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Original Article

Endocrinological evaluation of children and adolescents with hereditary spherocytosis: a cross-sectional retrospective multicenter study

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ABSTRACT

Background: Hereditary spherocytosis (HS) is one of the most common causes of hereditary hemolytic anemia among erythrocyte membrane disorders. Endocrine complications are commonly seen in chronic anemias, such as β thalassemia major and sickle cell anemia; these include growth retardation, thyroid dysfunction, hypoparathyroidism, carbohydrate metabolism disorders, bone metabolism disorders, vitamin D3 deficiency/ insufficiency, delayed puberty, and adrenal insufficiency. However, studies on endocrine problems in HS are limited.

Methods: This study evaluated 40 children with HS. Data included clinical features, anthropometric parameters, pubertal stages, and laboratory evaluation for growth, thyroid, parathyroid, carbohydrate metabolism, bone metabolism, gonadal, and adrenal functions.

Results: The cohort comprised 24 females and 16 males, with a median age of 10.0 years. Two patients (5%) had severe HS requiring regular transfusions and chelation therapy. Short stature was observed in 5%, low body mass index in 10%, obesity in 5%, and subclinical hypothyroidism in 5% of patients. Vitamin D insufficiency or deficiency was noted in 55% of the cohort. Patients with vitamin D insufficiency or deficiency were significantly older than those with sufficient levels ($p = 0.043$). Impaired fasting glucose was found in 32.5%. Neither diabetes mellitus nor adrenal insufficiency was detected. Ferritin levels were elevated in 62.5% of patients, but showed no significant association with anthropometric parameters. None of the patients had signs of delayed puberty.

Conclusions: Endocrine complications, such as vitamin D insufficiency/ deficiency, short stature, and impaired fasting glucose, necessitate regular monitoring and early intervention in HS. Older age was associated with vitamin D insufficiency and deficiency in this population, underscoring the importance of age-specific surveillance. Further research with larger cohorts is required to validate these findings and optimize monitoring strategies for pediatric HS patients.

Keywords: hereditary spherocytosis, pediatric, endocrine, hemolytic anemia, complication

INTRODUCTION

Hereditary spherocytosis (HS) is the most common cause of hereditary hemolytic anemia among erythrocyte membrane disorders, with an incidence of approximately 1:2000. It typically follows an autosomal dominant inheritance, although recessive and de novo cases have also been reported.[1-3] The majority of HS cases are due

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to defects in erythrocyte membrane proteins such as spectrin or ankyrin, although defects in band three and protein 4.2 can also occur.[4] Clinical severity is variable, ranging from asymptomatic cases to severe hemolytic anemia, and common findings include anemia, jaundice, and splenomegaly.[5,6] Diagnosis is based on clinical and laboratory findings such as spherocytes in peripheral blood smear, elevated mean corpuscular hemoglobin concentration (MCHC), and a positive osmotic fragility (OF) test.[7] Quantitative examination of erythrocyte membrane proteins may be performed in atypical cases or when the diagnosis is uncertain.[8] Management of HS includes supportive care and, when necessary, splenectomy.[9] In addition to hematologic manifestations, chronic hemolysis in HS may result in complications such as bilirubin gallstones, aplastic crises, and, rarely, iron overload due to repeated transfusions or increased iron absorption.[9] Severe cases may present with hemosiderosis due to repeated transfusions, skeletal abnormalities from bone marrow expansion, growth retardation, and secondary endocrinopathies.[10] However, most patients compensate for hemolysis and remain asymptomatic, apart from fatigue and pallor.[11]

Endocrine complications are commonly seen in other chronic anemias like β-Thalassemia Major and Sickle Cell Anemia, which include growth retardation, thyroid dysfunction, hypoparathyroidism, carbohydrate metabolism disorders, bone metabolism disorders, vitamin D3 deficiency/insufficiency, delayed puberty, and adrenal insufficiency. However, studies on endocrine problems in HS are limited.[12,13]

Transfusion-related iron overload is a major concern in HS and other chronic anemias, affecting various organs, including the liver, heart, and endocrine system.[14] In addition to transfusional iron overload, non-transfusional iron overload due to hemochromatosis gene heterozygosity has also been documented in HS patients.[15,16] Lifelong chronic hemolysis and erythropoietic activity may increase iron absorption in patients with mild HS, suggesting that even mild HS is not entirely benign, and patients with mild HS should be monitored for iron overload. In addition, chronic hemolysis and ineffective erythropoiesis lead to increased tissue oxygen demand and chronic hypoxia, which, together with the persistent inflammatory state induced by ongoing hemolysis, may contribute to dysfunction of endocrine organs and dysregulation of the hypothalamic–pituitary axis.[10,11,16]

Although endocrine dysfunctions are expected to be relatively rare in HS patients, they can cause significant problems. To prevent these complications, regular monitoring of anemia severity, growth, and development is essential. Ferritin levels should be checked periodically, and iron chelation therapy should be initiated when necessary.[9]

We hypothesized that children and adolescents with HS may experience endocrine complications, and this study aimed to perform a comprehensive endocrine evaluation to better characterize their frequency and nature, highlighting the importance of early recognition and follow-up.

MATERIAL AND METHODS

This cross-sectional, retrospective study included 40 patients diagnosed with HS between 2004 and 2020 at the Departments of Pediatric Hematology in two tertiary referral centers: Aydın Adnan Menderes University Faculty of Medicine and Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital. The study was approved by the Non-Interventional Clinical Research Ethics Committee of Aydın Adnan Menderes University Faculty of Medicine (date: 21.03.2023, number: 2024-63)

HS diagnosis was based on a positive family history, MCHC > 35 g/dL, spherocytes in peripheral blood smears, reticulocytosis, elevated serum total and indirect bilirubin levels, a negative direct Coombs test, and a positive OF test. Other potential causes of hemolytic anemia, such as pyruvate kinase (PK) and glucose-6-phosphate dehydrogenase (G6PD) deficiencies, were excluded. Data collected from the hospital records included birth dates, age at diagnosis, presenting complaints, height, weight, body mass index (BMI), pubertal stages, number of erythrocyte transfusions, and chelation therapy. Puberty was defined by testicular volume ≥4 ml in boys and breast development at Tanner stage 2 in girls. Pubertal delay was defined as the absence of pubertal signs after age 14 in boys and 13 in girls.[17] Anthropometric parameters (height, weight, and BMI) were compared between prepubertal and pubertal patients to evaluate whether pubertal status could influence the presentation or detection of endocrine abnormalities. Laboratory tests performed after an eight-hour fast included glucose, ferritin, cortisol, parathormone (PTH), adrenocorticotropic hormone (ACTH), calcium (Ca), phosphorus (P), alkaline phosphatase (ALP), free thyroxine (fT4), thyroid-stimulating hormone (TSH), glycosylated hemoglobin (HbA1c), and insulin-like growth factor-1

(IGF-1). Pubertal patients were also tested for luteinizing hormone (LH), estradiol (E2)/testosterone (T), and follicle-stimulating hormone (FSH). Glucose, Ca, P, and ALP were measured using spectrophotometry, ferritin, cortisol, ACTH, PTH, fT4, TSH, IGF-1, FSH, LH, E2, and T were measured using Electrochemiluminescence Immunoassay (ECLIA), and 25-OH vitamin D3 and HbA1c were measured using High-Performance Liquid Chromatography (HPLC).

Definitions

Growth[18,19]

- Short stature: Height <-2 SDS for age and gender,
- Obesity: BMI >2 SDS for age and gender

Carbohydrate metabolism[20]

- Impaired fasting glucose: Fasting glucose 100-125 mg/dL,
- Diabetes mellitus: Fasting glucose ≥126 mg/dL, HbA1c ≥6.5%,

Bone metabolism[21]

- Vitamin D insufficiency: Serum 25-OH vitamin D3 12-20 ng/mL,
- Vitamin D deficiency: Serum 25-OH vitamin D3 <12 ng/mL,
- Asymptomatic elevated parathormone: PTH >65 pg/mL with normal Ca, P, and ALP levels

Thyroid[22]

- Overt hypothyroidism: Free T4 <0.8 ng/dL (Reference range for free T4: 0.8–1.48 ng/dL),
- Subclinical hypothyroidism: TSH> 5 mIU/mL with normal free T4,

Adrenal[23]

- Primary adrenal insufficiency: Basal cortisol <3 µg/dL and ACTH >100 pg/mL.

Statistical analysis

Statistical analyses were performed using IBM SPSS Version 21 (Statistical Package for the Social Sciences for Windows, Armonk, NY, IBM Corp.). The behavior of the quantitative variables was specified using measures of centralization and variance: Mean ± SD. Fisher's Exact (where sample size was low) and Chi-square test were used to determine differences in proportions or relationships between categorical variables. For a categorical variable, percentages and population proportions were compared using a One-Sample chi-square test. Non-parametric methods were used to compare group means when the assumptions of normality and homogeneity of variance were not met. Specifically, the Mann–Whitney U test was applied for comparisons between two independent groups (e.g., ferritin levels, vitamin D status, and impaired fasting glucose) with respect to anthropometric and laboratory parameters. For each case, the statistical significance was established at $p<0.05$.

RESULTS

Of the 40 patients included in the study, 24 (60%) were female and 16 (40%) were male. The median age of the patients was 10 years (1.47-17.66 years). Two patients (5%) had severe HS requiring regular blood transfusions, and one of these patients had undergone splenectomy. Both patients were receiving oral chelation therapy (deferasirox). Despite the splenectomy performed 13 years ago, the need for regular monthly transfusions continued. The average height, weight, and BMI SDS of the patients were -0.15 ± 0.67, -0.26 ± 0.4, and -0.34 ± 0.91, respectively. Seventeen patients (42.5%) were pubertal. Four patients (10%) had a BMI below -2 SDS, and two patients (5%) had short stature and obesity. Those with severe HS growth retardation were not observed in one, while the other, who had undergone splenectomy, later developed persistent short stature and required growth hormone treatment six years after the procedure, with subsequent improvement in height SDS. None of the patients showed signs of delayed puberty. There were no significant differences in height, weight, and BMI SDS between prepubertal and pubertal patients (p=1, p=0.565, and p=0.624, respectively) (Table 1).

Ferritin levels were elevated in 62.5% of the patients with a mean level of 129.88 ± 160.5 ng/mL. High ferritin levels were observed in one of two patients with short stature, two of three with low weight, and in three of four with low BMI. Ferritin levels were not significantly associated with short height, low weight, or low BMI (p=0.44, p=0.23, and p=0.31, respectively). No significant difference in ferritin levels was found between prepubertal and pubertal patients (p=0.652) (Table 1).

IGF-1 levels were normal for age in all patients. The average basal cortisol level was 9.10 ± 3.93 µg/dL, and the average ACTH level was 20.57 ± 10.1 pg/mL. No patient had a basal cortisol level <5 µg/dL. The average 25 (OH)

Table 1. Mean height, weight, and BMI SDS values of the patients

	All patients	Prepubertal	Pubertal	p*
n	40	23	17	
Height SDS	-0.15 ± 0.67	-0.04 ± 0	-0.31 ± 0.71	1
Weight SDS	-0.26 ± 0.4	-0.23 ± 0.62	-0.33 ± 0.4	0.565
BMI SDS	-0.34 ± 0.91	-0.38 ± 1.075	-0.21 ± 0.759	0.624
Ferritin (ng/mL)	129.88 ± 160.5	144.4 ± 198.59	110.24 ± 88.6	0.652

BMI, body mass index; SDS, standard deviation score.
* Comparison between prepubertal and pubertal patients.

vitamin D3 level was 19.91 ± 10.32 ng/mL. Eighteen (45%) patients had normal 25 (OH) vitamin D3 levels, 13 (32.5%) had insufficiency, and 9 (22.5%) had deficiency. All patients had normal Ca, P, and ALP values. Seven patients (17.5%) had elevated parathormone levels, and 42.9% of these had low 25 (OH) vitamin D3 levels. No patients had symptoms of rickets. Subclinical hypothyroidism was found in two patients (5.0%), but no cases with goiter or overt hypothyroidism were detected. Thirteen (32.5%) patients had impaired fasting glucose, whereas 27 (67.5%) patients had normal fasting blood glucose levels. None of the patients had hypoglycemia or diabetes mellitus (DM). The mean hemoglobin A1c was 4.2 ± 1.02%. In two (5%) patients, the HbA1c level was found to be <2%. The fasting blood glucose levels of these individuals were within normal ranges, and they did not belong to the transfusion-dependent severe HS patient group. No patient had an HbA1c level > 6.5% (Table 2).

No significant differences were found in subclinical hypothyroidism rates, fasting blood glucose levels, or 25(OH) vitamin D3 levels (insufficiency/deficiency) between prepubertal and pubertal patients (p=0.388, p=0.301, p=0.499, p=0.986, respectively) (Table 3).

In post hoc analyses, additional comparisons were performed to assess whether vitamin D3 insufficiency or deficiency and impaired fasting glucose were associated with clinical parameters. These two conditions were selected for subgroup analysis due to adequate sample sizes. Patients with vitamin D3 insufficiency or deficiency were older than those with sufficient vitamin D3 levels (121.5 vs. 68.5 months, p = 0.043). Hemoglobin levels at diagnosis did not differ significantly between these groups (8.10 vs. 9.65 g/dL, p = 0.34). Similarly, patients with impaired fasting glucose did not show significant differences in age (111 vs. 121 months, p = 0.644) or diagnostic hemoglobin levels (8.2 vs. 8.9 g/dL, p = 0.84) compared to those without impaired fasting glucose (Table 4).

Table 2. Laboratory characteristics of children with hereditary spherocytosis

	All patients, n=40	Prepubertal, n=23	Pubertal, n=17	p
Glucose (mg/dL)	91.9 ± 11.55	91.48 ± 13.85	92.47 ± 7.78	0.775
HbA1c (%)	4.2 ± 1.02	4.21 ± 1.05	4.19 ± 1.0	0.923
Calcium (mg/dL)	9.61 ± 0.39	9.63 ± 0.39	9.58 ± 0.4	0.697
Phosphorus (mg/dL)	4.9 ± 0.8	4.99 ± 0.9	4.79 ± 0.63	0.691
Alkaline phosphatase (U/L)	167.1 ± 50.16	169.87 ± 48.72	163.35 ± 53.33	0.69
Parathyroid hormone (pg/mL)	41.52 ± 25.57	37.49 ± 19.32	46.98 ± 32.02	0.292
25(OH) vitamin D3 (ng/mL)	19.91 ± 10.32	21.77 ± 9.71	17.39 ± 10.87	0.151
fT4 (ng/dL)	1.04 ± 0.1	1.06 ± 0.09	1.03 ± 0.12	0.428
TSH (mIU/mL)	2.14 ± 1.14	2.32 ± 1.27	1.9 ± 0.91	0.389
Cortisol (µg/dL)	9.10 ± 3.93	9.49 ± 4.19	8.16 ± 3.52	0.298
Adrenocorticotropic Hormone (ACTH) (pg/mL)	20.57 ± 10.1	21.24 ± 10.97	19.67 ± 9.03	0.805

mg/dL, milligrams per deciliter; HbA1c, glycated hemoglobin; U/L, units per liter; pg/mL, picograms per milliliter; 25(OH) vitamin D3, 25-hydroxyvitamin D3; ng/mL, nanograms per milliliter; fT4, free thyroxine; ng/dL, nanograms per deciliter; TSH, thyroid-stimulating hormone; mIU/mL, milli-international units per milliliter; µg/dL, micrograms per deciliter.

Table 3. Frequency of endocrinological problems in hereditary spherocytosis

	Patient (n)	%
Short stature	2	5
Low BMI	4	10
Obesity	2	5
Overt hypothyroidism	0	0
Subclinical hypothyroidism	2	5
Vitamin D insufficiency	13	32.5
Vitamin D deficiency	9	22.5
Asymptomatic elevated parathyroid hormone levels	7	17.5
Impaired fasting glucose	13	32.5
Diabetes mellitus	0	0
Adrenal insufficiency	0	0
Hypoparathyroidism	0	0

BMI: Body mass index

DISCUSSION

Despite being less frequent than other complications, endocrine problems in HS can lead to significant health issues. The strength of our study lies in being the first to conduct a comprehensive endocrinological evaluation of HS in childhood; however, the absence of a healthy control group limits our ability to determine the extent to which these findings differ from the general pediatric population. Another limitation of our study is the relatively small sample size, which may have reduced the statistical power of subgroup analyses. In addition, fructosamine levels, which may provide a more accurate assessment of glucose metabolism in hemolytic anemias, were not measured. This study focused on endocrinological problems, which revealed short stature (5%), low BMI (10%), obesity (5%), subclinical hypothyroidism (5%), vitamin D deficiency and insufficiency (55%), asymptomatic elevated parathyroid hormone levels (17.5%), and impaired fasting glucose (32.5%) (Table 3).

In our cohort, patients with vitamin D insufficiency or deficiency were significantly older than those with sufficient levels. This finding may suggest that vitamin D deficiency becomes more apparent over time due to the cumulative effects of chronic hemolysis, reduced sunlight exposure, or nutritional factors. Alternatively, older age itself may act as an independent risk factor, emphasizing the need for age-specific surveillance in pediatric patients with HS. However, no significant difference was observed in hemoglobin levels at diagnosis — a parameter commonly used to reflect disease severity in HS — between groups with and without vitamin D deficiency.

Similarly, patients with impaired fasting glucose did not show significant differences in age or diagnostic hemoglobin levels compared to those without impaired fasting glucose. These results suggest that the development of certain endocrine abnormalities in HS may not be directly related to disease severity or age alone. Further studies with larger patient populations are warranted to better elucidate the underlying risk factors and mechanisms contributing to endocrine dysfunction in this setting.

Research has not shown a significant gender difference for HS; in our study, girls were more common.[24,25] Severe cases of HS with life-threatening anemia requiring frequent transfusions constitute about 3–5% of cases.[11] Consistent with previous research, 5% of the patients in our study had severe HS requiring frequent blood transfusions.

Among the 40 individuals diagnosed with HS in our study, 5% were underweight, 5% were short, and 10% had a BMI <-2 SDS. None of these patients with growth retardation had undergone splenectomy. On the other hand, among severe patients, growth retardation was not observed in one, while the other, who had undergone splenectomy, later developed it. The patient in the severe HS group who had a splenectomy 13 years prior was started on growth hormone treatment seven years ago due to short stature. After a five-year follow-up, the height SDS value was -0.74 SDS. Growth and developmental delay have been reported

Table 4. Comparison of clinical parameters according to 25(OH)D3 status and fasting glucose levels

Characteristic	25(OH)D3 Insufficiency/ Deficiency (n=22)	Sufficient 25(OH) D3 (n=18)	p value	Impaired Fasting Glucose (n=13)	Normal Fasting Glucose (n=27)	p value
Median age (months, IQR)	121.5 (107–179)	68.5 (68–191)	0.043	111 (78–191)	121 (83–133)	0.644
Median hemoglobin at diagnosis (g/dL, IQR)	8.1 (6.5–10.1)	9.65 (7.2–10.6)	0.34	8.2 (7.2–10.6)	8.9 (6.8–10.4)	0.84

IQR, interquartile range; 25(OH)D3, 25-hydroxyvitamin D3; g/dL, grams per deciliter

in severe HS cases, but there is no clear information on its prevalence.[26] Chronic anemia and long-standing tissue hypoxia are the most significant underlying mechanisms. The relatively mild symptoms in HS patients compared to other chronic hemolytic anemias and the resulting delay in seeking healthcare services contribute to these mechanisms and exacerbate growth retardation.[27] Hemoglobin levels, in particular, increase significantly after splenectomy, positively affecting growth.[6] Therefore, suboptimal growth in children with HS is often considered a relative indication for splenectomy.[28] The growth retardation observed in our subjects did not involve those with severe HS, as the mild or moderate HS group likely sought medical attention later, undergoing a chronic anemic process before experiencing symptoms. Additionally, there were only two patients with severe HS. One of these two patients had a splenectomy, but required growth hormone treatment six years later due to short stature. Several previous investigations present differing findings: In a 2017 study by Das et al.[29] involving 82 HS patients, 32% of the children were underweight, and 26% were short. They reported that while splenectomy did not reverse growth retardation, anemia significantly improved over an average follow-up of 4.5 years post-splenectomy. Another study by Bader-Meunier et al.[30] reported that five prepubertal adolescents with HS showed a height increase of approximately two SDS along growth charts after surgery.

Pubertal delay may result from hemosiderosis due to repeated transfusions in individuals with severe HS who do not undergo splenectomy.[31] Of the patients in our study, 42.5% had reached puberty, and none of the patients experienced delayed puberty.

Extramedullary hematopoiesis (EMH), the abnormal formation of hematopoietic tissue outside of the bone marrow, has been reported in HS. Calhoun et al.[32] reported the first case of an EMH-related tumor in the right adrenal gland of a nine-year-old male with HS in 2001. Demir et al.[33] reported a 13-year-old girl with HS who had an adrenal gland ganglioneuroma in 2012. Although EMH is a rare cause of adrenal mass, it should be considered in patients with congenital hemolytic anemia such as HS.[32] We did not find any evidence of adrenal insufficiency in any of the patients in our study.

While numerous studies have examined bone metabolism in hemolytic anemias, few have focused on HS.[34] Schündeln et al.[35] conducted a study with 45 hemolytic anemia patients and found that the average 25-OH vitamin D level was 19.1 ± 5.7 (12.8–30.2) ng/mL in HS patient and 9.3 ± 7.4 (1-25.2) ng/mL in sickle cell anemia patients. The 25-OH vitamin D level was below 20 ng/mL in 86.7% of patients with sickle cell anemia and 61.5% of patients with HS. In a different study, the average 25-OH vitamin D level was significantly lower in children with HS than that of healthy controls (17.74 ± 7.76 ng/mL and 24.04 ± 11.70 ng/mL, respectively).[34] In our study, the average 25 (OH) vitamin D3 level was 19.91 ± 10.32 ng/mL, and 55% suboptimal vitamin D levels. These findings indicate the importance of monitoring the vitamin D status of patients with HS.

Excessive iron load can lead to thyroid dysfunction, particularly in the first decade of life, along with growth retardation. Most data on transfusional iron overload relates to thalassemia major. Studies indicate that thyroid dysfunction often presents as overt hypothyroidism without goiter and with negative autoantibodies.[36] Masuno et al. reported a case of primary hypothyroidism in HS in 1982.[37] In our study, overt hypothyroidism was not observed, but subclinical hypothyroidism was present in 5% of the patients. Although treatment indications for subclinical hypothyroidism are unclear, we believe HS patients should be regularly monitored for thyroid dysfunction.

Hypoparathyroidism, a late complication of iron overload, is frequently seen in the second decade of life. It results from the suppression of parathyroid secretion caused by bone resorption due to increased erythropoiesis secondary to chronic anemia or from iron accumulation in the parathyroid glands.[36] Secondary hyperparathyroidism can also occur due to low 25-OH vitamin D levels. In a study conducted by Schündeln et al.[35] in 2014, comparing 17 homozygous sickle cell anemia patients with 14 HS patients, they reported that approximately half of the patients with severe vitamin D deficiency developed secondary hyperparathyroidism. In our study, while none of the patients were found to have hypoparathyroidism, 17.5% had hyperparathyroidism. In parallel with the study by Schündeln et al.,[35] vitamin D deficiency was observed in 42.9% of the patients with hyperparathyroidism.

In hereditary hemolytic anemias, causing iron overload, impaired glucose tolerance, and diabetes mellitus are mostly seen in the second decade of life. Iron accumulation in the pancreas leads to defective microcirculation, resulting in impaired oxygen supply and, consequently, insulin deficiency. Most studies on this subject are related to thalassemia major.[36] In hemolytic anemias, metabolic control of glucose should be done through plasma or serum fructosamine levels. Hemolysis reduces overall glucose uptake and HbA1c, leading to falsely low values. Therefore,

HbA1c should be interpreted with caution in the presence of hemolysis.[38] In our study, 32.5% of the patients had impaired fasting glucose. No patient had diabetes mellitus.

CONCLUSION

We believe that the results of this study, which investigated endocrine complications in children diagnosed with hereditary spherocytosis and reported low vitamin D status, short stature, subclinical hypothyroidism, and impaired fasting glucose, need to be validated by studies conducted with larger patient populations and appropriate control groups. Notably, vitamin D insufficiency/deficiency was found to be associated with older age, which may suggest a potential age-related vulnerability in this group. Additionally, similar to other hemolytic anemias, HS patients should be closely monitored for endocrine problems.

Ethical approval

This study has been approved by the Aydın Adnan Menderes University Ethics Committee (approval date 21.03.2023, number 2024-63). Written informed consent was obtained from the participants.

Author contribution

The authors declare contribution to the paper as follows: Study conception and design: AA, YZA, ŞT; data collection: ŞT, YO, SOA, BÖ; analysis and interpretation of results: ŞT, AA, SG; draft manuscript preparation: ŞT, SG. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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