelet indices include MPV, PDW, and PCT. Platelets are closely related to hemostasis, inflammation, immune cell activation, tissue regeneration and other physiological and pathological processes [21]. Young thrombocytes released from the bone marrow due to inflammation reach larger sizes. Inflammatory mediators such as chemokines, cytokines, and procoagulant molecules are secreted by activated platelets. MPV, which reflects the platelet size and the speed of platelet production in the bone marrow, is a frequently used parameter to assess platelet activation and function [22]. MPV reflects platelet size and activity and is used as a measure of platelet dysfunction. Larger thrombocytes are thought to be more active and tend to be aggregated, thus leading to endothelial dysfunction. Larger and functionally more reactive platelets increase the tendency to thrombosis [23]. There are many studies in the literature on the role of MPV in different systemic diseases including cerebrovascular disorders and cardiovascular disorders. In addition, MPV has been reported to increase in patients with vascular risk factors such as diabetes, hypertension, hypercholesterolemia, smoking, and subclinical hypothyroidism [23,24]. Yılmaz and colleagues found no association between hypothyroidism and MPV in their study [25]. In our study, we did not detect changes in MPV levels. Mean MPV levels in DS patients were not different from control group. However DS patients with SCH had lower MPV levels than DS patients without SCH and the control group.

PDW is another platelet activation marker. PDW increases in patients with thrombocytopenia due to an increase of young platelets by bone marrow response. PDW indicates platelet activation more specifically than MPV in the activation process [26]. There are studies in the literature that examine the relation of PDW with various diseases. PDW values were found to be significant in distinguishing patients with ITP and aplastic anemia. PDW was found to be increased in ITP. Platelet production increases due to platelet destruction in ITP and anisocytosis occurs. However, PDW was found to be low due to inadequate platelet production in the aplastic anemia [27]. In vasocclusive crisis of patients with sickle cell anemia, PDW was found to be increased. This is mainly due to increased coagulation and increased megakaryocyte volume [28]. In patients Kawasaki disease, PDW and MPV were found to be lower than healthy control group. This low level of MPV and PDW is attributed to the use of large active platelets in vascular events and to the erroneous production of thrombopoietin in inflammatory event [29]. In our study we found that mean PDW levels were lower in DS patients than in the control group. DS patients without SCH had lower PDW levels than DS patients with SCH and the control group.

PCT is the percentage of platelets in total blood volume. PCT is measured from platelet count and MPV. Below 0.1% of PCT is indicative of platelet transfusion indications and is indicative of a greater risk of bleeding than thrombocyte counts in thrombocytopenic patients. It may be useful in diseases where the platelet count is low but the diameter is large. Although platelet counts are low, platelet functions may be provided with large platelets, so it may be more useful to look at PCT level instead of platelet count [30]. Plateletcrit was found to be less than 1% in patients undergoing transfusion due to bleeding after cardiopulmonary bypass. This suggests that PCT is as important as the platelet count in thrombocytopenic patients [31]. It was determined that there was a significant relationship between platelet count and PCT suggesting that platelet count and platelet count are two important factors for hemostasis [32]. PCT levels were higher in DS patients than in the control group. In DS patients both with SCH and without hypothyroidism, it was found to be higher than the control group. We think that hypothyroidism affects thrombocyte indices in patients with DS.

### **Limitations**

As our study was a retrospective study, it didn't cover our prospective observations. Since patients with hypothyroidism are obliged to receive replacement therapy, we were not able to exclude these patients from the study. Additionally, thyroid hormone therapy might have affected hematological parameters.

### **Conclusion**

We found significant differences among hematological parameters including WBC, neutrophil count, hemoglobin, hematocrit, platelet count, PDW and PCT values in patients with DS. The results indicated that SCH influences RDW, platelet count and MPV. Knowing the incidence and severity of hematologic abnormalities in DS patients will be beneficial for physicians in clinical practice.

**Conflict of interest:** None

**Financial disclosure:** None

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