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Original Articles

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Original Article

Self-esteem and depressive symptom levels in adolescents with Type 1 Diabetes

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ABSTRACT

Objective: This study aimed to examine self-esteem and depressive symptom levels in adolescents with Type 1 Diabetes, shedding light on the impact of living with a chronic illness on adolescent mental health.

Material and Methods: The study population consisted of patients followed in the Pediatric Endocrinology Outpatient Clinics of three Educational and Research Hospitals located on the Anatolian side of Istanbul between September 2023 and November 2023. The sample consisted of 202 adolescents aged 13-18 who met the inclusion criteria and agreed to participate in the study. Data were collected using the "Personal Information Form," "Coopersmith Self-Esteem Inventory (CSEI)," and the "Adolescent Quick Depressive Symptom Inventory (AQ-DSI-17-SF)." Data were analyzed using the SPSS for Windows 26.0 software package.

Results: The results of this study revealed that the self-esteem levels of adolescents with Type 1 Diabetes were moderate (26.06±7.9), while their depressive symptom levels were mild (10.73±3.5). There was a negative correlation between HbA1c levels and CSEI scores (r = -0.228; p=0.001), and a statistically significant positive correlation between HbA1c levels and AQ-DSI-17-SF scores (r = 0.401; p=0.001).

Conclusion: The findings indicate that the HbA1c levels of the adolescents who participated in the study were generally within the target range, reflecting a successful approach to disease management. In this context, it can be suggested that adolescents who manage their disease effectively are also able to maintain their psychological well-being in a healthier manner.

Keywords: Adolescent, depression, nursing, self-esteem, Type 1 Diabetes mellitus

INTRODUCTION

Type 1 Diabetes is one of the most frequently encountered chronic diseases during adolescence. In Türkiye, it is estimated that approximately 17.000 to 18.000 adolescents under the age of 18 have Type 1 Diabetes (1). According to the 2022 IDF Diabetes Atlas, Türkiye ranks 13th globally in terms of the number of adolescents under 20 with Type 1 Diabetes. By 2035, Türkiye is expected to be among the top 10 countries in this ranking (2).

Receiving a diagnosis of Type 1 Diabetes, which requires lifelong adherence to diet and treatment protocols, may cause adolescents who are already going through a turbulent period to encounter various psychosocial problems (3). It has been reported that adolescents with Type 1 Diabetes experience a decrease in self-esteem due to feeling different from their peers and the widespread perception that individuals with chronic illnesses are not "normal," leading to reduced adaptation to the disease (4). The limitations they experience in peer relationships and interactions due to treatment programs may result in feelings of worthlessness and hopelessness (5-7). Adolescents with Type 1 Diabetes have reported experiencing stress because the disease is incurable, feeling restricted by the need for a diet, and feeling embarrassed due to frequent fingerstick blood glucose measurements and insulin injections. They also expressed that their social lives and interpersonal relationships were negatively affected due to being excluded from social activities because of diabetes (8).

It has been observed that adolescents with Type 1 Diabetes feel different from their peers and are unable to integrate into their

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groups, leading to a negative impact on their self-esteem (9). As self-esteem decreases, depression emerges as the most common psychiatric problem among adolescents with Type 1 Diabetes (7). Depression, which often accompanies Type 1 Diabetes, affects adolescents' adaptation to the disease, response to treatment, quality of life, and diabetes control and progression (10).

During adolescence, ongoing monitoring is required to ensure proper adaptation to Type 1 Diabetes and successful disease management (7). Since Type 1 Diabetes affects adolescents both psychologically, physiologically, and socially, nurses must be aware of these challenges (11). Early identification of self-esteem problems and depressive symptoms will help reduce potential complications (12). Managing Type 1 Diabetes, which begins in childhood, during adolescence is critical for ensuring better disease adaptation and control in adulthood (13). Educational interventions provided to adolescents during this period aim to facilitate disease adaptation, improve quality of life and self-esteem, and reduce depressive symptoms (6, 12).

Literature suggests that low self-esteem is a significant risk factor for the development of depression. The vulnerability model of depression posits that low self-esteem predisposes individuals to depression, contributing to its development through both interpersonal processes (e.g., excessive reassurance seeking, negative feedback seeking, social avoidance) and intrapersonal processes (e.g., focusing on negative aspects of the self) (14). Research has confirmed the relationship between self-esteem and depression, indicating that implicit self-esteem can predict future depressive symptoms (15). Furthermore, it has been reported that low self-esteem is not only a predictor of depression but may also have indirect effects on depression through a lack of psychological flexibility (16,17).

In adolescents with Type 1 Diabetes, the stress of managing a chronic illness, fear of exclusion, and concerns about body image can result in both decreased self-esteem and increased depressive symptoms. The interaction between these two psychological constructs is crucial in understanding mental health risks in this population.

Given the importance of self-esteem development for all adolescents, particularly in the context of chronic illness, it is evident that a more detailed examination of these issues and the prevention of potential psychiatric problems is crucial. Thus, this study aims to contribute to the field by providing a more in-depth examination of the risks faced by adolescents with Type 1 Diabetes.

Research Questions:

- What are the depressive symptom levels of adolescents with Type 1 Diabetes?
- What are the self-esteem levels of adolescents with Type 1 Diabetes?
- Is there a relationship between depressive symptoms and self-esteem levels in adolescents with Type 1 Diabetes?
- Are there differences in self-esteem and depressive symptom levels based on specific descriptive characteristics?

MATERIALS and METHODS

This study was designed as a descriptive and cross-sectional research aimed at determining the self-esteem and depressive symptom levels of adolescents with Type 1 Diabetes.

Population and Sample

The study population consisted of 260 adolescents with a diagnosis of Type 1 Diabetes who had been followed for at least one year at the pediatric endocrinology outpatient clinics of the University of Health Sciences Zeynep Kâmil Women and Children's Diseases Training and Research Hospital, the University of Health Sciences Ümraniye Training and Research Hospital, and the Marmara University Pendik Training and Research Hospital, Department of Pediatric Endocrinology, all located on the Anatolian side of Istanbul, between August 1 and August 31, 2023. A sample size calculation based on a known population size with 95% confidence level and 5% margin of error determined a required minimum of 155 participants. Considering possible data loss, a 30% increase was applied, resulting in 202 participants. A stratified sampling method, one of the probabilistic sampling techniques, was used in the study. Stratification was based on the hospitals where the study was conducted. For this purpose, the "k" constant was first calculated, and based on this constant, the number of adolescents with Type 1 Diabetes to be included from each unit was determined.

Inclusion Criteria:

- Willingness to participate in the study
- Being between the ages of 13 and 18
- Patients diagnosed with Type 1 Diabetes by a relevant specialist physician and followed for at least one year (criteria such as antibody status and type of diabetes [MODY, Type 2] were taken into consideration, and only children diagnosed with Type 1 DM were included).
- Being literate
- No cognitive or communication impairments
- No psychiatric diagnosis (Adolescents with psychiatric diagnoses were excluded from the study to reduce confounding factors that could directly impact depression scores. This exclusion also allowed the study to focus on subclinical symptoms in a general adolescent diabetic population.)

Data Collection and Instruments

The researcher collected the data for the study. Adolescents and their families who visited the outpatient clinics were interviewed,

and those who voluntarily agreed to participate were included in the study. During the data collection phase, an environment where adolescents could feel comfortable was provided, and interviews lasting approximately 20-25 minutes were conducted at a time that would not interfere with diagnosis or treatment.

Data Collection Tools:

Personal Information Form: The personal information form includes 17 questions regarding the participants' gender, age, education, diabetes history, daily insulin doses, diabetes education status, diet, and daily activities (7, 8, 11).

Coopersmith Self-Esteem Inventory (CSEI): The Coopersmith Self-Esteem Inventory measures individuals' attitudes toward themselves and can be applied to children and adults (18). The inventory consists of 58 items and five subscales, each scoring separately. The subscales include: 1) General self-esteem (26 items), 2) Academic self-esteem (8 items), 3) Social self-esteem (8 items), 4) Family and home self-esteem (8 items), and 5) Lie scale (8 items). The lie scale is included to measure defensive attitudes rather than self-esteem, and its scores are not added to the total score. Participants answer the items with "yes" or "no," and scores of 1 or 2 are given for answers indicating high self-esteem, while other answers receive a score of 0. After removing the eight lie items, the maximum possible score for self-esteem is 50 or 100 (if doubled). The Cronbach's alpha value of the scale was found to be 0.745 in previous studies, and 0.71 in this study.

Adolescent Quick Depressive Symptom Inventory (AQ-DSI-17-SF): The Adolescent Quick Depressive Symptom Inventory (AQ-DSI-17) consists of 17 items and is used to assess the presence and severity of depressive symptoms over the past seven days. The inventory addresses nine significant categories of major depressive disorder, with each item scored between 0 and 3, yielding a total score between 0 and 27. The highest score among items addressing the same depressive criterion is considered valid. The first four items assess sleep patterns; items 5 and 6 evaluate sad and irritable mood; items 7 to 10 determine appetite; item 11 evaluates concentration and decision-making; item 12 addresses self-perception; item 13 assesses suicidal thoughts, item 14 addresses general interest, item 15 evaluates energy levels, and items 16 and 17 assess restlessness and agitation. The Turkish validity and reliability of the AQ-DSI-17-SF were confirmed by Mergen et al. (19), with a Cronbach's alpha value of 0.81. In this study, the Cronbach's alpha value was 0.77.

Statistical analysis

The study data were analyzed using the IBM SPSS for Windows, version 26.0 software package (IBM Corp., Armonk, N.Y., USA). Skewness and kurtosis values were examined to assess normal distribution, while Cronbach's alpha reliability coefficient was used to evaluate the reliability of the scales. Descriptive statistics such as counts, means, minimum, maximum, standard deviations and percentages were presented. The t-test was used to compare normally distributed variables, while the Mann-Whitney U test was used to compare non-normally distributed variables. Correlations between continuous variables were calculated using Pearson's correlation coefficient since the distribution of the data was approximately normal based on skewness and kurtosis values. In addition, multiple regression analysis was conducted to evaluate the effects of the independent variables on the dependent variable. In the regression analysis, the dependent variable was the level of depressive symptoms (AQ-DSI-17-SF total score). Independent variables included HbA1c level, duration of diabetes diagnosis, and age. These variables were selected based on their clinical relevance reported in the literature and the correlations observed in the present study, as they are known to be associated with psychosocial outcomes in adolescents with type 1 diabetes. It was assumed that a result with a p-value less than 0.050 was statistically significant.

RESULTS

EEvaluation was made of 202 adolescents, the majority of whom were male (52.5%). The proportion of individuals diagnosed with diabetes 1-2 years ago was 61.9%, and 94.6% of the participants reported receiving diabetes education. The percentage of those using insulin 3-4 times daily was 74.3%, while 69.8% of participants indicated they frequently measure their blood sugar levels. The proportion of participants using

Table I: Descriptive information about the participants

Gender*	
Female	96 (47.5)
Male	106 (52.5)
Duration of diabetes diagnosis*	
1-2 years ago	125 (61.9)
3-4 years ago	77 (38.1)
Diabetes education*	
Yes	191 (94.6)
No	11 (5.4)
Daily insulin use*	
1-2 times	52 (25.7)
3-4 times	150 (74.3)
Frequency of daily blood glucose measurement*	
Sometimes	61 (30.2)
Frequently	141 (69.8)
Using an insulin pump*	
Yes	77 (38.1)
No	125 (61.9)
Family history of depression*	
Yes	15 (7.5)
No	187 (92.5)
Age†	15.5±1.4 (12-18)
HbA1c†	6.6±.4 (5-7)

:** *n(%),* **†:** *mean±SD (min-max),* ***HbA1c: *hemoglobin A1c*

Tablo II: Symptoms of diabetes

	n(%)
Dry mouth	
No	130 (64.4)
Yes	72 (35.6)
Fatigue	
No	114 (56.4)
Yes	88 (43.6)
Tiredness	
No	99 (49)
Yes	103 (51)
Desire to drink water	
No	100 (49.5)
Yes	102 (50.5)
Abdominal pain	
No	121 (59.9)
Yes	81 (40.1)
Vomiting	
No	175 (86.6)
Yes	27 (13.4)
Weight loss	
No	190 (94.1)
Yes	12(5.9)

Table III: Mean and Standard Deviations of CSEI and AQ-DSI-17-SF Scores

Variable	Mean±SD
CSEI Total	26.06±7.9
General self-esteem	15.22±4.5
School academic self-esteem	4.32±2
Social self-esteem	2.92±1.7
Self-esteem related to family and home	3.60±1.3
AQ-DSI-17-SF Total	10.73±3.5
Sleep	2.02±0.5
Sad and irritable mood	1.4±0.6
Appetite	0.7±0.7
Concentration and decision-making	1.2±0.6
Interview with him	1.2±0.8
Suicidal thoughts	1.05±0.8
General interest	0.10±0.7
Energy level	1.1±0.4
Restlessness and agitation	1.1± 0.5

CSEI: *Coopersmith Self-Esteem Inventory,* ***AQ-DSI-17-SF:*** *Adolescent Quick Depressive Symptom Inventory*

an insulin pump was 38.1%, while 61.9% did not use one. The average age of the participants was 15.5±1.4 years, and the average HbA1c level was 6.6±0.4. (Table I).

The findings related to diabetes symptoms are summarized in Table II. As seen in the table, 35.6% of the participants experienced dry mouth, 43.6% reported fatigue, 51% felt tiredness, 50.5% experienced excessive thirst, and 40.1% reported abdominal pain.

The results of the Coopersmith Self-Esteem Inventory (CSEI) and the Adolescent Quick Depressive Symptom Inventory (AQ-DSI-17-SF) have been summarized (Table III). The average total score for the CSEI was 26.06±7.9, with the subscales as follows: General Self-Esteem (15.22±4.5), School Academic Self-Esteem (4.32±2), Social Self-Esteem (2.92±1.7), and Family and Home Self-Esteem (3.60±1.3).

For the AQ-DSI-17-SF, the average total score was 10.73± 3.5, with subscales as follows: Sleep (2.02±0.5), Sad and Irritable Mood (1.4±0.6), Appetite (0.7±0.7), Concentration and Decision Making (1.2±0.6), Self-Perception (1.2±0.8), Suicidal Thoughts (1.05±0.8), General Interest (0.1±0.7), Energy Level (1.1±0.4), and Restlessness and Agitation (1.1±0.5).

As shown in Table IV, the median score of the Coopersmith Self-Esteem Inventory (CSEI) for those who received diabetes education was 25 (min–max: 5–43), while for those who did not receive diabetes education, the median CSEI score was 19 (min–max: 17–38). A statistically significant difference was found between the two groups ($Z = -2.174$; $p=0.030$), indicating that the self-esteem levels of those who received diabetes education are higher.

The mean CSEI score for those who reported measuring their blood sugar sometimes was 28.07±7.7, while for those who reported measuring it frequently, the mean score was 25.19±7.8. A statistically significant difference was found between the two groups ($t = 2.411$; $p=0.017$), suggesting that adolescents who measure their blood sugar less frequently had higher self-esteem.

The mean score of the Adolescent Quick Depressive Symptom Inventory (AQ-DSI-17-SF) for those diagnosed with diabetes 1-2 years ago 11.45±3.3, whereas for those diagnosed 3-4 years ago, the mean score was 9.56±3.6. A statistically significant difference was found between the two groups ($t = 3.833$; $p=0.000$), indicating that adolescents more recently diagnosed with diabetes have higher levels of depressive symptoms.

There was a negative correlation between HbA1c levels and CSEI scores ($r = -0.228$; $p=0.001$), and a statistically significant positive correlation between HbA1c levels and AQ-DSI-17-SF scores ($r = 0.401$; $p=0.001$). This finding indicates that as the HbA1c levels of adolescents with diabetes increase, their self-esteem decreases and their levels of depressive symptoms rise.

No statistically significant relationship was found between the Self-Esteem Inventory's total score and the Quick Depressive Symptom Inventory ($r = 0.058$; $p=0.415$) (Table V).

Among the independent variables, only the HbA1c level was found to be a significant predictor of self-esteem ($B = –3.857$; $\beta = –0.211$; $p = 0.003$), indicating that higher HbA1c levels were associated with lower self-esteem. The regression model was statistically significant, $F(3,198) = 4.016$, $p=0.000$, explaining 5.7% of the variance ($R^2 = 0.057$). The findings further revealed that duration of diabetes ($B = 0.428$; $\beta = 0.026$; $p =0.740$)

Table IV: Comparison of mean scores of CSEI and AQ-DSI-17-SF according to some descriptive characteristics

Variable	n	CSEI			AQ-DSI-17-SF		
		Values	t/z	p	Values	t/z	p
Gender*							
Female	96	26.39±8.7	0.559	0.577	10.40±3.4	-1.278	0.203
Male	106	25.76±7.1			11.03±3.7		
Duration of diabetes diagnosis*							
1-2 years ago	125	26.11±7.6	0.121	0.904	11.45±3.3	3.833	0.000
3-4 years ago	77	25.97±8.4			9.56±3.6		
Diabetes education†							
Yes	191	103.64 (5-43)	-2.174	0.030	101.77 (2-22)	-0.280	0.779
No	11	64.36 (17-38)			97.73 (8-14)		
Daily insulin use*							
1-2 times	52	25.98±6.5	-0.083	0.934	11.35±3.3	1.476	0.142
3-4 tmes	150	26.09±8.3			10.51±3.6		
Daily blood glucose measurement*							
Sometimes	61	28.07±7.7	2.411	0.017	11.26±3.6	1.425	0.156
Frequently	141	25.19±7.8			10.50±3.5		
Using an insulin pump*							
Yes	77	26.27±8.2	0.302	0.763	11.33±3.8	1.906	0.058
No	125	25.93±7.7			10.36±3.3		

: mean±SD (Indepented t test), †: Mean Rank (min-max) (Mann Whitney U test), **CSEI: Coopersmith Self-Esteem Inventory, **AQ-DSI-17-SF:** Adolescent Quick Depressive Symptom Inventory, **r:** Pearson's Correlation Coefficient, **HbA1c:** Hemoglobin A1c*

and age (B = –0.472; β = –0.085; p = 0.293) did not have a significant effect on self-esteem (Table VI).

Among the independent variables in the second model, the HbA1c level significantly predicted depressive symptoms (B = 3.372; β = 0.413; p=0.001), indicating that higher HbA1c levels were associated with increased depressive symptoms. In addition, duration of diabetes was a significant negative predictor (B = –1.461; β = –0.202; p = 0.005), suggesting that a longer duration of diagnosis was related to lower depressive symptom levels. By contrast, age (B = –0.241; β = –0.098; p = 0.184) did not have a significant effect on depressive symptoms. The regression model was statistically significant, F(3,198) = 19.728, p=0.001, accounting for 23% of the variance (R^2 = 0.230) (Table VII).

Table V: Association between CSEI, AQ-DSI-17-SF

Variable	(1)	(2)	(3)	(4)	(5)	(6)
CSEI Total (1)	1	-	-	-	-	.058
CSEI General self-esteem (2)		1	.661	.503	.379	.146
CSEI School academic self-esteem (3)			1	.639	.484	-.195
CSEI Social self-esteem (4)				1	.447	-.315
CSEI Self-esteem related to family and home (5)					1	-.150
AQ-DSI-17-SF Total (6)						1

***CSEI:** Coopersmith Self-Esteem Inventory, **AQ-DSI-17-SF:** Adolescent Quick Depressive Symptom Inventory*

DISCUSSION

In this study, the mean age of adolescents with Type 1 Diabetes was 15.5 years, with most having been diagnosed within the past 1-2 years. The mean HbA1c level was found to be 6.6%. The fact that this value is below the American Diabetes Association's recommended target level of 7% indicates successful disease management among the participants (20). This outcome may be associated with the participants having received diabetes education and being newly diagnosed. However, some studies in the literature have reported higher HbA1c levels (21, 22). It has also been noted that as the duration of diabetes increases, metabolic control becomes more challenging, and the risk of complications rises (23). The participants were selected from among all patients who volunteered at the time of admission; the relatively low HbA1c levels in the sample may be due to the fact that the majority consisted of patients who received regular follow-up and education.

Fatigue was the most frequently reported symptom among participants, consistent with previous studies (24, 25). The prevalence of fatigue is related to impaired cellular energy utilization due to insulin deficiency. In contrast, dry mouth was uncommon among participants, likely reflecting good glycemic control.

The adolescents' self-esteem levels were found to be moderate. The multiple regression analysis revealed that HbA1c level significantly and negatively predicted self-esteem, whereas diabetes duration and age did not have a significant effect on self-esteem. The model explained 5.7% of the variance in self-esteem. This finding indicates that metabolic control influences

Table VI: Multiple regression analysis results for predicting self-esteem

Variable	B	Std. Error $_B$	β	T	p	Zero-order r	Partial r
Constant	58.338	9.487	-	6.149	0.000	-	-
HbA1c level	-3.857	1.295	-0.211	-2.978	0.003	-0.228	-0.207
Duration of diabetes	0.428	1.287	0.026	0.333	0.740	-0.009	0.024
Age	-0.472	0.447	-0.085	-1.055	0.293	-0.112	-0.075
R=0.239	R^2 =0.057						
$F_{(3, 198)}$=4.016	p = .000						

Table VII: Multiple Regression Analysis Results for Predicting Depression

Variable	B	Std. Error $_B$	β	T	p	Zero-order r	Partial r
Constant	-5.885	3.830	-	-1.536	0.126	-	-
HbA1c level	3.372	0.523	0.413	6.447	0.000	0.401	0.417
Duration of diabetes	-1.461	0.519	-0.202	-2.812	0.005	-0.262	-0.196
Age	-0.241	0.180	-0.098	-1.333	0.184	-0.119	-0.094
R=0.480	R^2 =0.230						
$F_{(3, 198)}$=19.728	p = .000						

psychosocial outcomes; however, self-esteem is a multifactorial construct. Artuvan and Yurtsever (26) found that adolescents who adhered to their dietary regimen had higher self-esteem levels. Powers et al. (27) reported that among adolescents under 18 with high HbA1c levels and diabetic stress scores, increased dietary restrictions were associated with decreased self-esteem and life satisfaction. In this study, normal HbA1c levels, diabetes education, adherence to insulin regimens, and attention to diet suggest that participants managed their disease well, which may have prevented negative effects on self-esteem. Additionally, it has been noted that adolescents who adhere to their diet, receive family support, and continue school have higher self-esteem (28, 29).

In this study, depressive symptom levels were found to be mild among adolescents with Type 1 Diabetes. Trief et al. (2019) reported that adolescents with higher depressive symptoms experienced severe hypoglycemic and hyperglycemic episodes more frequently than those without depressive symptoms (30). According to the regression analysis, HbA1c level was found to significantly increase depressive symptoms, whereas the duration of diabetes diagnosis had a reducing effect on depressive symptoms. The model explained 23% of the variance in depressive symptoms. This result suggests that impaired glycemic control may increase depressive symptoms, whereas longer disease duration may contribute to the development of psychological adaptation. Additionally, adolescent depression has been linked to genetic, environmental factors, adverse life events, and parental history of depression, particularly maternal depression (31). In this study, factors such as normal HbA1c levels, the majority of participants having a diagnosis duration of 1–2 years, frequent blood glucose monitoring, the limited presence of diabetes symptoms, and the absence of a family history of depression may account for the low levels of depressive symptoms.

In this study, a positive but weak relationship was found between depressive symptom levels and HbA1c levels. This suggests a possible association.

Contrary to some previous studies, this study did not find a significant relationship between depression and self-esteem in children with type 1 diabetes. This finding may have been influenced by factors such as the majority of participants having received diabetes education, maintaining good glycemic control, and not using insulin pumps. Although the literature frequently reports an association between depression and glycemic control or overall health outcomes, the direct link between depression and self-esteem has not always been consistently demonstrated. This highlights the multifactorial nature of the relationship and underscores the importance of considering potential mediating and moderating variables. Therefore, it is recommended that future research adopt a more holistic approach by taking these variables into account.

Consequently, nurses who adopt a holistic approach to care should assess not only the physical but also the psychosocial needs of adolescents with Type 1 Diabetes in clinical practice; by integrating psychological screening and self-esteem enhancing interventions into routine care, they can contribute to improved health outcomes.

Limitations

This study has several limitations. First, its cross-sectional design prevents establishing causal relationships between psychosocial variables and metabolic outcomes. Second, although HbA1c provides a general estimate of glycemic control over the previous 2–3 months, it does not reflect glycemic variability or the frequency of hypoglycemic and hyperglycemic

episodes. Future studies using continuous glucose monitoring and longitudinal designs may provide a more comprehensive understanding of the relationship between glycemic control and psychosocial outcomes in adolescents with Type 1 diabetes.The cross-sectional design of this study does not allow for causal inferences or forward-looking interpretations. Additionally, self-reporting may introduce social desirability bias. Depression symptoms may also fluctuate due to seasonal or individual stressors, which a single-time assessment may not fully capture.

CONCLUSION

Adolescents with chronic diseases like diabetes frequently experience mental health issues. These challenges may affect their social relationships, family dynamics, and peer interactions, ultimately damaging their self-esteem and increasing the risk of depression. As nurses, it is essential to identify such risks early, especially in adolescents newly diagnosed with diabetes, and refer them for appropriate care. This study found that newly diagnosed adolescents had higher depressive symptom levels. Therefore, educating families of adolescents with Type 1 Diabetes, encouraging participation in programs to enhance self-esteem, organizing peer education on chronic diseases, and promoting awareness campaigns involving adolescents with diabetes could help improve their self-esteem and act as a protective factor against depression. Future studies should employ longitudinal designs and consider mediating/moderating variables such as social support, body image, and coping strategies to better understand the complex relationship between depression and self-esteem in this population.

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Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Maltepe University's Non-Interventional (clinical and human) Research Evaluation Board on February 2, 2023, with the number 2022/03-13.

Contribution of the authors

Concept – ŞÖ, GD; Design –ŞÖ, GD; Supervision - ŞÖ; Resources – ŞÖ, GD; Data Collection and Processing – GD; Analysis and Interpretation – ŞÖ, GD Literature Search – ŞÖ, GD; Writing Manuscript – ŞÖ, GD; Critical Review - ŞÖ.

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The authors declare that there is no conflict of interest.

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Original Article

Retrospective cross-sectional analysis of Vitamin D deficiency in pediatric patients: Clinical findings from a tertiary care center

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ABSTRACT

Objective: The 25-Hydroxyvitamin D (25(OH)D) deficiency is a prevalent global health concern, particularly among children, leading to conditions such as rickets and increasing the risk of respiratory infections and chronic diseases. Contributing factors include limited sun exposure, poor dietary intake, and growth demands. This study aimed to assess the clinical and laboratory characteristics of pediatric paients with 25-Hydroxyvitamin D (25(OH)D) deficiency at our clinic.

Material and Methods: This retrospective study was conducted at a tertiary care center in İstanbul, Türkiye, including pediatric patients diagnosed with 25-Hydroxyvitamin D (25(OH)D) deficiency between January 2020 and December 2023. Data on sociodemographic, medical history, symptoms, physical examinations, and laboratory results were extracted from electronic medical records. Patients with 25-Hydroxyvitamin D levels below 20 ng/mL were classified as deficient. Correlation analyses were employed to assess the associations between 25-Hydroxyvitamin D (25(OH)D) levels and clinical factors. The study was approved by the Istanbul Medipol University Ethical Review Board.

Results: A total of 5229 pediatric patients with 25-Hydroxyvitamin D (25(OH)D) deficiency or insufficiency were included in the study, with a slight female predominance (51%). The highest frequency of deficiency was observed among children aged 2 to 3 years. Symptom-onset complaint records were retrospectively reviewed. The most commonly documented complaints at presentation were fatigue (30.75%), followed by non-specific or asymptomatic presentations (28.95%). Given the retrospective design of the study, these symptoms may not be specific to 25-Hydroxyvitamin D (25(OH)D) deficiency and could be attributable to other concurrent conditions. Notably, in several cases, 25-Hydroxyvitamin D (25(OH)D) deficiency was detected incidentally during medical evaluations performed for unrelated reasons.

Conclusion: 25-Hydroxyvitamin D (25(OH)D) deficiency is a common condition in childhood and may present with a wide range of symptoms or remain asymptomatic. Early detection is crucial, particularly in at-risk groups such as toddlers and children with limited sun exposure. Clinicians should be aware of the non-specific nature of symptoms and consider 25-Hydroxyvitamin D (25(OH)D) status in routine pediatric evaluations. Broader awareness and preventive strategies are needed to reduce the clinical burden of this silent but prevalent deficiency.

Keywords: Asymptomatic presentation, pediatrics, primary health care, vitamin d deficiency

INTRODUCTION

The 25-Hydroxyvitamin D (25(OH)D) deficiency represents a significant global health concern, particularly among children, with notable clinical implications. In response to this growing issue, the Turkish Ministry of Health launched a "25-Hydroxyvitamin D (25(OH)D) Deficiency Prevention and Protection Program" in 2005 to prevent and control deficiency nationwide (1). Despite these efforts, 25-Hydroxyvitamin D (25(OH)D) deficiency remains a significant pediatric health problem in Türkiye, as shown in recent regional studies (2).

Clinically, 25-Hydroxyvitamin D (25(OH)D) deficiency is most notably associated with rickets, a disease marked by bone softening, skeletal deformities, delayed growth, and in severe cases, hypocalcemic seizures (3). Beyond skeletal health, emerging evidence suggests links between inadequate 25-Hydroxyvitamin D (25(OH)D) levels and mental health issues, immune-related disorders, and other chronic conditions (4). Recent findings also link deficiency to non-specific symptoms, such as fatigue and muscle weakness, which are often overlooked in clinical settings (5).

Children are particularly vulnerable due to several risk factors. Limited sun exposure (often influenced by seasonal changes,

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clothing habits, and urban indoor lifestyles) restricts natural 25-Hydroxyvitamin D (25(OH)D) synthesis, which is triggered by skin exposure to ultraviolet B (UVB) rays (3,4). In addition to frequently insufficient dietary intake, the increased physiological demand during growth further compounds the risk, as adequate 25-Hydroxyvitamin D (25(OH)D) levels are essential for bone development and overall health (6,7).

Considering the critical importance of 25-Hydroxyvitamin D (25(OH)D) in children, the associated health risks, and the ongoing national efforts, our study aimed to evaluate the clinical and laboratory characteristics of children diagnosed with 25-Hydroxyvitamin D (25(OH)D) deficiency at our clinic.

MATERIALS and METHODS

Study Design

This retrospective cross-sectional study was conducted at İstanbul Medipol University Mega Hospital in İstanbul, Türkiye. Patients who were diagnosed with 25-Hydroxyvitamin D (25(OH)D) deficiency in the pediatric clinic between January 1, 2020, and December 31, 2023, were included in the study. The epicrisis forms and laboratory records of the patients were retrospectively reviewed through electronic records. The data collected included sociodemographic information, patients' medical history, presenting symptoms, physical examination findings, and laboratory test results. These data were recorded in an Excel data form.

Data Collection and Patient Selection

Patients were included in the study if they had a confirmed diagnosis of 25-Hydroxyvitamin D (25(OH)D) deficiency or insufficiency, as defined by serum 25-Hydroxyvitamin D (25(OH)D) levels below 20 ng/mL for deficiency and between 21–30 ng/mL for insufficiency. In order to be included in the study, participants were required to have complete medical records, which should encompass demographic, clinical, and laboratory data.

Data were extracted from the electronic medical records at İstanbul Medipol University Mega Hospital by trained research staff. Collected data included demographic information such as age and gender, relevant medical history (including dietary intake and sun exposure), and comprehensive laboratory results. Although data on relevant medical history were collected from the medical records, these variables were inconsistently recorded across the patient population. Due to the limited availability and incomplete nature of these entries, a comprehensive correlation analysis could not be performed. Therefore, these factors were not included in the final statistical analysis, as their incorporation could have introduced bias or misinterpretation.

The laboratory results encompassed serum 25-Hydroxyvitamin D levels and various hematological parameters. Specifically, the hematological parameters included hemoglobin (Hb), hematocrit (Hct), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width – standard deviation (RDW-SD), red cell distribution width – coefficient of variation (RDW-CV), white blood cell count (WBC), platelet count (PLT), differential counts (lymphocytes, neutrophils, monocytes, eosinophils, and basophils), plateletcrit (PCT), platelet distribution width (PDW), immature granulocytes (IG#), immature granulocytes percentage (IG%), platelet large cell ratio (P-LCR), nucleated red blood cell count (NRBC#), nucleated red blood cell percentage (NRBC%), and mean platelet volume (MPV). Records with missing key data, such as serum 25-Hydroxyvitamin D (25(OH)D) levels or critical hematological parameters, were excluded from the analysis to maintain data integrity and avoid bias. No data imputation was performed.

Clinical symptoms were recorded systematically during the initial clinical visits, prior to the confirmation of 25-Hydroxy25-Hydroxyvitamin D (25(OH)D) status. However, due to the retrospective design, these presenting complaints cannot be considered specific to 25-Hydroxyvitamin D (25(OH)D) deficiency and may also be attributable to other concurrent conditions. Therefore, the documentation of symptoms in this study should be interpreted as presenting complaints rather than definitive clinical manifestations of 25-Hydroxyvitamin D (25(OH)D) deficiency.

Statistical Analysis

Descriptive statistics were employed to summarize the demographic and clinical characteristics of the study population. Continuous variables, such as age and laboratory values, were reported as either means with standard deviations (SD) or medians with interquartile ranges (IQR), depending on the distribution of the data. Categorical variables, including gender, comorbidities, and treatment outcomes, were expressed as frequencies and percentages.

Correlation analyses were conducted to investigate the potential relationships between 25-Hydroxyvitamin D (25(OH)D) levels and other hematologic parameters. Pearson's correlation coefficients were calculated based on the distribution of the data.

The significance level was set at $p<0.050$ for all tests. All statistical analyses were performed using the software package SPSS version 25.0.

RESULTS

A total of 5229 cases diagnosed with 25-Hydroxyvitamin D (25(OH)D) deficiency or insufficiency were included in the study. Of the total number of cases, 2561 (49.0%) were male and 2668 (51.0%) were female, indicating a slight predominance of 25-Hydroxyvitamin D (25(OH)D)-related issues in femaleswithin

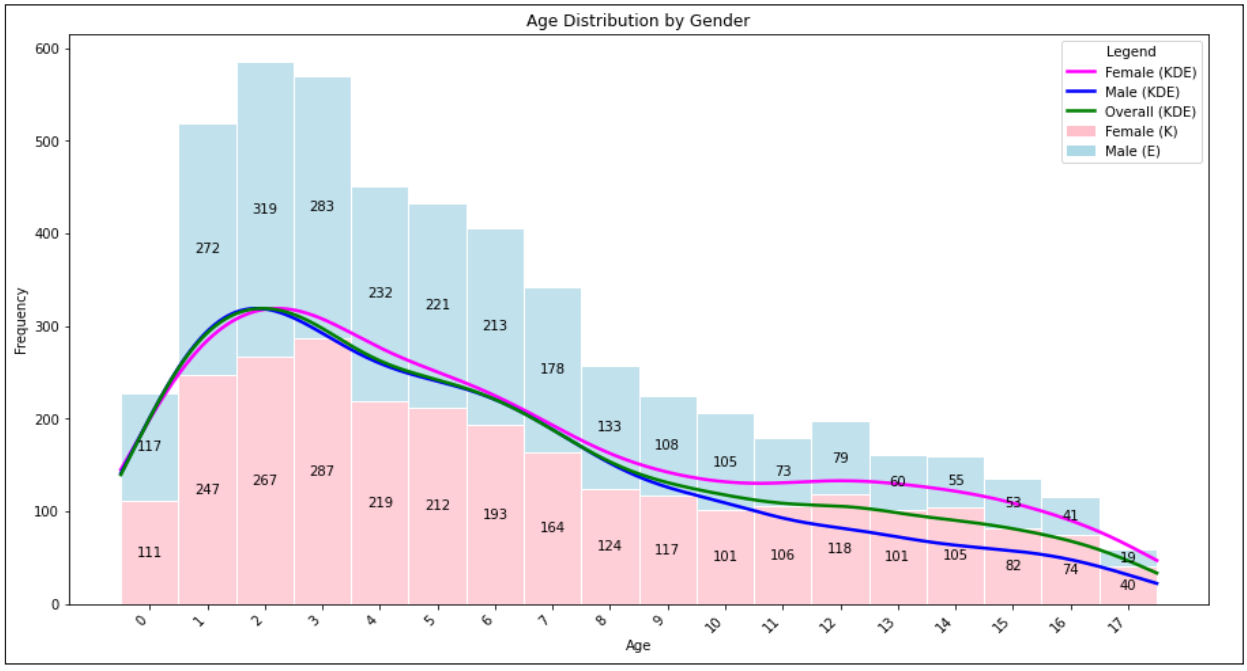

Figure 1: 25-Hydroxyvitamin D (25(OH)D) Level Gender Distribution Across Different Age Group

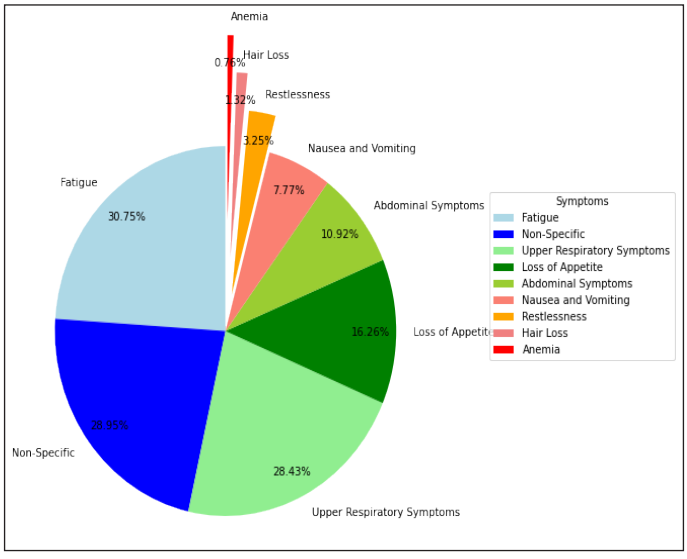

Figure 2: Symptom Distribution in Pediatric Patients with 25-Hydroxyvitamin D (25(OH)D) Deficiency or Insufficiency

the study population. The analysis of age-related data revealed a notable concentration of 25-Hydroxyvitamin D (25(OH)D) deficiency and insufficiencies in early childhood. The highest prevalence was observed in children aged 2 and 3 years, comprising 11.21% and 10.90% of the cohort, respectively. The gender distribution across different age groups demonstrated that both genders were similarly affected by 25-Hydroxyvitamin D (25(OH)D) challenges. The detailed age and gender breakdown is provided in Figure 1, which elucidates the distribution patterns across the cohort.

The records related to patients' presenting complaints documented at the time of the initial visit were examined. These complaints represent symptoms recorded during presentation and cannot be considered specific clinical findings of 25-Hydroxyvitamin D (25(OH)D) deficiency. The most frequently reported complaint was fatigue, observed in 30.75% of cases, while non-specific or asymptomatic presentations were noted in 28.95%. The distribution of presenting complaints is illustrated in Figure 2. Upper respiratory tract–related complaints, including cough, sore throat, and rhinorrhea, were reported by 1,487 children (28.43%). Loss of appetite was documented in 850 children (16.26%). Abdominal complaints, encompassing abdominal pain, diarrhea, and constipation, were reported by 571 children (10.92%). Nausea and vomiting were noted in 406 children (7.77%). Restlessness, including irritability, severe crying, and sleeplessness, was documented in 170 children (3.25%). Hair loss was recorded in 69 children (1.32%). Anemia was the least frequently noted complaint, affecting 40 children (0.76%). A total of 1.514 children (28.95%) did not present with any of the listed complaints.

In this study, we conducted a Pearson correlation analysis to investigate the relationships between 25-Hydroxyvitamin D levels and various hematological parameters. Our analysis revealed several statistically significant correlations; however, the strength of these associations was generally weak.

The correlation analysis showed a weak positive correlation between 25-Hydroxyvitamin D and both lymphocyte count ($r=0.229$, $p<0.001$) and lymphocyte percentage ($r=0.211$, $p<0.001$). Also, there is weak negative correlation between neutrophil percentage and 25-Hydroxyvitamin D ($r=-0.203$, $p<0.001$). Weak negative correlations between 25-Hydroxyvitamin D and both hematocrit ($r=-0.169$, $p<0.001$) and hemoglobin ($r=-0.140$, $p<0.001$).

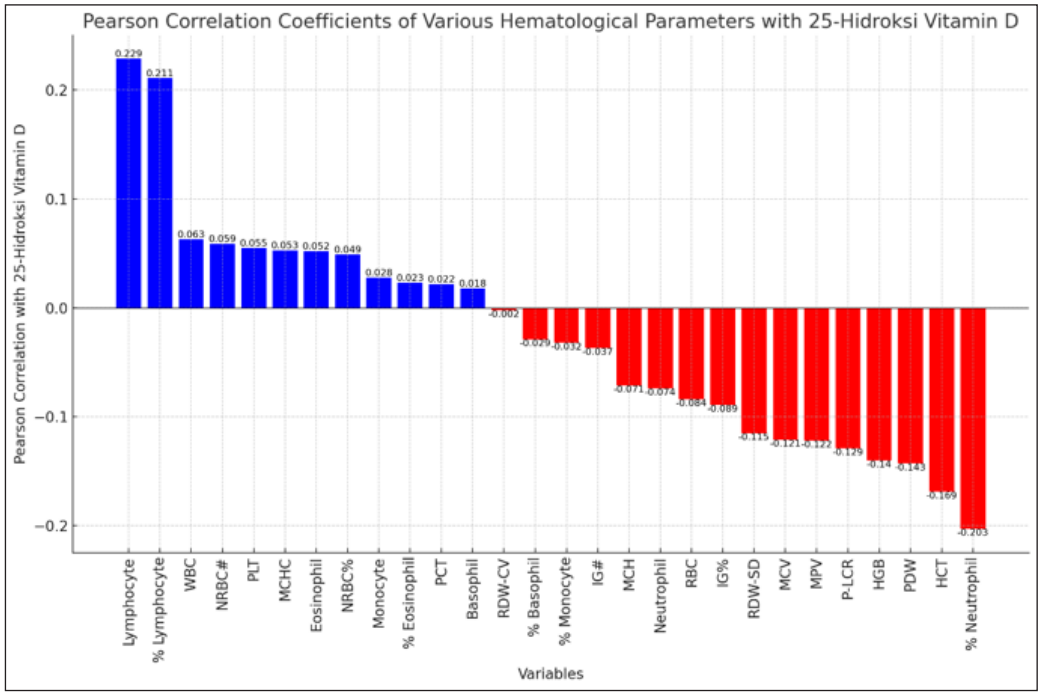

Figure 3: Pearson Correlation Coefficients of Various Hematological Parameters with 25- Hydroxyvitamin D

DISCUSSION

25-Hydroxyvitamin D (25(OH)D) deficiency in children remains a significant global and national public health concern. Our study, which includes one of the largest recent pediatric cohorts from Turkey, provides valuable insights into the prevalence of deficiency, the distribution of presenting complaints, and hematological correlations.

In this study, the prevalence of 25(OH)D deficiency was highest among children aged 2–3 years. This age range represents a critical developmental period characterized by rapid skeletal growth and immune maturation. The relatively lower prevalence observed in infants under one year of age may reflect the effectiveness of the Turkish Ministry of Health's free 25(OH)D supplementation program, which aims to prevent rickets and related complications during early infancy (1).

With respect to clinical presentation, fatigue was the most frequently documented complaint. Fatigue and muscle weakness have often been described in the literature as possible manifestations of 25(OH)D deficiency, given its role in muscle metabolism and energy regulation (5,7). Research has also linked 25(OH)D deficiency with chronic fatigue syndrome, suggesting that adequate levels are important for maintaining energy balance and overall vitality (8,9). Nevertheless, due to the retrospective design of our study, these findings should be interpreted with caution, as non-specific symptoms such as fatigue may also arise from a variety of infectious or non-infectious causes. Therefore, the observed complaints should be considered as presenting symptoms rather than definitive clinical manifestations of 25(OH)D deficiency.

Upper respiratory complaints, including cough, rhinorrhea, and sore throat, were the second most frequently recorded. Previous studies have suggested that 25(OH)D contributes to immune regulation and may play a protective role against respiratory infections (10). Research has shown that supplementation can reduce the incidence of respiratory infections (11,12) and enhance the expression of antimicrobial peptides in the respiratory epithelium, thereby strengthening the first line of defense against pathogens (13,14). However, in our cohort it was not possible to determine whether 25(OH)D testing was requested as part of the evaluation for acute respiratory illness or as a routine laboratory investigation. Given the retrospective nature of the study, these findings should be interpreted with caution and not considered direct evidence of causality. Nevertheless, previous research supports a potential link between low 25(OH)D status and impaired immune defense mechanisms, which may increase susceptibility to respiratory tract infections.

Loss of appetite was another significant complaint. The association between 25(OH)D deficiency and reduced appetite has been documented in previous studies, with suggested mechanisms including effects on leptin and other appetite-regulating hormones (15), as well as disruption of the hypothalamic-pituitary-adrenal (HPA) axis that may influence appetite and food intake (16).

Gastrointestinal complaints such as abdominal pain, diarrhea, and constipation were also commonly reported, representing the third most frequent group of complaints in our study. Previous research has suggested a possible association between

25(OH)D deficiency and gastrointestinal health, particularly through its effects on calcium absorption and maintenance of gut homeostasis (17,18). Studies have further indicated that deficiency may exacerbate gastrointestinal disorders such as irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD), leading to symptoms like abdominal pain and altered bowel habits (19,20). Moreover, 25(OH)D contributes to gut mucosal integrity and regulation of the gut microbiome, underscoring its potential role in gastrointestinal function (21). However, due to the retrospective design of this study, it is not possible to determine whether these complaints were primarily related to 25(OH)D deficiency or whether 25(OH)D levels were measured as part of an additional work-up in children presenting with other complaints. Therefore, the observed association between gastrointestinal complaints and 25(OH)D deficiency should be interpreted cautiously, considering the methodological limitations.

Interestingly, nearly one-fourth of the children in our study did not present with any of the listed complaints, underscoring that 25(OH)D deficiency can be asymptomatic or manifest only through subtle, non-specific findings. In such cases, serum 25(OH)D levels were often measured during routine check-ups, upon parental request, or as part of broader diagnostic evaluations. Although routine 25(OH)D testing is not generally recommended in healthy children, it can be justified in specific clinical contexts. According to the Turkish Ministry of Health's Vitamin D Deficiency Prevention and Protection Program, measurement of serum 25(OH)D is advised only for children at risk—such as those showing signs of rickets, with chronic conditions affecting absorption (e.g., celiac disease, cystic fibrosis), long-term use of corticosteroids or antiepileptic drugs, or limited sun exposure due to neurological or cultural reasons (1). However, given the retrospective nature of our study, detailed clinical justifications were not consistently documented, making it difficult to determine the exact indication for testing in asymptomatic cases.

In terms of hematological findings, we observed several statistically significant but weak correlations between serum 25(OH)D levels and hematological parameters, most notably a positive correlation with lymphocyte counts and percentages and a negative correlation with neutrophil percentages. These findings are consistent with previous reports, including the study by Konuksever et al. (22), which demonstrated a significant negative correlation between 25(OH)D levels and the neutrophil-to-lymphocyte ratio (NLR). While our study supports the presence of certain associations, the strength of these correlations was modest, and several expected associations were not observed.

Overall, our findings indicate that 25(OH)D deficiency in childhood is not limited to a specific clinical presentation but may manifest through a wide spectrum of complaints—or remain entirely asymptomatic, being detected only through incidental or routine evaluations. Given these findings, targeted testing of at-risk pediatric populations is essential for timely detection and prevention. Furthermore, healthcare professionals should play an active role in educating families about the importance of adequate sun exposure, appropriate supplementation, and balanced nutrition. To clarify the causal pathways between 25(OH)D status, symptomatology, and hematological outcomes, further prospective, multicenter studies with larger sample sizes and standardized clinical documentation are warranted.

CONCLUSION

This study demonstrates that 25-Hydroxyvitamin D (25(OH)D) deficiency is a frequently encountered condition in childhood and may often be identified incidentally during medical evaluations for unrelated complaints. It may present with non-specific symptoms or remain entirely asymptomatic. Due to the retrospective design of the study, establishing a direct causal relationship between 25(OH)D deficiency and accompanying symptoms was not possible. Nevertheless, the findings are noteworthy in highlighting the overall frequency and potential clinical relevance of the condition. Regular assessment of 25(OH)D levels in at-risk children is important for preventive healthcare. Healthcare providers should also play an active role in educating families about the importance of adequate sun exposure, appropriate 25(OH)D supplementation, and a balanced diet. Further large-scale, multicenter studies are warranted to better clarify the underlying causes and broader impact of 25(OH)D deficiency in pediatric populations.

Limitations

This study has several limitations, primarily related to its retrospective design. Clinical records frequently lacked detailed documentation regarding the onset, duration, and clinical context of symptoms, which limited the ability to establish direct causal relationships between 25-Hydroxyvitamin D (25(OH)D) deficiency and the reported complaints. In some cases, 25(OH)D levels may have been measured as part of broader diagnostic workups unrelated to the presenting symptoms. Furthermore, the absence of standardized symptom classification and potential variability in physician documentation may have influenced the accuracy of symptom frequency data. Despite these limitations, the study provides valuable insights into the prevalence, clinical presentations, and hematological correlations of 25(OH)D deficiency in pediatric patients.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The Istanbul Medipol University Non-Interventional Clinical Research Review Board granted ethical approval for this study (date: 12/07/2023; number: 1009).

Contribution of the authors

Study conception and design: **GM, SN**; data collection: GM; analysis and interpretation of results: **GM,ÖN,SN**; draft

manuscript preparation: **GM,ÖN,SN**. 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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Original Article

Pediatric syncope: Clinical and demographic findings from a neurological outpatient cohort

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ABSTRACT

Objective: Syncope, a temporary loss of consciousness caused by cerebral hypoperfusion, is often benign but can signal serious neurological or cardiac issues. We retrospectively analyzed pediatric syncope cases in this study.

Material and Methods: We analyzed 514 patients aged 6–18 years who presented with syncope to a pediatric neurology outpatient clinic.

Results: Most patients (36.7%) had a single episode, though recurrent cases were also common. The primary triggers were prolonged standing (17.2%) and sudden postural changes (14.4%). Prodromal symptoms such as dizziness, visual disturbances, and nausea were reported in 69.5% of cases. Electroencephalography (EEG) was performed in 72.2% of patients, revealing epileptiform activity in 27 individuals. EEG requests increased significantly in patients with recurrent syncope episodes ($p<0.010$). Cranial MRI was performed in 37.5% of the patients, and abnormalities were detected in 16.6%, most commonly arachnoid cysts. However, no statistically significant correlation was found between MRI utilization and the frequency of syncope episodes. Final diagnoses were predominantly vasovagal syncope (75.6%), followed by psychogenic syncope (10.3%), seizures (8.75%), cardiogenic syncope (4.5%), and hypoglycemia (0.85%).

Conclusion: These results highlight the mostly benign nature of pediatric syncope, with vasovagal syncope as the most frequent diagnosis. EEG is useful for identifying underlying epilepsy, while neuroimaging should be reserved for selected cases.

Keywords: Children, EEG, syncope, vasovagal syncope

INTRODUCTION

Syncope is a clinical disorder defined by abrupt onset, brief duration, spontaneous recovery, and reversible loss of postural tone and consciousness. The duration may range from several seconds to one or two minutes. Presyncope is defined as the presence of prodromal symptoms without actual loss of consciousness. Syncope is relatively common in children and adolescents, and should not be overlooked (1-4).

The fundamental pathophysiological mechanism of syncope is temporary cerebral hypoperfusion. Common causes of syncope in children encompass benign conditions such as vasovagal syncope, orthostatic hypotension, and breath-holding episodes. Although rare, syncope may occasionally be the initial manifestation of serious underlying cardiac or neurological conditions (5,6). Certain symptoms observed in individuals before syncope may assist in identifying the underlying etiology. Prodromal symptoms including dizziness, lightheadedness, transient visual loss, hot flushes, and pallor are primarily associated with vasovagal syncope; nevertheless, palpitations, chest pain, or loss of consciousness during physical exercise need the elimination of cardiac etiologies (5). In neurological syncope, involuntary jerks and contractions accompanied by abrupt and significant loss of muscle tone may be detected (7,8).

Syncope, a prevalent reason for visits to pediatric neurology outpatient clinics, is perceived as a distressing event for both the patient and the family, despite typically not signifying a serious illness (9,10). Our study sought to retrospectively assess the clinical and demographic attributes of patients presenting to the pediatric neurology outpatient clinic with syncope complaints.

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MATERIALS and METHODS

This retrospective analysis included patients who presented with syncope to the pediatric neurology outpatient clinic of Ankara Etlik City Hospital between January 2023 and December 2024. The demographic features, frequency of syncope, prodromal symptoms, triggering factors, comorbidities, diagnostic procedures, laboratory findings, and final diagnoses of the patients included in the study were retrospectively retrieved from the hospital data system.

A total of 603 patients diagnosed with the code 'syncope' were identified in the hospital data system. After identifying patients with the ICD code for syncope, individual electronic medical records were manually reviewed to confirm that each event met the clinical criteria for syncope. Patients with incomplete data or with episodes that did not meet diagnostic criteria for syncope were excluded. Following file analyses, 514 patients were identified who met the inclusion criteria. Fifty-seven patients with incomplete data were omitted from the study, and 32 patients were excluded because their events did not fulfill the criteria for syncope.

Syncope was defined as a transient loss of consciousness associated with loss of postural tone, with rapid onset and spontaneous recovery, attributed to cerebral hypoperfusion. Presyncope was defined as a state in which patients experienced prodromal symptoms such as dizziness or visual dimming without actual loss of consciousness.

Statistical analysis

Statistical analyses were performed using the NCSS 2007 program (Kaysville, Utah, USA). The data distribution was assessed using the Shapiro-Wilk test in addition to descriptive statistical methods (mean, standard deviation, minimum, and maximum). A comparison between qualitative data sets was undertaken, with chi-square analysis being implemented as a statistical method. Significance was assessed at the $p < 0.050$ levels.

RESULTS

A total of 514 participants participated in our study. Among the patients, 194 (38%) were male and 320 (62%) were female. The average age was 12.86±3.47 years. The demographic information of the patients is presented in Table I. Upon analysis of the syncope occurrences, it was noted that the predominant category comprised patients with a single episode of syncope. Among the 514 patients, 337 (65.5%) experienced true syncope, while the remaining 177 (34.5%) had presyncope episodes without actual loss of consciousness. Upon analysis of the triggering variables, it was shown that 218 patients (42.4%) exhibited no identifiable triggering factor. Among the remaining patients, the predominant causes were prolonged standing, rapid postural changes, and active infections, in that order. Prodromal symptoms were absent in 157 patients (30.5%) and present in 357 patients (69.5%). The predominant prodromal symptoms included dizziness and visual obscuration; nevertheless, several patients indicated experiencing multiple prodromal symptoms. Among patients who experienced loss of consciousness, the majority (n=157; 30.5%) reported a duration of less than 1 minute, with the most common being under 10 seconds (n=104; 20.3%). Additionally, 80 patients (15.6%) reported a duration between 1 and 2 minutes. Laboratory investigations—including complete blood count, metabolic panel, vitamin B12 and D levels, and iron studies—were unremarkable in 70% (n = 358) of the patients.

Table I: Demographic characteristics

Variables	Value
Age (years)*	12.86±3.47 (6-18)
Gender†	
Male	194 (38)
Famele	320 (62)
Number of syncope†	
1	189 (36.70)
2	150 (29.20)
3	78 (15.20)
4	27 (5.20)
5	25 (4.90)
>5	45 (8.80)
Triggering factor†	
Prolonged standing	88 (17.20)
Sudden standing up	74 (14.40)
Presence of infection	24 (4.67)
Hunger	23 (4.51)
Emotional stress	18 (3.50)
Pain	13 (2.50)
Exercise	8 (1.43)
Others	37 (7.20)
Prodromal symptom†	
Dizziness	166 (32.22)
Transient visual loss	181 (35.19)
Nausea	61 (11.97)
Palpitations	20 (3.93)
Sweating, hot flushes	16 (3.19)
Fading	13 (2.6)
Loss of consciousness†	
Yes	337 (65.5)
No	177 (34.5)

**: mean*±SD (range), *†: n(%)*

Electroencephalography (EEG) was conducted in 371 patients (72.2%), while 143 patients (27.8%) did not undergo the procedure. Abnormalities were not detected in the EEGs of 344 out of 371 patients who underwent the procedure. Abnormal epileptic abnormalities were identified in the EEG of the remaining 27 patients. Generalized epileptic discharges were detected in 15 patients, while focal epileptic discharges were detected in 12 patients. These patients received an epilepsy diagnosis based on their medical history and EEG findings. Among the 45 patients diagnosed with seizures, 27

Table II: EEG findings and final diagnoses of patients with seizures

EEG Findings	Epilepsy diagnosed	No epilepsy	Total
Abnormal	27	0	27
Normal	7	11	18
Total	34	11	45

Table III: Neuroimaging findings

Neuroimaging Findings	n (%)
Arachnoid cyst	16 (45.7)
Nonspecific findings	7 (20)
Venous anomaly	4 (11.1)
Cystic formations other than arachnoid cyst	3 (8.7)
Sinusitis	1 (2.9)
Cerebellar ectopia	1 (2.9)
Optic glioma	1 (2.9)
Chiari malformation	1 (2.9)
Bifrontal polymicrogyria	1 (2.9)
Total	36 (100)

had abnormal EEG findings consistent with epilepsy. In the remaining 18 patients, although EEG results were normal, the clinical history supported a seizure diagnosis. Of these, 7 had recurrent episodes fulfilling epilepsy criteria, 4 had febrile seizures, and 7 were classified as first afebrile seizures. Forty-five patients remain under the supervision of pediatric neurology. The patients' data are presented in Table II.

Neuroimaging was not conducted in 321 patients (62.2%), while cranial magnetic resonance imaging (MRI) was performed in the remaining 193 patients. Thirty-six patients exhibited abnormal imaging results. Table III presents the neuroimaging results. The predominant neuroimaging observation was an arachnoid cyst. The second most prevalent results, including millimetric gliotic foci and ventricular asymmetry, were categorized as nonspecific.

When all patients were evaluated as a result of history, laboratory and neuroimaging findings, 389 patients (75.6%) were diagnosed with vasovagal syncope, 53 patients (10.3%) with psychogenic syncope, 45 patients (8.75%) with seizure, 23 patients (4.5%) with cardiogenic syncope and 4 patients (0.85%) with syncope caused by hypoglycaemia. In the vasovagal syncope cohort, the largest among the patients, 268 individuals (68.9%) underwent EEG, while 136 individuals (35%) underwent cranial MRI. One hundred eight patients (27.8%) underwent both procedures.

Cardiogenic syncope was diagnosed based on abnormal findings in physical examination, electrocardiography (ECG), and/or echocardiography. Prodromal symptoms were typically absent or minimal, in line with the expected clinical course of cardiogenic syncope. All cardiology evaluations were conducted by pediatric cardiologists. In the assessment of 23 patients diagnosed with cardiogenic syncope following ECG, echocardiography, and Holter monitoring, long QT syndrome was identified in 7 patients, arrhythmia in 6 patients, ventricular extrasystole (VES) in 6 patients, second-degree atrioventricular (AV) block in one patient, one patient presented with multiple ventricular septal defects (VSD), and one patient exhibited mitral valve prolapse.

The EEG and cerebral MRI were evaluated according to the quantity of syncope patients. The request rate for EEG was 60.8% during the initial syncope, and this rate escalated with the frequency of syncopes, achieving statistical significance ($p<0.001$). The MRI request rate was 27.5% following the initial syncope, and this rate escalated with the frequency of syncopes; however, statistical significance was not detected.

DISCUSSION

This study retrospectively evaluated the clinical and demographic characteristics of patients admitted to the pediatric neurology outpatient clinic for syncope. The average age of the 514 patients in our study was 12.86 years, with a standard deviation of 3.47 years; 62% of the patients were female. Literature indicates that the incidence of syncope rises during adolescence and is more prevalent among girls (1,6).

Analysis of syncope episode frequency revealed that 36.7% of patients experienced syncope only once, while recurrent cases represented a notable proportion as well. Prolonged standing, sudden standing, and the presence of infection were the most frequently reported triggering factors (11). The vasovagal mechanism is the predominant cause of syncope in childhood and adolescence, and these findings align with existing literature (12,13).

In this study, 69.5% of patients exhibited prodromal symptoms. Dizziness, transient visual loss, and nausea were the most frequently reported symptoms, particularly associated with vasovagal syncope (14). Prodromal symptoms may serve as a significant indicator in distinguishing the etiology of syncope. In cardiogenic syncope, the prodromal period is notably brief, while patients experiencing seizures typically report little to no prodromal period. In the majority of cases involving psychogenic syncope, the prodromal phase resembles that of vasovagal syncope. However, individuals experiencing vasovagal syncope typically regain consciousness quickly, while those with psychogenic syncope require a longer duration for recovery of consciousness (15-17).

Diagnostic tests play a crucial role in patient evaluation. In our clinic, EEG was conducted in 72.2% of patients, revealing a significant increase in the request rate for EEG as the frequency of syncope episodes rose ($p<0.001$). EEG is commonly

requested in instances of suspected seizure activity. Our study identified epileptiform abnormalities in 27 out of 371 patients who underwent EEG, leading to a diagnosis of epilepsy in these individuals. Seizures were diagnosed in 18 patients initially considered to have epilepsy based on clinical evaluation, despite normal EEG results. The findings indicate a clinical overlap between epilepsy and syncope, highlighting the utility of EEG as a diagnostic tool in suspected cases (18,19).

Analysis of neuroimaging evaluations revealed that 37.5% of patients had cranial MRI. Despite the rise in MRI requests correlating with an increase in syncope occurrences, no statistically significant difference was seen ($p>0.001$). Pathological abnormalities were identified in 16.6% of patients who underwent imaging, with arachnoid cysts and nonspecific gliotic alterations being the most prevalent results. Previous studies suggest that brain MRI often has limited diagnostic value in children presenting with syncope. In most cases, especially when the neurological examination is normal and the clinical history is typical, MRI findings are either unremarkable or incidental. Therefore, neuroimaging is usually recommended only for selected patients—those with unusual symptoms, abnormal neurological signs, or when there is a specific concern for an underlying structural cause. This approach helps avoid unnecessary procedures and focuses resources where they are most likely to be helpful (13,19-21).

The most common diagnosis was vasovagal syncope, consistent with previous literature, followed by psychogenic syncope as the second most frequent diagnosis. The majority of patients with psychogenic syncope had a history of at least two syncopes, and the mean number of syncopes was significantly greater than that of the remaining population. Forty-five individuals diagnosed with seizures and/or epilepsy were recorded in the system as experiencing syncope upon their clinic visit. The patients received a diagnosis of seizure or epilepsy following an assessment that included medical history, physical examination, and EEG findings. Cardiogenic syncope and hypoglycemia were the least prevalent categories. While cardiological causes are prevalent in adults, they are infrequent in children (22, 23).

First limitation of this study is the reliance on ICD codes to initially identify patients, which may introduce classification bias. Although manual chart reviews were conducted to confirm the diagnosis, retrospective data collection is inherently limited by the accuracy and completeness of medical records. Additionally, the absence of long-term follow-up data prevents the assessment of recurrence rates and long-term outcomes. Future prospective studies with extended follow-up periods could provide more comprehensive insights into pediatric syncope management.

CONCLUSION

In conclusion, our study demonstrates that syncope in childhood and adolescents primarily arises from benign etiologies, and unnecessary investigations can be avoided. EEG is a crucial diagnostic instrument for suspected seizures, although neuroimaging assessments should be conducted with greater selectivity. Despite the retrospective design of our study and the absence of long-term follow-up data, it offers insights that could enhance clinical practice in the management of pediatric syncope. Future extensive investigations may yield more accurate guidelines for the therapy of pediatric syncope.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Ankara Etlik City Hospital (15/04/2025, reference number: AEŞH-badek2-2025-008).

Contribution of the authors

Study conception and design: MD, YD; data collection: SS; analysis and interpretation of results: MD, ÖP, ÖPE; draft manuscript preparation: MD 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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Original Article

Biologic therapy in juvenile idiopathic arthritis-associated uveitis: Does it make a difference?

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ABSTRACT

Objective: Juvenile idiopathic arthritis (JIA) is the most common pediatric rheumatic disease, and uveitis is its most frequent extra-articular complication. Despite advances in management, uveitis remains a major cause of morbidity.

The aim of this study was to evaluate the demographic, clinical, laboratory, and treatment characteristics of patients with JIA-associated uveitis (JIA-U), with a focus on the impact of biologic therapies and potential risk factors for ocular complications.

Material and Methods: This single-center retrospective cohort study included 49 JIA-U patients followed among 550 JIA cases at Ankara Etlik City Hospital (October 2022–November 2023). Demographics, laboratory parameters, clinical features, and treatment outcomes were collected. Patient characteristics were compared according to biologic therapy use and presence of ocular complications.

Results: The prevalence of uveitis was 8.9%. The mean age was 12.8±4.5 years; 61.2% were female. Oligoarticular JIA was the most frequent subtype (57.1%). Uveitis was asymptomatic in 81.6% of patients, and ocular complications occurred in 34.6%. All patients received methotrexate; 67% required biologic therapy, with adalimumab as the first-line agent. At last follow-up, 84% were in remission, 8% had active disease, and 8% were in drug-free remission. No significant differences were found between groups with or without biologic therapy or ocular complications.

Conclusion: Biologic therapies, particularly adalimumab, are effective in managing JIA-U, but their benefits may not be universal. Early diagnosis, regular ophthalmologic screening, and close collaboration between pediatric rheumatologists and ophthalmologists remain essential to reduce complications and improve outcomes.

Keywords: Arthritis, biologic therapy, uveitis

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most common pediatric rheumatic disease, defined by arthritis of unknown origin that begins before the age of 16 and persists for more than six weeks (1,2). Uveitis, the most frequent and severe extra-articular complication of JIA, is characterized by inflammation of the iris, choroid, and retinal tissues (3-5). Chronic anterior uveitis, which affects 10-20% of JIA patients, is often asymptomatic, bilateral, and predominantly associated with the oligoarticular and rheumatoid factor (RF)-negative polyarticular subtypes (1,6,7). In contrast, acute anterior uveitis, typically presenting unilaterally, is linked to enthesitis-related arthritis (ERA) and HLA-B27 positivity (6).

The most common ocular complications of JIA-associated uveitis (JIA-U), include cataracts, band keratopathy, posterior synechiae, macular and optic nerve edema, and secondary glaucoma (8). Systemic treatment, including conventional and/or biologic disease-modifying antirheumatic drugs (DMARDs) such as methotrexate (MTX), is essential to prevent the progression of ocular complications.

This study aimed to evaluate the demographic, laboratory, and treatment characteristics of pediatric patients with JIA-U, with a particular focus on the impact of biologic therapies and the identification of potential risk factors for complications.

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MATERIALS and METHODS

This single-center retrospective cohort study analyzed clinical data from JIA-U patients treated at Ankara Etlik City Hospital, (October 2022 - November 2023). All cases were diagnosed by pediatric rheumatologists following the International League of Associations for Rheumatology (ILAR) 2001 classification criteria. Inclusion criteria were: (1) age ≤16 years old at disease onset; (2) confirmed JIA diagnosis meeting ILAR criteria; and (3) consulted an ophthalmologist and diagnosed with uveitis. The exclusion criteria were as follows: (1) infectious uveitis (viral, bacterial, parasitic, or mycoplasma-induced); (2) ocular inflammation caused by metabolic diseases; and (3) other rheumatic diseases complicated by uveitis. All clinical data were extracted and reviewed from the hospital's electronic medical record system.

Demographic and clinical data, including gender, age at arthritis onset, affected joints, ophthalmic examination findings, and ocular complications, were recorded for all patients. Laboratory parameters such as white blood cell count (WBC), hemoglobin (HB), platelet count (PLT), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), antinuclear antibody (ANA), rheumatoid factor (RF), and HLA-B27 status were collected from patient files. Information on therapeutic medications and follow-up was also documented. Patients were classified into two groups based on whether they received biologic therapy and the presence of ocular complications, and these groups were compared.

Statistical analysis

Data were analyzed using IBM Statistical Package for the Social Sciences, version 26.0 (SPSS Inc., Armonk, NY, IBM Corp., USA). The normality of continuous variables was assessed using the Shapiro–Wilk test. Continuous variables were expressed as mean and interquartile range and standart deviation or median (IQR) and compared using Student's t-test or Mann–Whitney U test, as appropriate. Categorical variables were presented as frequencies and percentages (%) and compared using the chi-square or Fisher's exact test. A p value <0.050 was considered statistically significant.

RESULTS

Clinical data of 49 patients diagnosed with uveitis among 550 patients followed with JIA were analyzed. At the time of analysis, the mean age was 12.8±4.5 years, and 61.2% of the cohort were female. At the time of JIA diagnosis, 81.6% of patients were asymptomatic for uveitis. The most common JIA subtype was oligoarticular JIA, identified in 57.1% of cases. Regarding uveitis symptoms, 18.3% of patients were symptomatic, whereas 81.6% were asymptomatic at the time of diagnosis. In 74% of cases, arthritis was the initial presenting complaint and uveitis developed subsequently. Uveitis preceded arthritis in 20% of patients, while both conditions were diagnosed simultaneously in 6%. Uveitis-related complications were observed in 34.6% of cases. The median follow-up duration for all patients was 72 months (min–max; 48–108).

Among the JIA subtypes, 57.1% of patients were diagnosed with oligoarticular JIA, 32.6% with ERA, and 10.2% with polyarticular JIA. Bilateral uveitis was more common than unilateral uveitis (65.3% vs. 34.7%). Chronic anterior uveitis was the most prevalent type (77.5%), followed by acute anterior uveitis (18.3%), while panuveitis was rare (4%). All cases of panuveitis occurred in female patients and involved bilateral eye involvement. ANA positivity was observed in 49% of patients, RF positivity in 2%, and HLA-B27 positivity in 14%. Asymptomatic uveitis was most frequently observed in patients with oligoarticular JIA (90%), followed by ERA (69%) and polyarticular JIA (80%).

Topical corticosteroid eye drops were used as the initial treatment in all patients with uveitis. Prednisolone acetate 1% or its equivalent (1–2 drops, administered 1–2 times daily) was prescribed. In patients who showed no response to topical therapy after three months, methotrexate (MTX; 10–15 mg/m²/week, subcutaneously) and biologic agents were added to the treatment regimen. MTX was administered to all patients (100%), while biologic agents were used in 67%. Adalimumab (20–40 mg every two weeks, subcutaneously) was employed as the first-line biologic therapy in all cases. Biologic therapy was initiated due to inadequate response to MTX in 61% of patients and due to MTX-related adverse effects in 6%. Six patients required a switch in biologic therapy, in which adalimumab was replaced with infliximab (5–10 mg/kg/month, intravenously); among these, three patients were subsequently treated with tocilizumab (8 mg/kg every 2–4 weeks, intravenously). At the last follow-up, 84% of patients were in remission with their current treatment, 8% had active uveitis, and 8% were in drug-free remission.

The demographic data, laboratory findings, and treatment characteristics are summarized in Table I. No statistically significant differences were observed between patients receiving biologic therapy and those who did not in terms of demographic characteristics, uveitis type, JIA subtype, treatment responses, or complications. Additionally, demographic data for patients with and without ocular complications are presented in Table II.

DISCUSSION

The findings of this study contribute significantly to the growing body of evidence supporting the effectiveness of biologic therapies in the management of JIA-U. The findings of this study are largely consistent with the existing literature, particularly regarding the prevalence, clinical characteristics, and treatment outcomes of JIA-U.

Table I: Comparison of patients receiving and not receiving biologic treatment

	Total	Biological treatment		
		No	Yes	p
Number of patients	49	16	33	-
Demography				
Age,* years	12.8±4.5	12.3±5.4	13±4	0.620§
Female†	30 (61.2)	7 (43.8)	22 (66.7)	0.380‖
Age in years at diagnosis of uveitis‡	6 (4-10)	6.4 (4.2-10.6)	5.8 (4-9.5)	0.410¶
Age in years at diagnosis of JIA‡	4 (2-8)	5 (2.2-11)	4 (2-7.5)	0.440¶
Follow-up period‡ months	72 (48-108)	54 (48-105)	84 (54-114)	0.460¶
Laboratory				
Hemoglobin*,g/dl	12.4±1.5	12.35 ±1.12	12.40±1.67	0.850§
White blood cell count‡/mm^3	8120 (6975-9870)	8550 (7285-9962)	7970 (6655-9695)	0.240¶
Platelet count* /mm^3	383.979±98.237	387.265±100.131	382.212±98.824	0.850§
Sedimentation‡ mm/h	22 (7.5-43)	16 (5-53)	24 (8.5-43)	0.510¶
C-reactive protein‡, g/dl	7.5 (3-16.7)	10 (3-23)	5.5 (3-11)	0.360¶
RF positivity†	1 (2)	0	1 (3)	0.480**
ANA positivity†	24 (49)	7 (43.8)	17 (51.5)	0.610‖
HLA B27 positivity†	7 (14)	4 (25)	3 (9.1)	0.130**
Type of uveitis				
Anterior uveitis†	47 (95.9)	16 (100)	31 (94)	0.600**
Panuveitis†	2 (4,1)	0	2 (6)	
Presence of symptoms				
Symptomatic uveitis†	9 (18.4)	3 (18.8)	6 (18.2)	0.960‖
Presence of ocular complications	17 (34.6)	5 (31.2)	12 (36.4)	0.720‖

:** *mean±SD,* **†:** *n (%),* **‡:** *median (IQR),* **§:** *Student's t-test,* **‖:** *Chi-square test* **¶:** *Mann–Whitney U test,* *:** *Fisher's Exact test,* ***RF:** rheumatoid factor,* ***ANA:** antinuclear antibody*

Table II: Demographic data on 49 patients who developed uveitis with and without ocular complications

	Total	Ocular complications		
		No	Yes	p
Total cases*	49 (100)	32 (65.3)	17 (34.7)	
Gender (Female)*	30 (61.2)	21 (65.6)	9 (52.9)	0.386§
Age in years at diagnosis of JIA†	4 (2-8)	5.5 (2-11.5)	3 (2-6)	0.136‖
Age in years at diagnosis of uveitis†	6 (4-10)	7 (4-11.4)	5.8 (4-7)	0.128‖
Interval in months from diagnosis of JIA to diagnosis of uveitis ‡	12 (-39-87)	6 (-39-87)	12 (-12-62)	0.574‖
Follow-up period months†	72 (48-108)	66 (48-108)	84 (48-120)	0.759‖
JIA subtype				
Persistent oligoarticular JIA	28 (57.1)	17 (53.1)	11 (64.7)	0.176§
Enthesitis related arthritis	16 (32.7)	13 (40.6)	3 (17.6)	
Polyarticular JIA	5 (10.2)	2 (6.3)	3 (17.6)	
ANA positivity*	24 (49)	13 (40.6)	11 (64.7)	0.108§
Anterior uveitis*	47 (96)	31 (96.9)	16 (94.1)	0.298§
Bilateral uveitis*	32 (65.3)	23 (71.9)	9 (52.9)	0.318§
Asymptomatic uveitis*	40 (81.6)	28 (87.5)	12 (70.6)	0.244§
Using of biological drugs*	33 (67.3)	21 (65.6)	12 (70.6)	0.724§

***:** *n (%),* **†:** *median (IQR),* **‡:** *median (min-max),* **§:** *Chi-square test,* **‖:** *Mann–Whitney U test*

In terms of treatment, this study provides further evidence supporting the use of biologic therapies, particularly adalimumab, in the management of JIA-U. The remission rate of 84% observed in this study is comparable to the rates reported in other studies evaluating adalimumab's efficacy. For example, Biester et al. (9) and Tynjälä et al. (10) demonstrated similar remission rates with adalimumab, particularly when used in combination with MTX. The study also highlights the role of alternative biologic agents, such as infliximab and tocilizumab, in cases where adalimumab was either ineffective or poorly tolerated. This finding aligns with the growing body of evidence suggesting that switching biologic agents can be an effective strategy for treatment-resistant uveitis (11-19).

The reported prevalence of uveitis (8.9%) falls within the range observed in previous studies, which typically report rates between 6% and 20% depending on the population studied and the duration of follow-up (6, 7). The predominance of oligoarticular JIA as the most common subtype associated with uveitis (57.1%) is also well-documented in the literature. For instance, studies by Saurenmann et al and Edelsten et al. (8, 20) similarly identified oligoarticular JIA as the subtype with the highest risk of uveitis, particularly in ANA-positive patients. This study further supports these findings by demonstrating that ANA positivity was observed in 49% of patients, a rate consistent with other reports linking ANA positivity to an increased risk of uveitis.

The high proportion of asymptomatic uveitis cases (81.6%) at the time of JIA diagnosis is another critical finding that aligns with prior research. Angeles-Han et al (6) emphasized that the asymptomatic nature of uveitis in many JIA patients necessitates routine ophthalmologic screening to prevent complications. This study reinforces the importance of such screenings, particularly in high-risk subgroups such as oligoarticular JIA patients, where asymptomatic uveitis was observed in 90% of cases. Additionally, the study's finding that 34.6% of patients experienced uveitic complications is consistent with the complication rates reported in the literature, which range from 20% to 40% (6, 7) These complications, including cataracts, glaucoma, and band keratopathy, highlight the need for early and aggressive treatment to preserve visual outcomes.

One unique contribution of this study is its detailed analysis of the demographic and clinical characteristics of patients with and without ocular complications. While no statistically significant differences were observed between these groups, the data provide valuable insights into the potential risk factors for complications and the overall effectiveness of current treatment strategies. Additionally, the study's finding that there were no significant differences in treatment responses or complications between patients receiving biologic therapy and those who did not raises important questions about the factors influencing treatment outcomes. This suggests that while biologic therapies are highly effective in many cases, their benefits may not be universal, and further research is needed to identify predictors of treatment success.

Another notable contribution of this study is its focus on the timing of uveitis onset relative to arthritis. The finding that uveitis preceded arthritis in 20% of cases and was diagnosed simultaneously in 6% of cases highlights the variability in disease presentation. This variability has been reported in other studies, such as those by Saurenmann et al. (8), and underscores the importance of maintaining a high index of suspicion for uveitis in JIA patients, even in the absence of arthritis symptoms.

In conclusion, this study not only corroborates existing findings in the literature but also provides new insights into the clinical characteristics, treatment responses, and outcomes of JIA-associated uveitis. By emphasizing the importance of early diagnosis, regular screening, and individualized treatment strategies, this study contributes to the ongoing efforts to optimize the management of this challenging condition. Future research should focus on identifying biomarkers for treatment response, understanding the long-term outcomes of biologic therapies, and exploring novel therapeutic approaches for refractory cases.

This study has several limitations that should be acknowledged. First, its retrospective design may introduce selection bias and limit the ability to establish causal relationships. Second, the study was conducted at a single tertiary referral center, which may not fully represent the broader population of JIA-U patients. Third, the sample size, while sufficient for descriptive analysis, may not have been large enough to detect subtle differences in outcomes between treatment groups, particularly regarding the use of biologics. Additionally, the lack of long-term follow-up data limits our ability to assess the durability of treatment responses and the long-term impact of early interventions. Finally, while we relied on clinical records for data collection, variability in documentation practices may have influenced the accuracy of certain findings, such as the exact timing of uveitis onset or the severity of complications.

Future studies with prospective designs, larger sample sizes, and multicenter collaborations are needed to validate our findings and provide a more comprehensive understanding of JIA-associated uveitis. Long-term follow-up studies would also be valuable to evaluate the sustained efficacy and safety of different treatment strategies.

CONCLUSION

The findings suggest that advancements in early diagnosis and management, rather than the use of biologic therapy alone, play a key role in minimizing complications in JIA-U. Close collaboration between pediatric rheumatologists and ophthalmologists is essential for early detection and effective management of complications.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Ankara Etlik City Hospital (10.01.2024, reference number: 2024-006).

Contribution of the authors

AA, EB, EAE analyzed and interpreted the patients data. AA was a major contributor in writing the manuscript. YO performed the examination of the eye. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Behavioral feeding challenges, nutritional deficiencies, and obesity in children with autism spectrum disorder: a cross-sectional study

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ABSTRACT

Objective: This study aimed to investigate behavioral feeding disorders among children with Autism Spectrum Disorder (ASD) and to examine their associations with dietary intake and selected anthropometric measurements.

Material and Methods: The sample included 70 children aged 6–15 years (49 males, 21 females) diagnosed with ASD. The parents or caregivers of children with ASD provided sociodemographic details, answered nutrition-related questions, and completed the Behavioral Pediatric Feeding Assessment Scale (BPFAS) to evaluate behavioral feeding difficulties in their children. Height and weight were measured to calculate BMI percentiles, while body composition was assessed via bioelectrical impedance analysis.

Results: Based on age- and gender-specific cutoffs, 45.7% of the children were classified as obese. Additionally, 37.1% of the children exhibited feeding behavior challenges. Children with feeding behavior problems were found to have significantly lower intake levels of fiber, thiamine, riboflavin, niacin, pantothenic acid, zinc, and iron and significantly higher body fat percentages compared to their peers without such issues (p=0.013, p=0.012, p=0.019, p=0.027,p=0.019, p=0.008, p=0.018, p=0.049 respectively).

Conclusion: This study highlights the high prevalence of obesity and feeding behavior problems among children with ASD, emphasizing the association between behavioral feeding issues, inadequate nutrient intake, and increased body fat percentage. These findings underscore the need for nutritional interventions and behavioral strategies to address feeding challenges and promote healthier dietary patterns in this population.

Keywords: Autism spectrum disorder, feeding behavior, nutritional deficiencies, obesity

INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental condition characterized by persistent difficulties in social communication, along with restricted and repetitive patterns of behavior, interest or activities (1). According to a recent report by the Centers for Disease Control and Prevention (CDC), ASD affects approximately 1 in 31 children aged 8 years (2). Children with ASD often face challenges related to communication, behavior, and feeding (3). Feeding difficulties are particularly prevalent, with rates ranging between 76.0% and 82.4% in this population (4-5).

The most frequently reported issue is food selectivity, followed by problematic mealtime behaviors (6). Food selectivity, influenced by factors such as type, texture, and presentation, frequently manifests as a strong preference for carbohydrates, snacks, and processed foods, while fruits and vegetables are often avoided (7). Problematic mealtime behaviour problems include food neophobia, an aversion to trying new foods, as well as rigid routines, tantrums and adverse reactions such as spitting out or vomiting food (6). These challenges are closely linked to dietary and nutritional concerns, affecting both the quantity and quality of food intake. Limited consumption of nutrient-dense foods such as vegetables, fruits, and dairy products can result in insufficient intake of essential nutrients, including iron, calcium, zinc, omega-3 and omega-6 polyunsaturated fatty acids (PUFAs), and fiber key elements for optimal growth and cognitive development (8). If left unaddresses, feeding difficulties may lead to developmental delays, stunted growth, and nutritional imbalances, increasing the risk for both malnutrition and obesity (3).

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Numerous studies have indicated that children with ASD exhibit higher rates of obesity and are more prone to nutritional deficiencies compared to their typically developing peers (9-11).

While existing research has primarily focused on selective eating and undernutrition in children with ASD, limited attention has been given to how specific feeding behaviors affect nutrient intake and growth parameters and anthropometric indicators. Therefore, this study aimed to investigate the relationship between feeding behaviors, dietary intake, and anthropometric development in children with ASD, thereby addressing a notable gap in the current literature.

MATERIALS and METHODS

Participants and data collection

This cross-sectional study involved, between January-May 2017, children aged 6–15 years with a confirmed diagnosis of ASD involved children aged 6–15 years with a confirmed diagnosis of ASD, enrolled in Special Education and Rehabilitation Centers (SERCs) under the Ministry of National Education in Ankara. Written informed consent was obtained from all participating parents or caregivers.

The study's inclusion criteria required participants to be between 6 and 15 years old with a confirmed ASD diagnosis. Individuals with dental or swallowing difficulties, or with medical conditions that might interfere with normal dietary behaviors, known food allergies, or adherence to dietary restrictions such as a gluten-free or casein-free diet were excluded from the study.

A total of 100 children diagnosed with Autism Spectrum Disorder (ASD) were identified at the SERCs. Based on the predefined inclusion and exclusion criteria, 85 children were included in the study. However, 15 parents were excluded due to missed treatment appointments (n=6), loss of interest (n=4), or refusal to allow weight and height measurements (n=5). Consequently, the study was completed with 70 children (49 males, 21 females) whose parents provided consent to participate.

Data for the study were collected through a questionnaire administered via face-to-face interviews with parents. The questionnaire gathered socio-demographic details about both the parents and children with ASD and included the Behavioral Pediatric Feeding Assessment Scale (BPFAS). Additionally, anthropometric measurements such as weight and body fat percentage of the children with ASD were assessed using bioelectrical impedance analysis and height was measured using a tape measure.

Behavioral pediatric feeding assessment scale

The BPFAS is a standardized questionnaire comprising 35 items, designed to assess children's mealtime behaviors through caregiver reports using a Likert scale ranging from "never" to "always" (12). The Turkish adaptation of the scale was conducted by Önal et al. (13). This assessment requires parents to evaluate how often specific mealtime behaviors occur using a Likert scale and then determine whether each behavior is problematic by selecting either "yes" or "no". A score greater than 84 suggests that a child exhibits feeding behavior challenges. To assess problem behaviors, parents were asked whether each item on the scale concerned them. If the number of reported problems exceeded 9 items, the child was considered to have problematic behaviors.

Anthropometric measurements

Body weight and body fat percentage were measured using a Tanita SC-330 Body Composition Analyzer (Tanita Corp., Tokyo, Japan), with a standard clothing weight of 1 kg assumed for all children. The body type setting was standardized across all participants. Each participant's height was measured once using a tape measure. All anthropometric measurements were recorded for each individual following CDC's recommendations given in anthropometry procedures manual 2021 by National Health and Nutrition Examination Survey (NHANES) (14). BMI values were calculated and interpreted using age-specific percentiles to account for children's growth and developmental stages. BMI was calculated and interpreted using CDC age- and sex-specific percentiles. Participants were categorized as underweight (<5th percentile), normal weight (5th–84th percentile), overweight (85th–94th percentile), or obese (≥95th percentile), based on CDC growth charts (15).

Statistical analysis

Statistical analysis was performed using IBM Statistical Package for the Social Sciences, version 22.0 (SPSS Inc., Armonk, NY, IBM Corp., USA), with statistical significance set at $p < 0.050$. The choice of statistical tests was guided by the distribution of the data, assessed through both visual methods (histograms) and analytical methods (Kolmogorov–Smirnov test). Baseline demographic characteristics and eating habits were reported as proportions of the total sample. Participants were categorized based on the presence or absence of feeding behavior challenges. Comparisons between groups were conducted using independent samples t-tests to examine differences in macro- and micronutrient intake, as well as selected anthropometric measurements.

RESULTS

Table I presents the general characteristics of the 70 participating children with ASD and their parents. Males comprised 70% of the children (n = 49). At the time of participation, 45.7% of the children were classified as obese. Similarly, 45.7% were reported to be using medication, with antipsychotics being the most commonly prescribed (53.1%). A large proportion of children (71.4%) did not engage in regular physical activity.

Table I: General characteristics, lifestyle habits for the children with ASD and parents

Child Age (year)*	12 (9.5-14.0)
Gender†	
Male	49 (70.0)
Female	21 (30.0)
BMI percentile for age†	
Underweight	5 (7.1)
Normal	26 (37.2)
Overweight	7 (10.0)
Obese	32 (45.7)
Medication†	
Use	32 (45.7)
Don't use	38 (54.3)
Medication type (n=32)†	
Antipsychotics	17 (53.1)
Stimulants	7 (21.9)
Antiepileptic	8 (25.0)
Regular physical activity†	
Yes	20 (28.6)
No	50 (71.4)
Mother's Education†	
High School	52 (74.3)
University/Master	18 (25.7)
Father's Education†	
High School	41 (58.6)
University/Master	29 (41.4)
Number of children in the family†	
One	28 (40.0)
Two or above	42 (60.0)
Feeding behavior challanges†	
Yes	26 (37.1)
No	44 (62.9)
Problematic feeding†	
Yes	10 (14.3)
No	60 (85.7)

***:** *median (Q_1-Q_3),* **†:** *n(%),* ***ASD:** Autism Spectrum Disorders,* ***BMI:** Body Mass Index*

Most parents had completed high school education. Feeding behavior challenges were identified in 37.1% of the children with ASD.

Table II presents the findings related to the eating habits of the children with ASD included in the study. A total of 65.7% of parents reported that their child consistently wanted to eat a specific food. More than half of the children with ASD (54.3%) showed a strong preference for consuming snacks foods such as chips, chocolate, cake, biscuits, and coke. Additionally, parents reported that most children refused to eat one or more food items. Among the most rejected foods were vegetables, particularly vegetable dishes, with a rejection rate of 45.5%.

Table III presents the energy intake, macro- and micronutrient consumption, and selected anthropometric measurements of children with ASD, grouped according to the presence or absence of feeding behavior challenges. The mean intake of fiber, thiamin, riboflavin, niacin, pantothenic acid, zinc, and iron was significantly lower in children with feeding behavior challenges

Table II: Some eating habits of children with ASD

	n %
Food that the child always wants to eat	
Yes	46 (65.7)
No	24 (34.3)
Foods (n=46)	
Snacks (chips, chocolate, cake, biscuit, coke)	25 (54.3)
Bread	7 (15.2)
Pasta	5 (10.9)
French fries	9 (19.6)
Food rejected by the child	
Yes	44 (62.9)
No	26 (37.1)
Rejected foods*	
Legumes	4 (9.0)
Meat or chicken or fish	9 (20.4)
Egg	5 (11.4)
Fruits	4 (9.0)
Vegetables (generally vegetable dishes)	20 (45.5)
Olive	6 (13.6)
Dairy	6 (13.6)

***:** *More than one answer was given*

compared to those without such challenges (p=0.013, p=0.012, p=0.019, p=0.027, p=0.019,p=0.008, p=0.018 respectively). No statistically significant differences were observed between the groups in terms of total energy intake or other macro- and micronutrients (p=0.013, p=0.012, p=0.019), p=0.027, p=0.019, p=0.008, p=0.018 respectively). Table III presents data on BMI percentiles and fat mass values of children with ASD, categorized based on the presence of feeding behavior challenges. Although the difference in BMI percentiles between the groups was not statistically significant (p>0.101), the mean fat mass was significantly higher in children with feeding behavior challenges (p<0.049).

DISCUSSION

This study examined whether energy intake, macro- and micronutrient consumption, as well as selected anthropometric measurements, differed based on the presence of feeding behavior challenges in children with ASD. To the best of our knowledge, this is the first study to evaluate both nutritional status and anthropometric indicators in relation to feeding difficulties within this population. The study also aimed to address a gap in the literature, responding to Kittana et al.'s (16) call for integrating nutritional assessment with mealtime behaviors and food preferences, given the substantial variability observed in ASD. The findings suggest that children with ASD who experience feeding behavior challenges tend to have lower nutrient intake and higher body fat compared to their peers without such difficulties.

Children and adolescents with ASD appear to be at an increased risk for excessive weight gain and obesity (17-18). In the present study, the obesity rate was comparable to that reported by Zeybek and Yurttagül (19) (47.5%), yet notably

Table III: Energy, macro- and micronutrient intake and some anthropometric measurements according to feeding behavior challenges

	No feeding behavior challenges	Having feeding behavior challenges	Statistic	p
Number of patients	44	26	-	-
Energy (kkal)*	1889.13±327.96 (1338.55-2581.66)	1819.83±292.94 (1386.14-2433.50)	0.884‡	0.380
Macronutrients				
Carbohydrate* (%)	47.31±4.78 (38.00-62.00)	47.80±3.44 (40.0-54.0)	-0.453‡	0.652
Protein† (%)	14.19±1.64 (13.00-15.00)	13.96±1.79 (12.75-15.00)	526.50§	0.932
Fat* (%)	38.31±4.40 (26.00-46.00)	38.38±2.92 (34.0-46.0)	-0.075‡	0.940
Fiber† (g)	18.51±5.05 (14.95-21.49)	15.72±5.21 (12.90-18.76)	339.50§	0.013
Micronutrients				
Vitamin A† (µg)	813.25±340.25 (593.15-895.51)	776.75±404.14 (536.38-939.77)	446.00§	0.389
Vitamin E* (mg)	16.37±4.89 (6.43-27.73)	14.33±4.99 (6.65-28.18)	1656.0‡	0.103
Vitamin C† (mg)	82.67±28.44 (75.85-102.26)	73.18±29.81 (44.98-92.28)	438.00§	0.222
Thiamin† (mg)	0.81±0.20 (0.63-0.93)	0.70±0.20 (0.56-0.76)	337.00§	0.012
Riboflavin† (mg)	1.42±0.33 (1.18-1.69)	1.24±0.36 (0.97-1.39)	351.50§	0.019
Niacin† (mg)	10.06±3.33 (7.44-12.12)	8.36±2.87 (6.54-9.22)	361.50§	0.027
Pantothenic acid* (mg)	4.38±1.02 (3.09-6.96)	3.76±1.07 (2.57-7.13)	2396.0‡	0.019
Vitamin B_6† (mg)	1.24±0.27 (1.02-1.45)	1.14±0.35 (0.90-1.29)	408.0§	0.108
Vitamin B_{12}† (µg)	4.30±1.77 (3.09-5.17)	3.71±1.28 (2.67-4.37)	420.0§	0.146
Zinc† (mg)	9.68±2.40 (7.67-11.48)	8.27±2.41 (6.61-9.26)	328.0§	0.008
Calcium* (mg)	769.74±177.08 (461.94-1222.95)	705.00±246.28 (309.08-1387.84)	1251.0‡	0.215
Iron* (mg)	10.34±2.41 (6.48-16.01)	8.88±2.42 (5.46±17.87)	2420.0‡	0.018
Anthropometric measurements†				
BMI percentile for age	70.27±32.93 (46.97-95.77)	74.74±30.40 (55.40-98.37)	437.0§	0.101
FM (%)	21.78±12.11 (13.12-28.42)	25.37±8.23 (17.75-33.40)	380.0§	0.049

***:** *mean±SD (min-max),* **†:** *mean±SD (Q_1-Q_3),* **‡:** *Student T test,* **§:** *Mann-Whitney U test,* ***BIA:** Bioelectric impedance analysis,* ***BMI:** Body Mass Index,* ***FM:** Fat Mass*

higher than the prevalence reported in a systematic review and meta-analysis of 20 studies, which found a maximum obesity rate of 31.8% (18). Given the potential for outlier effects on weight-related data, the relatively small sample size in this study may contribute to a risk of sampling bias.

Youth with ASD exhibit several behavioral risk factors for obesity, including food selectivity, problematic eating habits, sedentary lifestyles, and sleep disturbances (20). Additionally, the use of antipsychotic medications such as risperidone, aripiprazole, and olanzapine has been associated with increased weight gain and obesity risk (21). The high prevalence of obesity observed in this study may be explained by multiple contributing factors, including antipsychotic medication use (45.7%), lack of regular physical activity (71.4%), and the presence of feeding behavior challenges (37.1%).

Children with ASD frequently avoid nutrient-dense foods, such as legumes and dairy products, instead preferring energy-dense but nutrient-poor options, such as sugary beverages and snack foods (22). In this study, nearly half of the children with ASD refused to eat vegetables, around one-fifth avoided meat, chicken, or fish, and 13.6% rejected olives and dairy products. Additionally, more than half of the children exhibited a persistent preference for snacks. Feeding challenges are commonly observed in children with ASD (3). Furthermore, children with ASD are particularly vulnerable to imbalances in their nutrient intake. These feeding difficulties can exacerbate inadequate nutrition, potentially leading to deficiencies in folic acid, calcium, sodium, potassium, zinc, and vitamins A, B5, B6, C, and D, which may have adverse effects on their development (16).

As indicated in Table III, children with ASD who exhibited feeding behavior challenges had significantly lower intakes of fiber, thiamin, riboflavin, niacin, pantothenic acid, zinc, and iron compared to those without such challenges. These findings are consistent with previous research, which has shown that food selectivity and restrictive eating patterns commonly observed in children with ASD can lead to nutritional deficiencies, particularly in essential vitamins and minerals crucial for growth and development. Furthermore, the results of this study align with earlier studies indicating that children with ASD often have inadequate dietary fiber intake compared to their typically developing peers (23-24). The lower fiber intake is especially concerning, as insufficient fiber consumption has been linked to gastrointestinal issues, which are commonly reported in children with ASD (22). However, the specific impact of feeding behavior challenges on nutrient intake in the ASD population remains insufficiently examined.

Feeding challenges are commonly observed in children with ASD (3). Furthermore, children with ASD are particularly vulnerable to imbalances in their nutrient intake. These feeding difficulties can exacerbate inadequate nutrition, potentially leading to deficiencies in folic acid, calcium, sodium, potassium, zinc, and vitamins A, B5, B6, C, and D, which may have adverse effects on their development (16).

Interestingly, although differences were observed in the intake of specific nutrients, overall energy, macronutrient, and other micronutrient consumption did not differ significantly between children with and without feeding behavior challenges. This suggests that while total energy intake may be similar for children with ASD, the quality and variety of the diet may be insufficient for children with ASD experiencing feeding challenges. These findings emphasize the need for targeted nutritional interventions to improve dietary diversity and address potential nutrient deficiencies in this population.

The results of this study indicate that although there were no statistically significant differences in BMI percentiles between children with ASD based on feeding behavior challenges, children with feeding behavior challenges had a significantly higher mean fat mass (Table III). This finding suggests that BMI percentile alone may not fully reflect differences in body composition within this population. Since BMI primarily measures overall body weight relative to height, it does not distinguish between fat mass and lean mass. Therefore, children with ASD who experience feeding behavior challenges may be at an increased risk of adiposity, despite having similar BMI percentiles to their peers without such challenges.

The clinical implications of these findings underscore the importance of assessing body composition beyond BMI percentile when evaluating nutritional status and obesity risk in children with ASD. Future research should examine the long-term metabolic consequences of increased fat mass in this group and explore targeted nutritional and behavioral interventions to promote healthier body composition outcomes.

This study provides valuable insights into the relationship between feeding behavior challenges, dietary intake, and body composition in children with ASD. The findings suggest that children with ASD who experience feeding difficulties tend to have lower intakes of essential nutrients, such as fiber, B vitamins, zinc, and iron, while also exhibiting higher fat mass despite no significant differences in BMI percentile. These results underscore the importance of assessing not only overall energy and macronutrient intake but also the quality and diversity of the diet in this population.

Study Limitations

This study has several limitations, including its cross-sectional nature and the fact that it was conducted at a single point in time. Moreover, the relatively limited sample size may restrict the applicability of the results to broader populations.

CONCLUSION

The findings highlight the need for targeted nutritional interventions that address both feeding behavior challenges and nutrient deficiencies in children with ASD. Strategies such as sensory-based feeding therapies, gradual exposure to nutrient-dense foods, and personalized dietary guidance may help improve nutritional intake and overall health outcomes. Future research should further explore the long-term effects of feeding behavior challenges on metabolic health and investigate effective interventions to optimize growth and development in children with ASD.

In addition to direct interventions, it is essential to involve families and caregivers in the process. Educating parents about the importance of varied, nutrient-dense diets and the potential long-term effects of feeding behavior challenges on their child's health could help facilitate more positive mealtime interactions and promote healthier eating habits.

Ethics committee approval

The study was approved by Ankara University Noninvasive Clinic Ethics Committee (date: 22.02.2016, number: 04-132-16).

Contribution of the authors

Study conception and design: SÖ, AU; data collection: SÖ; analysis and interpretation of results: SÖ, AU; draft manuscript preparation: SÖ, AU. 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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Original Article

One button, big risk: Recent experience of button battery ingestion in a pediatric emergency department

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ABSTRACT

Objective: Button battery ingestion causes serious health problems by corrosively damaging the mucous membrane. Early diagnosis and rapid intervention are very important. This study aimed to investigate the demographic and clinical characteristics of button battery ingestion.

Material and Methods: This retrospective cross-sectional study analyzed data from patients aged 1 month to 18 years admitted to a tertiary pediatric hospital's emergency department between January 2023 and December 2024 due to button battery ingestion.

Results: A total of 72 patients were included (69.4% male; median age 36 months [IQR; 22–59.5]). The median presentation time was 90 minutes (IQR; 56.25–180), and only 6 patients (8.3%) were symptomatic. All ingestions were accidental, with 22 (30.6%) witnessed. On direct radiography, the batteries were found in the esophagus (4.2%), stomach (48.6%), and intestine (47.2%). Endoscopic battery removal was performed in 11 patients (15.3%), with a median endoscopy duration of 12 hours (IQR; 6–19). Mucosal changes were observed in 7 (63.6%) of the 11 cases that underwent endoscopy. Batteries in the esophagus were removed within 6 hours. Of the 35 stomach batteries, 8 (22.9%) were removed endoscopically, while the others passed spontaneously. All patients were discharged in stable condition without mortality.

Conclusion: Button battery ingestion is a critical pediatric emergency that particularly affects young children. It must be removed endoscopically as soon as possible to prevent serious complications. However, preventive strategies that limit children's access to batteries or reduce their harmful effects are of great importance.

Keywords: Button battery, ingestion, endoscopy, pediatric

INTRODUCTION

Button batteries are widely used in household electronic devices and can cause serious health problems if accidentally ingested by children. Children under 5 years of age are especially at high risk as they tend to put such foreign bodies in their mouths (1, 2). The most dangerous feature of button batteries is their corrosive effect, causing alkaline burns to surrounding tissues. Complications such as mucosal damage, necrosis, and perforation can develop in a few hours. Patients may be asymptomatic to variably symptomatic (hypersalivation, dysphagia, chest pain, bloody vomiting, wheezing, cough, and tracheoesophageal fistula in the later stages) (3). In addition, various studies indicate that this problem has increased over the years (4, 5).

The appearance of a double ring or halo sign on a direct radiograph is characteristic of a button battery and is also useful in determining its location in the gastrointestinal tract. Foreign bodies are most lodged in the upper esophageal sphincter (cricopharyngeal stenosis), the narrowest part of the esophagus. Button batteries ingested into the esophagus start tissue damage within minutes. For this reason, it is recommended to perform endoscopy as soon as possible (<2 hours) in patients with esophageal button battery ingestion (6, 7). Endoscopy of the upper gastrointestinal tract is performed to evaluate the corrosive damage and to remove the button battery. Giving

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honey or sucralfate to patients reduces mucosal damage by creating a mechanical barrier around the battery and should be started as soon as possible (8, 9). Button batteries ingested in the stomach should be removed endoscopically if the patient is symptomatic, has co-ingested a magnet, or if the diagnosis is delayed (>12 hours) (10).

Button battery ingestions in children are critical cases that require rapid evaluation and early intervention in pediatric emergency services due to high morbidity and mortality. This study aimed to investigate the demographic and clinical characteristics of button battery ingestions.

MATERIALS and METHODS

This study is a retrospective, descriptive, and cross-sectional study. The patients aged between 1 month and 18 years who were admitted to Etlik City Hospital pediatric hospital emergency department due to foreign body ingestion between January 2023 and December 2024 were analyzed. Patients with a history of button battery ingestion were included in the study. Patients aged less than 1 month, those who ingested another foreign body, and those whose file data could not be accessed were excluded from the study.

Demographic characteristics of the patients (age, sex, race), history of chronic disease, history of additional foreign body ingestion, whether the event was witnessed or not, number, size, localization of the ingested button battery, signs and symptoms, duration of admission, whether endoscopy was performed or not, the time of endoscopy, hospitalization data, length of hospital stay, intensive care requirements and complications that developed during follow-up were evaluated.

Button batteries lodged in the esophagus are removed urgently by endoscopy, regardless of the time of ingestion, symptoms, or fasting compliance. Batteries located beyond the esophagus are removed as soon as possible if the patient is symptomatic. If the patient is not symptomatic, the final decision is made by the relevant departments, taking into account the individual circumstances of each case.

Statistical analysis

IBM SPSS for Windows, version 27 (IBM Corp., Armonk, N.Y., USA) software performed all statistical analyses. The Kolmogorov-Smirnov test was used to assess the suitability of numerical variables for normal distribution. Descriptive statistics (percentage, median, and interquartile range [IQR]) for demographic and clinical characteristics of all patients were used. For comparisons between groups, the $\chi 2$ or Fisher's Exact Test was used for categorical variables, and the Mann-Whitney U test was used for continuous variables that were not suitable for normal distribution (after reviewing for appropriateness). For all analyses, $p<0.050$ was determined as statistically significant.

RESULTS

Seventy-two patients admitted to the pediatric emergency department with button battery ingestion were included in the study. Median admission time was 90 min (IQR; 56.25-180). Fifty (69.4%) of the patients were male, and the median age was 36 months (IQR; 22-59.5 years). Four (5.6%) patients had known psychiatric disorders (3 with autism spectrum disorder and 1 with ADHD). All ingestions were accidental, and 22 (30.6%) were witnessed by parents. Only 6 (8.3%) patients were symptomatic at presentation (5 vomiting, 1 abdominal pain).

Direct radiography was performed in all patients to evaluate the presence and location of the button battery. Three (4.2%) of the button batteries were in the esophagus, 35 (48.6%) in the stomach, and 34 (47.2%) in the intestine. The diameter of the button battery was ≥20 mm in 58 (80.6%) patients and <20 mm in 14 (19.4%) patients. The number of ingested batteries was 1 battery in 60 (83.3%) patients, 2 batteries in 10 (13.9%) patients, and 3 batteries in 2 (2.8%) patients. None of the patients had a history of co-ingestion of another foreign body. 59 (81.9%) of the patients were hospitalized, and the median length of hospital stay was 24 hours (IQR; 21-46). Demographic and clinical characteristics of the patients are given in Table I.

Endoscopic battery removal was performed in 11 patients (15.3%), and the median duration of endoscopy was 12 hours (IQR; 6-19). Mucosal hyperemia, erosions, and ulcers were detected in 7/11 (63.6%) of the patients who underwent endoscopy. There were no anesthesia or endoscopy-related complications during the battery removal procedure. Clinical characteristics of the patients with endoscopic button battery removal are given in Table II.

Table I: Demographic and clinical characteristics of the patients

All features	Total (n=72)	Endoscopic removal (n=11)
Age, month*	36 (22-59.5)	37 (18-53)
Gender†		
Male	50 (69.4)	9 (81.8)
Witnessed event†	22 (30.6)	7 (63.6)
Button battery size†		
<20 mm	58 (80.6)	3 (27.3)
≥20 mm	14 (19.4)	8 (72.7)
Number of button batteries†		
1	60 (83.3)	11 (100)
2	10 (13.9)	-
3	2 (2.8)	-
Button battery location†		
Esophagus	3 (4.2)	3 (27.3)
Stomach	35 (48.6)	8 (72.7)
İntestine	34 (47.2)	-
LOS, hours*	24 (21-46)	51 (18-72)

: median (IQR), †: n(%), **LOS: length of hospital stay*

Table II: Details of patients with endoscopic button battery removal

Age (month)	Gender	Battery Size	Battery Location	Symptoms	Endoscopy time (hours)	Mucosal Lesion
13	M	≥20 mm	Esophagus	Vomiting	6	Hyperemia
17	M	≥20 mm	Stomach	Asymptomatic	28	Normal
18	M	≥20 mm	Stomach	Asymptomatic	12	Normal
21	M	≥20 mm	Stomach	Asymptomatic	19	Hyperemia
36	M	<20 mm	Stomach	Asymptomatic	10	Normal
37	M	≥20 mm	Stomach	Asymptomatic	14	Normal
37	F	≥20 mm	Esophagus	Asymptomatic	4	Erosion
45	F	≥20 mm	Esophagus	Vomiting	4	Erosion and necrosis
53	M	<20 mm	Stomach	Stomachache	24	Erosion
64	M	<20 mm	Stomach	Asymptomatic	11	Erosion
192	M	≥20 mm	Stomach	Asymptomatic	15	Ulcer

Endoscopic removal of the button batteries lodged in the esophagus was performed in the first 6 hours. All patients had a battery size ≥20mm, and two had vomiting. While 8/35 (22.9%) of the gastric button batteries were removed endoscopically, the rest passed through the passage spontaneously during the follow-up period. Five of the patients' button batteries were ≥20 mm in size, and all patients were asymptomatic. Patients with intestinal button batteries were observed until spontaneous excretion occurred, and fecal softeners were given to accelerate passage.

DISCUSSION

Button battery ingestions are an important cause of pediatric emergency admissions, and successful management prevents serious morbidity and mortality.

Important risk factors include age younger than 5 years, button battery size ≥20 mm, ingestion at the level of the aortic arch of the esophagus, and prolonged time after ingestion. Presenting with witnessed or suspected ingestion of a button battery, direct radiography should be performed to differentiate the presence and location (11, 12). In our study, button battery ingestion and its location were determined by direct radiography.

In our study, most of the patients were male, and the median age was 36 months. In the literature, button battery ingestions are more common in early childhood when children are more curious and in males (13). Most children who ingest a button battery are asymptomatic, or symptoms may be difficult to recognize in nonverbal children, where the event was not witnessed. If the patient is symptomatic at presentation, it is a warning for poor prognosis, as it may be associated with battery ingestion or complications (14). In our study, most patients were asymptomatic, and endoscopy revealed mucosal damage in 50% of patients who were symptomatic at presentation.

It has been reported that in 75% of children, ingested button batteries will pass through the gastrointestinal tract without any problems. Narrow esophagus in infants and ingested large diameter button batteries (≥20mm) in children increases the risk of gastrointestinal tract entrapment and mucosal injury and predisposes to complications (13, 15). In our study, endoscopic battery removal was performed in 15.3% of patients.

The time of removal of button batteries is the most important factor to prevent complications. The first 2 hours after ingestion of the button battery are critical for the development of mucosal damage. After 6 hours, serious complications develop, including esophageal stenosis, tracheoesophageal fistula, aorto-esophageal fistula, and death (16-18). The highest risk contacts for mucosal injury are batteries ingested into the esophagus, which international guidelines have reported as an indication for emergency endoscopy in children (10, 19). In our study, endoscopic battery removal was performed within the first 6 hours in all patients with esophageal battery ingestion, and no serious complications were found except mucosal damage.

Removal of post-esophageal button batteries allows evaluation of possible damage to the esophagus and prevention of damage to the stomach or intestine. There is no consensus among the guidelines for the endoscopic management of post-esophageal button batteries. However, endoscopy is recommended if the patient is symptomatic, younger than 5 years of age, the button battery is ≥20mm, delayed presentation (>12 hours), and co-ingestion with more than one battery or magnet (3, 10, 19). In our study, 22.9% of patients with gastric button battery implantation underwent endoscopic removal, and half of them had a variable degree of gastric mucosal damage without esophageal damage.

Administration of honey and sucralfate until the button battery is removed prevents mucosal damage by creating a mechanical barrier and neutralizing alkali. However, caution should be exercised in delayed diagnosis (>12 hours), suspicion of perforation, honey or sucralfate allergy, and in children younger than 1 year due to the risk of botulism (20). Except for one patient under 1 year of age, honey was given to prevent mucosal damage.

CONCLUSION

Button battery ingestion is an important cause of emergency admission that requires timely and qualified medical intervention and is more common in young children. Because of the risk of serious complications, button batteries lodged in the esophagus should be removed as soon as possible. There is

less consensus on the management of gastric button batteries. However, it is well known that they cause mucosal damage and may lead to serious complications. Prevention strategies, such as preventing access by children or reducing the damaging properties of the battery, should be developed.

Ethics committee approval

This study was conducted by the principles outlined in the Declaration of Helsinki. Approval was granted by the Medical Ethical Committee of the Etlik City Hospital (AESH-BADEK1-28.05.2025/2025-218).

Contribution of the authors

Study conception and design: ***ASO, OA,*** and ***CC***, Data collection: ***FSE, MDK***; analysis and interpre-tation of results: ***BO, BA***; Draft manuscript preparation: ***FOH, AG, NT***; 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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Original Article

Diabetes-specific eating disorder, psychological flexibility and metabolic control in adolescents with Type 1 Diabetes

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ABSTRACT

Objective: This study aimed to evaluate the risk of diabetes-specific eating disorders (EDs) and disease acceptance in adolescents with type 1 diabetes mellitus (T1DM) and to examine their associations with metabolic control and anthropometric measurements.

Material and Methods: A total of 73 adolescent with T1DM (11-19 years) participated. Data were collected face to face using questionnaires on sociodemographic and clinical characteristics, the Diabetes Eating Problem Survey-Revised (DEPS-R), and Acceptance and Action Diabetes Questionnaire (AADQ). Biochemical results and anthropometric measurements were obtained from medical records and direct assessment. Data were analyzed via SPSS and JASP.

Results: Nearly half of the participants (45.2%) were at high risk for diabetes-specific EDs. The mean DEPS-R score was 21.3±12.0, and the mean AADQ score was 47.6±9.7. Skipping main meals was associated with higher DEPS-R scores (p=0.025) and lower AADQ scores (p=0.009). A weak negative correlation was found between HbA1c and AADQ score (r=-0.280, p=0.018).

Conclusion: A considerable proportion of adolescents with T1DM are at high risk for EDs, and poor disease acceptance is linked to worse metabolic control. These findings underscore the importance of routine screening for disordered eating in clinical practice and the potential value of incorporating psychological flexibility-based interventions to improve outcomes.

Keywords: Anthropometry, eating disorders, disease acceptance, metabolic control, T1DM

INTRODUCTION

Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disease characterized by insufficient insulin production, accounting for 5–10% of all diabetes cases worldwide. Its rising incidence and prevalence pose a major public health challenge with serious long-term effects on individuals, families, and communities (1,2). It is one of the most prevalent endocrine and chronic disorders in children and adolescents, and requires lifelong glycemic control to prevent long-term complications associated with hyperglycemia (3). Good metabolic control in T1DM patients, when HbA1c levels are maintained close to those of non-diabetic individuals, can prevent the onset of microvascular and cardiovascular complications and slow the progression of existing complications (4).

Managing T1DM is complex and requires active involvement from patients and caregivers. This burden is particularly high for children, who must adapt early to the demands of the disease, and for adolescents, who face additional challenges as they seek independence and assume greater responsibilities (5,6). Therefore, a diagnosis of diabetes in childhood or adolescence can cause interference with normal developmental changes and lead to facing psychological and social challenges (7). Psychological flexibility, along with factors such as diabetes-related stress, peer interactions, and family conflict, is reported to be significantly negatively associated with HbA1c in youth with T1DM (8). In this process, acceptance of the disease, which is related to recognizing the significance of the illness, encourages the patient to mobilize their strengths, facilitates the adaptation process, prevents a decrease in quality of life,

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and reduces the risk of disease-related complications (9). The Action and Acceptance Diabetes Questionnaire (AADQ) is used as a brief measure of general acceptance and psychological flexibility that has been validated in type 1 diabetes and type 2 diabetes populations (10).

Diabetes-specific eating disorders (EDs), which can significantly impact diabetes management and complicate both metabolic control and overall well-being, are more common in individuals with T1DM, especially in females (11). Hormonal changes, dietary restrictions, social pressures, higher body mass index (BMI), body image, and self-control concerns are potential factors that can affect the process of accepting the disease and lead to diabetes-specific EDs, which are common concerns among youth with T1DM (12,13). Although various screening tools are available to identify individuals at risk of developing EDs or those already experiencing eating problems, the Diabetes Eating Problem Questionnaire-Revised (DEPS-R) has been validated as an effective screening tool for EDs in individuals with T1DM (14). It is stated that young individuals with DEPS-R scores above the clinical threshold are 8.5 times more likely to be diagnosed with an eating disorder according to the DSM-5 classification (15).

Despite increasing recognition of these psychological and behavioral factors, the combined influence of psychological acceptance and diabetes-specific eating disorder risk on metabolic control and anthropometric outcomes in adolescents with T1DM remains underexplored. This study aims to fill this gap by examining the relationships between disease acceptance, EDs risk, and clinical outcomes in adolescents. Early identification of acceptance difficulties and diabetes-related eating disorders is essential for developing disease management skills and adopting a healthy lifestyle. This study may help improve the quality of life and optimize long-term health outcomes in adolescents with T1DM.

MATERIALS and METHODS

Participants

The inclusion criteria of the study were i) being a volunteer and having obtained permission from her/his parent, ii) being an adolescent (aged between 11-19 years), iii) being diagnosed with T1DM for more than one year, iv) receiving treatment the hospital where conducting this study, v) receiving regular follow-up for at least 1 year considering factors such as treatment adherence, stabilization of metabolic control, self-management, and psychological adaptation processes, and vi) having the cognitive and language skills to understand and respond to measurement tools. The exclusion criteria of the study were i) not being a volunteer and or lacking parental permission, ii) aged below 11 years or above 19 years, iii) diagnosis of T1DM for less than one year, iv) lack of metabolic control, v) presence of serious psychiatric disorders (evaluated through patient history and clinical records during general health consultations), or chronic gastrointestinal, endocrinological, or systemic illnesses (e.g., hypothyroidism, celiac disease, irritable bowel syndrome), and vi) insufficient cognitive and language skills to understand and respond to measurement tools.

The study was performed between June and December 2023, and 90 adolescents with T1DM were reached and assessed for eligibility in the data collection process (six months). seven patients were excluded with reasons including lack of time (n=12), out of the study age range (n=2), or without any reason (n=3). Finally, the study was completed with 73 adolescents with T1DM, and their data were analyzed. In post-hoc power analysis, the observed power (one-tailed hypothesis) with 0.8 observed effect size (Cohen's d) and 0.050 probability level was 96.7% using the Free Statistics Calculators website (Soper, D., Free Statistics Calculators, Version 4.0).

Study design

The type of this study was self-reported, face-to-face, cross-sectional, and it was conducted with adolescents with T1DM receiving treatment at the Pediatric Endocrinology Clinic of Mardin Training and Research Hospital.

Data collection instruments

Data from this study was collected using the face-to-face interview method via a questionnaire created by researchers after literature searching and consisted of sections including the participants' characteristics (age, gender, diabetes duration, onset of diabetes, parental education status, family size), information on diabetes health (family diabetes history, carbohydrate counting, insulin pump usage, daily blood sugar measurement), eating habits (meal time, snack habit, meal skip, etc.), DEPS-R, and AADQ.

Diabetes Eating Problem Survey-Revised: Markowitz et al. (14) developed the DEPS-R self-report instrument to screen for eating disorders in individuals with T1DM with excellent internal consistency (Cronbach's α=0.86). Atik Altınok et al. (16) conducted the reliability and validity of the scale in Turkish children and adolescents with T1DM (Cronbach's α= 0.847). DEPS-R is a 16-item, 6-point Likert-scale self-report questionnaire designed to test diabetes-specific eating disorders. The lowest score that can be obtained from the scale is 0, and the highest score is 80. As the score obtained from the scale increases, it reflects more disturbed eating behavior, while a total score of ≥20 indicates a high risk for eating disorders (16).

Acceptance and Action Diabetes Questionnaire: The AADQ was developed to measure acceptance of diabetes-related thoughts and feelings and the degree to which they interfere with valued action. High internal consistency (Cronbach's alpha 0.94) was found in Gregg et al.'s (10) study analysis. The reliability and validity of the Turkish version of the tool was

conducted by Karadere et al. (17) (Cronbach's α=0.84). The scale consists of 9 items in total while the original form is an 11-item scale. The items are rated on a 7-point Likert scale (1: never true, 7: always true). Except for the first item, the scores of the scale are reverse scored. The scores that can be obtained from the scale are between 9-63. A high score on the scale is evaluated in favor of acceptance of diabetes and psychological flexibility (17).

Laboratory Assessment

The most recent biochemical analysis results including fasting blood glucose (FBG) (mg/dL), HbA1c (%), C peptide (nmol/L), urea (mg/dL), creatinine (mg/dL), ALT (U/L), ALP (U/L), P (mg/dL), Mg (mg/dL), Na (nmol/L) and K (nmol/L) were obtained from the medical records of the hospital where the research was conducted. The laboratory parameters, including P, Mg, Na, and potassium K, were evaluated as part of a comprehensive assessment of the patients' metabolic and electrolyte status. Other values were included to monitor metabolic balance and overall biochemical status alongside kidney and liver function markers. The glycemic targets in the ISPAD Clinical Practice Consensus Guidelines were used for FBG and HbA1c, and the reference ranges of the measured laboratory were used for other parameters (18).

Anthropometric measurement

Body weight, height, waist circumference (WC), and middle upper arm circumference (MUAC) of adolescents were measured by the researcher in accordance with measurement techniques. Height (cm) was measured with a stadiometer, ensuring that the patients were without shoes and were in the Frankfort plane. Body weight (kg) was measured using a scale, considering that they were barefoot and wearing light clothing. WC (cm) was measured between the lowest rib bone and the crista iliac crest, with a non-stretchable tape measure passing through the midpoint. MUAC (cm) was measured using a non-elastic plastic tape at the midpoint between the olecranon and acromion process on the upper left arm, with patients in a comfortable standing position. BMI (kg/m^2) was calculated [(bodyweight, kg) / (body height, m^2)]. Height-for-age and BMI-for-age were assessed according to WHO Anthro (version 3.2.2) percentile values (19). MUAC was evaluated according to the NCHS (20). WC percentiles were evaluated and waist-to-height ratio (WHtR) was calculated based using the formula [WC (cm) / H (cm)] and considered (21,22).

Statistical analysis

The data obtained from this study were analyzed using the IBM SPSS Statistics 23.0 (Statistical Package for the Social Sciences) package program (Armonk, NY, USA: IBM Corp; 2013) and the JASP Statistical Software version 0.18.2 (JASP, Amsterdam, the Netherlands). Mean, standard deviation (SD), lower and upper values were calculated for the quantitative data, and the qualitative data were presented as frequency (n), percentage (%). The normality of the distribution for each variable was assessed using the Kolmogorov–Smirnov test.

For comparisons between two groups, the independent t test was applied, and for comparisons among more than two groups, the One-Way ANOVA test was performed. Post-hoc pairwise comparisons were conducted using the Bonferroni test. The One Sample t test was used to compare variables with established biochemical reference values. Effect sizes were reported as Cohen's d for t-tests and as eta-squared (η^2) for ANOVA to indicate the magnitude of observed differences. The Pearson and Spearman correlation coefficients were conducted to assess the strength and direction of relationships between continuous variables, depending on their distribution, with correlation coefficients interpreted as follows: 0.00-0.10 (negligible), 0.10-0.39 (weak), 0.40-0.69 (moderate), 0.70-0.89 (strong), and 0.90-1.00 (very strong). The statistical significance was set at $p<0.050$.

RESULTS

The study population comprised 31 (42.5%) female and 42 (57.5%) male adolescents with T1DM. The mean age, onset of diabetes, and diabetes duration were 15.2±2.3, 8.7±4.0, and 6.5±4.5 years, respectively. Most were in the 14-17 years middle-adolescent group (50.7%). A total of 42.5% of them had been diagnosed above 10 years old, and 46.6% of them had 1–5-year(s) diabetes duration.The proportion of parents with a high education status was 20.5% for mothers and 52.1% for fathers, and most fathers (91.8%) had working status. While only 6 (8.2%) participants used an insulin pump and 44 (60.3%) of them measured capillary blood glucose >4 times/day. The mean of DEPS-R score and AADQ were 21.3±12.0 and 47.6±9.7, respectively. The study found that 54.8% (n=40) of the participants were EDs risk-negative and 45.2% (n=33) were EDs risk-positive. When examining diabetes-specific eating disorders and accepting disease scores according to participants' characteristics, there were no statistically significant results (Table I).

DEPS-R score and AADQ score according to participants' eating habits are shown in Table II. Most adolescents did not use the carbohydrate counting method (n=44, 60.3%), had ≥3 main meals/day (n=65, 89.0%), and had 2 snacks/day (n=38, 52.1%). There were more than three hours between consecutive main and snacks in the diet of 58.9%. The mean DEPS-R score was significantly higher in adolescents who skipped main meals compared with those who did not (24.5 ±13.5 vs. 18.2±9.6; t=2.296; Cohen's d=0.540; p=0.025). In contrast, the mean AADQ score was significantly lower in those who skipped meals (44.6 ±11.0 vs. 50.5±7.3; t =–2.690; Cohen's d =–0.630; p=0.009).

Biochemical results of adolescents with T1DM and differences from reference values are in Table III. As metabolic parameters,

Table I: DEPS-R and AADQ scores by participants' general and diabetes characteristics

General and diabetes characteristics	Overall	DEPS-R score		AADQ score	
		values	p	values	p
Age (years)	15.2±2.3 (11-19)*	-0.130†	0.274	0.163†	0.169
Onset of diabetes (years)	8.7±4.0 (1-15)*	-0.022†	0.852	-0.037†	0.756
Diabetes duration	6.5±4.5 (1-16)*	-0.048†	0.686	0.118†	0.320
Age (years)					
11-13	21 (28.8)‡	22.6±12.2 (3-49)*	0.828§	45.9±9.0 (20-57)*	0.328§
14-17	37 (50.7)‡	21.0±13.3 (3-61)*		47.4±10.9 (19-60)*	
18-19	15 (20.5)‡	20.2±8.3 (5-35)*		50.7±7.1 (38-62)*	
Gender					
Female	31 (42.5)‡	23.0±14.1 (3-61)*		45.8±10.8 (19-60)*	0.166‖
Male	42 (57.5)‡	20.0±10.3 (3-49)*	0.310‖	49.0±8.7 (20-62)*	
Mother education status					
Low education status	58 (79.5)‡	20.9±11.8 (3-61)*	0.618‖	48.5±8.4 (20-60)*	0.128‖
High education status	15 (20.5)‡	22.7±13.4 (3-44)*		44.2±13.5 (19-62)*	
Father education status					
Low education status	35 (47.9)‡	22.7±13.9 (3-61)*	0.330‖	46.4±9.7 (20-60)*	0.297‖
High education status	38 (52.1)‡	20.0±10.0 (3-44)*		48.8±9.7 (19-62)*	
Mother working status					
Yes	10 (13.7)‡	25.8±14.1 (8-48)*	0.203‖	45.5±9.5 (28-62)*	0.463‖
No	63 (86.3)‡	20.6±11.6 (3-61)*		48.0±9.8 (19-60)*	
Father working status					
Yes	67 (91.8)‡	20.7±12.2 (3-61)*	0.200‖	47.6±9.9 (19-62)*	0.955‖
No	6 (8.2)‡	27.3±8.8 (14-37)*		47.8±8.2 (33-56)*	
Sibling number					
≤2	25 (34.2)‡	20.0±10.6 (3-44)*	0.063§	47.7±10.1 (19-62)*	0.141§
3-4	33 (45.2)‡	19.3±9.6 (5-42)*		49.5±6.7 (32-58)*	
≥5	15 (20.6)‡	27.7±16.9 (7-61)*		43.5±13.6 (20-60)*	
Onset of diabetes					
<5 years	16 (21.9)‡	21.6±12.2 (10-49)*	0.652§	47.8±10.8 (20-60)*	0.622§
5-10 years	26 (35.6)‡	19.6±11.1 (3-48)*		49.0±9.3 (19-62)*	
>10 years	31 (42.5)‡	22.6±12.9 (7-61)*		46.4±9.7 (21-59)*	
Diabetes duration					
<5 years	34 (46.6)‡	21.3±12.3 (7-61)*	0.865§	47.5±9.3 (21-59)*	0.478§
5-10 years	22 (30.1)‡	22.2±13.0 (3-49)*		46.1±11.5 (19-62)*	
>10 years	17 (23.3)‡	20.1±10.8 (5-44)*		49.9±7.9 (28-60)*	
Insulin pump usage					
Yes	6 (8.2)‡	17.4±14.1 (3-42)*	0.426‖	50.7±10.6 (32-60)*	0.426‖
No	67 (91.8)‡	21.6±11.9 (3-61)*		47.3±9.7 (19-62)*	
Family history of diabetes					
Yes	38 (52.1)‡	22.8±13.2 (3-61)*	0.257‖	46.1±10.8 (19-59)*	0.176‖
No	35 (47.9)‡	19.6±10.6 (3-44)*		49.2±8.3 (28-62)*	
Daily capillary blood glucose measurement (times)			0.830‖		0.997‖
≤4	29 (39.7)‡	20.9±6.7 (3-40)*		47.6±7.5 (19-62)*	
>4	44 (60.3)‡	21.5±13.5 (3-61)*		47.6±11.0 (20-60)*	

:** *mean±SD (min-max),* **†:** *r (Pearson correlation test),* **‡:** *n(%),* **§:** *One Way ANOVA test,* **‖:** *Independent t test,* ***AADQ: *Acceptance and Action Diabetes Questionnaire,* ***DEPS-R:*** *Diabetes Eating Problem Survey-Revised,* ***Low education status:*** *Literature/primary school/secondary school,* ***High education status:*** *High school/bachelor's degree*

the mean FBG (214.5±119.4 mg/dL) was found to be higher than the reference (upper level 144 mg/dL, mean difference=70.5 mg/dL, Cohen's d=0.590, p<0.001). The mean HbA1c (9.2±2.5) was higher than the reference (upper level 7%, mean difference=2.2%, Cohen's d=0.860, p <0.001). Additionally, the mean of ALP (U/L) differed from the maximum level of reference (129 U/L, mean difference=101.4 U/L, Cohen's d=0.996, p<0.001). The deviations from references were shown with raincloud plots. There was no relationship between biochemical results and DEPS-R, AADQ scores of participants (p>0.050). A weak and negative significant relationship was found between HbA1c and the AADQ score (rho=-0.280, p=0.018).

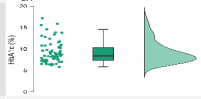
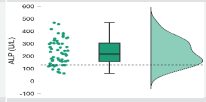
Most participants were in the normal percentile range of anthropometric measurements (height for age 69.8%, BMI for

Table II: DEPS-R and AADQ scores by participants' eating habits

Eating habits	Overall*	DEPS-R score		AADQ score	
		values†	p	values†	p
Carbohydrate counting method usage					
Yes	29 (39.7)	21.0±13.1 (3-61)	0.860‡	48.7±9.4 (21-59)	0.463‡
No	44 (60.3)	21.5±11.5 (3-49)		46.9±10.0 (19-62)	
Main meal(s)/day					
2	8 (11.0)	28.0±18.1 (8-61)	0.283‡	38.9±13.6 (19-53)	0.082‡
≥3	65 (89.0)	20.5±11.0 (3-49)		48.7±8.7 (20-62)	
Snack/day					
1	13 (17.8)	24.2±15.8 (8-61)		47.4±9.6 (24-60)	
2	38 (52.1)	20.4±11.0 (3-49)	0.630§	47.6±9.3 (20-62)	0.989§
≥3	22 (30.1)	21.1±11.7 (3-40)		47.9±10.9 (19-59)	
Main meal(s) skip habits					
Yes/sometimes	36 (49.3)	24.5±13.5 (8-61)	0.025‡	44.6±11.0 (19-59)	0.009‡
No	37 (50.7)	18.2±9.6 (3-40)		50.5±7.3 (32-62)	
Snack skip habits					
Yes/sometimes	46 (63.0)	22.4±12.8 (3-61)	0.323‡	47.4±10.5 (19-62)	0.760‡
No	27 (37.0)	19.4±10.6 (3-40)		48.1±8.3 (21-58)	
Time between consecutive main and snack (hours)					
≤3	30 (41.1)	21.4±12.4 (3-49)	0.957‡	46.9±11.2 (19-62)	0.596‡
>3	43 (58.9)	21.2±11.9 (3-61)		48.1±8.6 (24-59)	

:** *n(%),* **†:** *mean±SD (min-max),* **‡ :** *Independent t test,* **§ :** *One Way ANOVA test,* ***AADQ: *Acceptance and Action Diabetes Questionnaire,* ***DEPS-R:*** *Diabetes Eating Problem Survey-Revised*

Table III: DEPS-R and AADQ scores by participants' biochemical analysis results

Biochemical results	n	Overall*	Reference	p†	Raincloud plots	DEPS-R score	AADQ score
						rho, p‡	rho, p‡
FBG (mg/dL)	73	214.5±119.4 (46-569)	70-144	<0.001		-0.150, 0.206	0.126, 0.289
HbA1c (%)	71	9.2±2.5 (5.8-17.2)	≤7	<0.001		0.160, 0.183	-0.280, 0.018
C peptide (nmol/L)	52	0.2±0.4 (0.0-1.7)	0.2-0.5	N	N	0.178, 0.206	-0.177, 0.209
Urea (mg/dL)	60	29.9±25.4 (8.3-214.0)	10-50	N	N	0.228, 0.079	-0.107, 0.415
Creatinine (mg/dL)	69	0.7±0.1 (0.4-1.1)	0.5-1.1	N	N	-0.181, 0.137	0.193, 0.113
ALT (U/L)	68	22.5±30.6 (5-234)	10-49	N	N	0.230, 0.060	-0.195, 0.111
ALP (U/L)	56	230.4±101.8 (62-469)	45-129	<0.001		-0.054, 0.692	-0.262, 0.051
P (mg/dL)	58	4.3±0.8 (2.6-7.0)	2.5-4.5	N	N	-0.078, 0.562	-0.106, 0.430
Mg (mg/dL)	56	1.8±0.3 (1.3±2.6)	1.7-2.5	N	N	0.077, 0.571	-0.117, 0.391
Na (mmol/L)	64	137.8±4.1 (120-144)	132-146	N	N	-0.053, 0.676	-0.029, 0.823
K (mmol/L)	64	4.5±0.9 (3.1-10.5)	3.5-5.5	N	N	-0.146, 0.250	0.036, 0.775

:** *mean±SD (min-max),* **†:** *One Sample t test,* **‡ :** *Spearman correlation test* ***AADQ: *Acceptance and Action Diabetes Questionnaire,* ***DEPS-R:*** *Diabetes Eating Problem Survey-Revised,* ***FBG:*** *Fasting blood glucose,* ***ALT:*** *Alanine transaminase,* ***ALP:*** *Alkaline phosphatase,* ***P:*** *phosphorus,* ***Mg:*** *magnesium,* ***Na:*** *sodium,* ***K:*** *potassium,* ***MD:*** *mean difference,* ***N:*** *normal range*

age 60.3%, MUAC for age 56.2%, and WC for age 52.0%). The proportion of subjects in the high-risk WHtR group was found to be 16.4%. The mean DEPS-R score differed by height-for-age groups. This difference was found to be between the normal and tall–very tall groups using the Bonferroni multiple comparison test. The mean DEPS-R score of those who were in the normal height percentile range was higher than the tall–very tall group (23.4±12.8 vs 11.6±5.0, F=3.921, η^2=0.101, p=0.024) (Table IV). As shown in scatter plots, there was no statistically significant relationship between anthropometric percentiles and scale scores (p>0.050) (Figure 1).

Table IV: DEPS-R and AADQ scores by participants' anthropometric measurements

Anthropometric measurements	Overall*	DEPS-R score †	p	AADQ score †	p
Height for age (cm)					
Short–very short	14 (19.2)	19.0±8.7[ab] (7-33)	0.024‡	49.9±7.9 (32-60)	0.224‡
Normal range	51 (69.8)	23.4±12.8[a] (3-61)		46.4±10.5 (19-62)	
Tall–very tall	8 (11.0)	11.6±5.0[b] (3-18)		51.6±4.9 (46-59)	
BMI for age (kg/m^2)					
Severely underweight/underweight	13 (17.8)	22.1±8.9 (11-39)	0.384‡	48.4±9.9 (21-62)	0.953‡
Normal range	44 (60.3)	19.8±11.4 (3-49)		47.5±9.9 (19-60)	
Overweight/obese	16 (21.9)	24.6±15.6 (3-61)		47.4±9.7 (24-59)	
MUAC for age (cm)					
Low–too low	26 (35.6)	22.4±9.2 (7-39)	0.148‡	45.9±10.7 (19-62)	0.487‡
Normal range	41 (56.2)	19.4±13.4 (3-61)		48.3±9.6 (20-60)	
High–too high	6 (8.2)	29.2±11.1 (18-48)		50.2±4.7 (42-56)	
WC for age (cm)					
Low–too low	27 (37.0)	21.4±9.0 (7-37)	0.806‡	47.3±6.9 (32-58)	0.891‡
Normal range	38 (52.0)	20.7±12.7 (3-49)		48.1±11.5 (19-62)	
High–too high	8 (11.0)	23.8±18.2 (8-61)		46.5±9.8 (24-55)	
WHtR					
Low risk	61 (83.6)	21.4±11.3 (3-49)	0.809§	47.4±9.9 (19-62)	0.685§
High risk	12 (16.4)	20.5±16.0 (5-61)		48.7±9.0 (24-60)	

:** *n(%),* **†:** *mean±SD (min-max),* **‡:** *One Way ANOVA test,* **§:** *Independent t test,* ***AADQ: *Acceptance and Action Diabetes Questionnaire,* ***BMI:*** *Body mass index,* ***DEPS-R:*** *Diabetes Eating Problem Survey-Revised,* ***MUAC:*** *Middle upper arm circumference,* ***WC:*** *Waist circumference,* ***WHtR:*** *Waist-to-height ratio,* **[a-b]:** *Statistically significant difference between groups. Bonferroni correction was used to find the difference.*

DISCUSSION

Early detection of EDs is crucial in adolescents with T1DM, as these disorders increase the risk of developing diabetes-related complications (23). Findings of this study indicate that a significant proportion of adolescents with T1DM were at high risk for eating disorders, with no differences observed based on demographic or diabetes-related characteristics. Mean fasting blood glucose and HbA1c values were higher than reference ranges; however, no significant associations were found between these biochemical outcomes and DEPS-R scores. DEPS-R scores also did not differ according to BMI. Notably, a significant negative correlation was observed between HbA1c levels and AADQ scores, suggesting that higher disease acceptance was associated with better glycemic control in this cohort.

We found that 45.2% of adolescents with T1DM were at high risk for EDs, which did not differ by demographic and diabetes-related information. Ryman et al. (24) found that 21% of participants had EDs, with a higher prevalence in females, although no differences were observed based on age and duration of diabetes diagnosis. Daniel et al. (25) reported a prevalence of 43.3% among 395 adolescents aged 10–19 years, and Lawrence et al. (26) found a prevalence of 48.0% in a smaller Australian cohort. Nilsson et al. (27) reported 21.0% among 192 Danish children and adolescents, and Polat et al. (28) observed 30.5% in Turkish adolescents with T1DM. These findings highlight the increased risk of EDs in adolescents with chronic diseases such as diabetes, where food intake is closely related to disease management. It is also important to note that while screening tools such as the DEPS-R are useful in identifying at-risk individuals, they do not replace clinical diagnoses based on DSM-5 criteria. According to the DSM-5, eating disorders such as anorexia nervosa, bulimia nervosa, and binge eating disorder require the presence of specific behavioral and psychological characteristics, such as frequency, duration, and associated disorder (29). Therefore, our findings suggest a high risk, yet should not be interpreted as equivalent to a clinical diagnosis. However, these screenings can guide targeted interventions in adolescents with T1DM.

While some studies suggest an association between EDs and poorer diabetes control, as reflected by elevated HbA1c levels, the evidence is not entirely consistent. In this study, mean FBG and HbA1c values were higher than references, but no association was observed between HbA1c and DEPS-R. Some studies have shown an association between poorer glycemic control and EDs, while others have found a weak relationship (16,24,30). The differing results may be attributed to the type of EDs, characteristics of the studied population, and variations in approaches to diabetes management.

In this study, the mean DEPS-R score was higher in the normal height percentile group compared to the tall–very tall group, with no differences in other anthropometric indicators, including BMI. The literature on between BMI and EDs suggests that some studies have identified a link between increasing BMI and both the onset and persistence of EDs behaviors, whereas other studies found no such relationship (23,24,31). This finding should be interpreted cautiously, as the underlying mechanisms are unclear and may involve psychosocial or sociocultural factors not directly measured in this study.

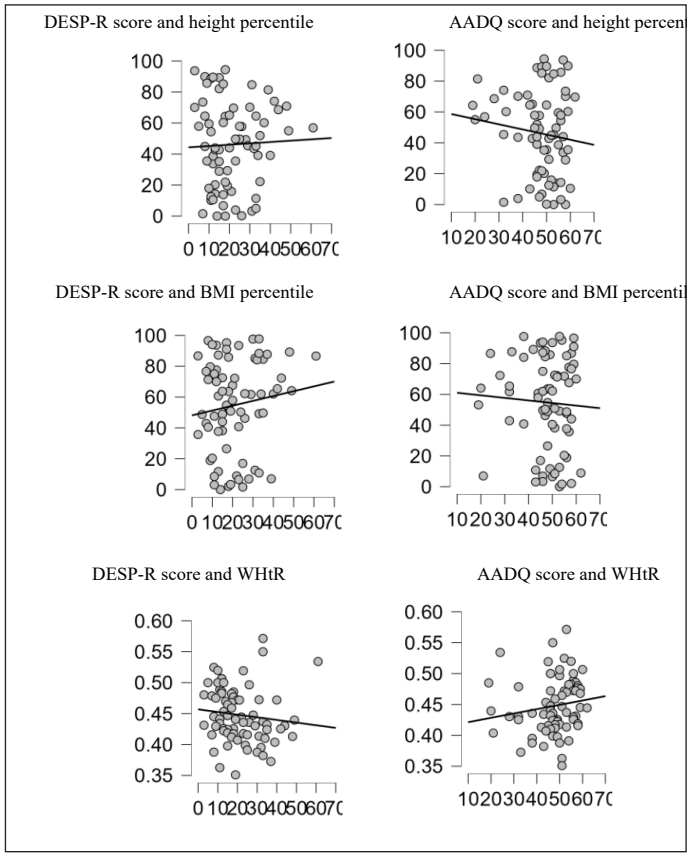


Figure 1: Scatter plots of correlation between anthropometric measurements' values and scale scores

T1DM is a serious condition associated with a high prevalence of impaired psychological health, with treatment targets being achieved by only a minority of individuals (32). In this study, we found a significant negative correlation between HbA1c and AADQ score. Saito et al. (33) showed that in type 2 diabetes, increased acceptance assessed with AADQ mediated improvements in HbA1c levels. Another study also reported improved AADQ scores linked to better HbA1c levels (32). Together with our findings, this suggests that enhancing acceptance may contribute to better psychological well-being and improved treatment outcomes, underscoring the importance of psychological factors in managing T1DM. Moreover, although insulin pump use was low in our sample (8.2%) and did not allow for subgroup analysis, it is important to note that diabetes management technologies such as insulin pumps, continuous glucose monitoring systems, and the frequency of self-monitoring have been shown in the literature to be associated with better psychological well-being and enhanced metabolic outcomes (34, 35).

In diabetes management, adherence to diet recommendations is crucial factor for preventing complications, and is influenced by psychosocial factors (36). We found that the adolescent who reported skipping main meals had significantly lower AADQ scores compared with those who did not skip meals. Jaworski et al. (37) similarly reported that patients' non-adherence to dietary recommendations was linked to lower levels of disease acceptance. This finding suggests that skipping main meals may reflect poorer acceptance of the disease, highlighting psychosocial adaptation and dietary adherence are closely intertwined in diabetes management.

In clinical practice, the DEPS-R and AADQ tools can support individualized treatment strategies by facilitating a more comprehensive assessment of both behavioral and psychological aspects of T1DM management. While not diagnostic tools, their ease of administration makes them suitable for routine follow-up visits and can help flag patients who may require further psychiatric evaluation. This allows healthcare providers to intervene early and provide appropriate psychological or nutritional support. However, given the reliance on self-report measures, clinicians should interpret the scores cautiously.

Several limitations should be considered when interpreting these results. The cross-sectional design limits the ability to conclude causality. Both DEPS-R and AADQ are self-report tools, which may introduce recall or reporting bias. DEPS-R cannot replace structured psychiatric evaluation, and AADQ would benefit from complementary objective assessments, such as neuropsychological testing, to more robustly capture psychological flexibility. Future research could incorporate objective measures, such as provider interviews or direct observations of eating behavior. The relatively small sample size may limit the generalizability and including a larger, more diverse cohort could improve understanding of the factors influencing eating behaviors in adolescents with T1DM. Exploring additional psychological factors, such as depression, anxiety, and family dynamics, would be valuable. Finally, the absence of a healthy control group limits interpretation, as it is unclear whether the DEPS-R findings are specific to T1DM or reflect general adolescent risk. Longitudinal studies are needed to examine the impact of eating disorders, psychological flexibility, metabolic control, and physical measures in T1DM.

CONCLUSION

This study demonstrates a high prevalence of eating disorder risk and highlights the importance of disease acceptance in adolescents with T1DM. Nearly half of the participants were identified as being at high risk for EDs. Lower acceptance was associated with poorer glycemic control, reflected by elevated HbA1c levels. Adolescents who skipped main meals showed lower disease acceptance, emphasizing the role of dietary behaviors in metabolic and psychological outcomes. These findings underscore the need for early screening and targeted psychological and behavioral interventions to improve both metabolic control and disease acceptance, particularly in adolescents at risk for eating disorders.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Mardin Artuklu University (14.12.2022, reference number: 2022/14-15).

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Contribution of the authors

Study conception and design: ACJ, GA; data collection: ACJ, GA; analysis and interpretation of results: ACJ, GA; draft manuscript preparation: ACJ, GA. 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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Original Article

Evaluation of the natural course and effective factors in egg allergy

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ABSTRACT

Objective: Egg allergy (EA) is one of the most common food allergies in early childhood, often resolving spontaneously over time. However, the course of the disease varies among individuals, and several factors have been proposed to influence its persistence. This study aimed to evaluate the clinical and laboratory features of children diagnosed with EA, assess the frequency and timing of tolerance development, and identify risk factors associated with persistent allergy.

Material and Methods: A retrospective review was conducted on children diagnosed with EA and followed for at least six months between June 2010 and June 2016. Demographic characteristics, clinical manifestations, laboratory parameters, skin prick test (SPT) results, and coexisting atopic conditions were recorded. Patients were classified as either tolerant or persistent based on follow-up oral food challenge results and clinical history.

Results: Among the 173 patients diagnosed with egg allergy, 83.2% (n=144) developed tolerance, while 16.8% (n=29) had persistent allergy. Tolerance was observed in 61% (n=105) by age 3, 73% (n=126) by age 4, and 79% (n=136) by age 5. Patients with persistent EA had significantly higher egg-specific IgE levels at both admission (5.34 kU/L [0.42–3.74] vs. 1.27 kU/L [0.42–3.74], p=0.002) and final control (8.56 kU/L [1.18–40.4] vs. 0.96 kU/L [0.29–3.30], p<0.001), as well as larger wheal diameters in SPTs with raw egg at admission (9 mm [6–14] vs. 6 mm [5–9], p=0.008) compared to those who developed tolerance. The presence of nut allergy (persistent: 6/27, 22.2% vs. tolerant: 8/141, 5.7%; p=0.004) and legume allergy (persistent: 5/27, 18.5% vs. tolerant: 9/141, 6.4%; p=0.037) was also significantly associated with persistence.

Conclusion: Higher initial and sustained egg-specific IgE levels, larger SPT responses, and concomitant nut and legume allergies are potential risk factors for the persistence of EA. Additionally, the younger age of tolerance development observed in this cohort compared to previous studies may reflect population-specific differences in allergy phenotype.

Keywords: Egg allergy, IgE, food allergy

INTRODUCTION

Worldwide prevalence of food allergy (FA) ranges from 1-10% percent and is estimated at approximately 4% in children and 1% in adults, with an increasing trend over the past two decades. Approximately 6% of children experience an allergic food reaction in the first three years of their lives. When the frequencies of FAs are examined, it has been shown that cow's milk (2.5%), egg (1.5%) and peanut (1%) allergies are the most frequently seen allergies (1–3). FA is a growing health concern in childhood, with varying prevalence rates reported worldwide. Among the most common food allergens, egg allergy (EA) is particularly prominent during early childhood. The prevalence of egg allergy in children has been reported to range from 1.6% to 10.1% in different studies (4–6). While egg allergy is more frequently observed in early childhood, its prevalence decreases in later years (7). Approximately half of children are expected to develop tolerance within the first 2 to 3 years of life, with up to 80% achieving tolerance by the time they reach school age (8). Natural resolution has been reported in up to

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80% of cases by the age of 3, and in 38–90% of children by the age of 5 to 6 years (4,6,9). Additionally, approximately 70% of children with EA can tolerate egg in baked forms (10–12). In a study conducted in the United States, it was reported that 64.2% of children with EA were able to tolerate baked egg (7). Baked egg allergy tends to resolve more rapidly, with 94% of affected children developing tolerance by 12 years of age (6). On the other hand, FA has been shown to negatively impact the quality of life of affected individuals, placing significant limitations on the social activities of both patients and their families (13–15). Previous studies have identified several factors associated with the resolution of EA, including age at first egg introduction, egg-specific IgE levels, skin prick test (SPT) results, and the presence of coexisting atopic diseases and other food allergies (7,8,16).

This study aimed to evaluate the clinical and laboratory characteristics of children diagnosed with EA and to assess the frequency and timing of tolerance development. Additionally, it sought to identify potential factors associated with the persistence of EA.

MATERIALS and METHODS

The study was carried out in pediatric allergy and immunology clinic of Ankara Child Health and Disease Hematology Oncology Training and Research Hospital. Patients diagnosed with EA between June 2010 and June 2016 who had been followed for at least six months were included in the study. Data from patients' initial visits and final follow-up evaluations regarding sociodemographic characteristics, personal and family history, clinical complaints and symptoms, laboratory findings, SPT results, egg-specific IgE levels, peripheral eosinophil counts, and coexisting atopic diseases and FAs were recorded.

Diagnosis of egg allergy

Diagnosis of IgE-mediated EA was made when patients met the following criteria; history of recurrent urticaria/angioedema, respiratory distress, abdominal pain/vomiting, or anaphylaxis emerging within the first 2 hours after egg consumption and positive SPT results and/or egg-specific IgE levels. In the diagnosis of mixed type (IgE and cell-mediated) EA, the SPT and/or egg-specific IgE results were evaluated in children with atopic findings such as skin itching and dryness, especially on the face and extensor areas in the history and/or detected during physical examination. In patients with egg atopy, the diagnosis was made according to the improvement in clinical findings after appropriate skin care and elimination of egg from patients' diet and maternal diet of the breastfed infants and recurrence of complaints after re-addition of egg to the diet. The elimination period in our study was applied for 4–8 weeks, after which reintroduction was performed. Reintroduction was carried out in a stepwise manner, beginning with extensively heated/baked egg and progressing to less cooked forms, as recommended in the guidelines (17).

The diagnosis of non-IgE-mediated EA was made by the history, physical examination findings, and the recurrence of the complaints when the symptoms were regressed with the elimination of egg from diet and recurred when the egg was added to the diet.

According to the results of OFC performed at the last controls of the patients, or the statements of the families about the development of a reaction after accidental or deliberately ingestion of egg at home, "development of tolerance" and "persistence of allergy" were decided. SPT and egg-specific IgE tests were repeated in children whose parents' consent could be obtained, and Oral Food Challenges (OFCs) were performed with egg and baked egg according to their results. Baked-egg OFC was performed in patients with IgE-mediated egg allergy who were sensitized to unheated egg, as an initial and safer step for tolerance assessment. Subsequently, raw or less-cooked egg OFC was conducted in those who tolerated baked egg, to further evaluate their level of tolerance, following a stepwise approach as recommended in the guidelines (18). Patients who could consume egg without any problem were considered to have developed tolerance. Those who could not consume egg in any way, or who could only consume egg in baked form, were recorded separately and both groups were classified as "persistent allergy" groups.

Laboratory methods

Egg-specific IgE levels were measured by UniCAP (up to April 2015) and IMMULITE (after April 2015) techniques. Quantitative values were given in units of "kU/L". An egg-specific IgE level of ≥0.35 kU/L was considered indicative of sensitization to egg (8).

In the SPT, the commercial egg white antigen and/or raw egg was applied on the skin of the inner surfaces of both forearms or in younger patients applied on the back. SPT testing for house dust mites, animal epithelium, cockroach, mold fungi, and pollen was performed in patients who generally reported rhinitis symptoms or had a history of bronchiolitis. However, not all of these patients were classified as having allergic rhinitis.

Histamine (10mg/ml) was used as positive control. The test was read by waiting 15-20 minutes after the application. Diameters of induration of 3 millimeters and above were accepted positive (19).

Oral food challenge

Oral food challenge tests were performed on the patients in order to diagnose EA and to evaluate tolerance status during follow-up. Test was not performed in patients with signs of active infection or a history of using antihistamines in the last week. Egg elimination test was performed by the mother for 2-4 weeks before OFC for sick or breastfed babies. Reactions that developed during the OFC or within 2 hours after termination of the test were accepted as early reactions (including urticaria, erythema, angioedema, cough, wheezing, and vomiting), and reactions observed within 72 hours after termination of the test as late reactions (such as eczematous skin lesions, abdominal pain, diarrhea, or exacerbations of atopic dermatitis [AD]).

Boiled egg or baked egg (in muffins) were fed in increasing doses at 15-minute intervals, depending on the type of OFC. For the egg, the patient was fed with a whole of one boiled egg (6 g of egg protein), and, a whole muffin (each muffin was prepared to contain 2 g of egg protein) for a baked egg (11).

Statistical analysis

IBM Statistical Package for the Social Sciences, version 23.0 (SPSS Inc., Armonk, NY, IBM Corp., USA) was used for statistical analysis. Categorical variables were evaluated as numbers and percentages, while numerical measurements were evaluated as mean, standard deviation, median, interquartile range (IQR). The chi-square test was used to compare categorical variables between patient groups, and the Mann–Whitney U test was applied to compare numerical variables that did not show a normal distribution. $p<0.050$ indicated statistical significance.

RESULTS

A total of 173 patients with EA were included in the study. The median age at the initial visit was 7 months (IQR= 5–12 months), with a median symptom onset at 4 months (IQR= 2–6 months) and a median age at diagnosis of 7 months (IQR= 5–11 months). The median duration of follow-up was 19 months (range: 6–80 months).

Of the patients, 123 (69.4%) were male. Comorbid atopic conditions were observed in 54 (31.2%) of patients for asthma, 7 (4%) for allergic rhinitis, and 16 (11% in 146 aeroallergen-tested patients) showed aeroallergen sensitivity. In addition to EA, 95 (54.9%) of patients had other food allergies, most commonly to cow's milk 82 (47.4%), followed by legumes 15 (8.7%), nuts 14 (8.1%), wheat 11 (6.4%), and fish 6 (3.5%). Demographic and clinical characteristics of the study population are detailed in Table I.

A family history of allergic disease was reported in 38% of the patients (49/129). Maternal smoking during pregnancy was noted in 10.3% (12/117) of the cohort.

The most frequent clinical manifestation of EA was skin involvement 168 (97.1%), particularly AD 140 (81%). Anaphylaxis was documented in 6 (3.5%) of patients, and gastrointestinal symptoms were present in 5 (2.9%).

At the time of admission, the median egg protein-specific IgE level was 1.53 kU/L (IQR= 0.43–4.85). SPT results showed a median wheal diameter of 5 mm (IQR= 4–7) with commercial egg antigen and 7 mm (IQR= 5–9) with raw egg. The median eosinophil percentage was 5.35 (IQR= 3.33–8.08), with a median absolute eosinophil count of 500/mm³ (IQR= 300–800). The median total IgE level was 66 U/L (IQR= 11.5–141.5).

After excluding five patients diagnosed with eosinophilic esophagitis and proctocolitis based on gastrointestinal symptoms, the remaining 168 patients were classified into two groups as IgE-mediated and mixed-type EA, and a comparison between these groups was performed (Table II). There were 35 patients with IgE-mediated and 133 patients with mixed-type EA. The median age at initial visit was significantly higher in the IgE-mediated group compared to the mixed-type group (12 months [IQR= 7–20] vs. 7 months [IQR= 5–11], $p<0.001$). Similarly, the median age at symptom onset (6 months [IQR= 4–9] vs. 4 months [IQR= 2–6], $p<0.001$) and the median age at diagnosis (10 months [IQR= 6–18] vs. 7 months [IQR= 5–10], $p=0.001$) were significantly higher in the IgE-mediated group.

In contrast, no statistically significant differences were found between the two groups regarding egg protein-specific IgE levels, SPT results (both with commercial egg antigen and raw egg), eosinophil percentages, absolute eosinophil counts, or total IgE levels at admission (all $p>0.050$).

Table III presents the number of patients followed in each age range and the frequencies of tolerance development within these age ranges. According to the Table III, 63 patients developed tolerance before the age of two years and were subsequently discharged from follow-up. Among the 110 patients followed up to two years of age, 42 (38.2%) developed tolerance between two and three years. Of the 61 patients followed up

Table I: Patient characteristics

Variable	n	Values
Age at initial visit (month)*	173	7 (5-12)
Age at symptom onset (month)*	173	4 (2-6)
Age at diagnosis (month)*	173	7 (5-11)
Duration of follow-up *	173	19 (6-80)
Gender†		
Male	173	123 (69.4)
Other atopic conditions†		
Asthma	173	54 (31.2)
Allergic rhinitis	173	7 (4)
Aeroallergen sensitivity	146	16 (11)
Any food allergy besides egg†	173	95 (54.9)
Cow's milk	173	82 (47.4)
Legumes	173	15 (8.7)
Nuts	173	14 (8.1)
Wheat	173	11 (6.4)
Fish	173	6 (3.5)
Family history of an allergic disease†	129	49 (38)
Pregnant smokers†	117	12(10.3)
Symptoms of egg allergy†		
Skin	173	168 (97.1)
AD	173	140 (81)
Anaphylaxis	173	6 (3.5)
Gastrointestinal	173	5 (2.9)
Laboratory at admission		
Egg protein-specific IgE (kU/L)*	173	1.53 (0.43-4.85)
SPT (commercial egg antigen) (mm)*	173	5 (4-7)
SPT (egg) (mm)*	173	7 (5-9)
Eosinophilia (%)*	173	5.35 (3.33-8.08)
ANE (/mm³)*	173	500 (300-800)
Total IgE (U/L)*	173	66 (11.5-141.5)

:** *median (IQR),* **†:** *n(%),* ***ANE: Absolute number of eosinophils ***AD:*** *Atopic dermatitis,* ***IQR=*** *Interquartile range,* ***SPT:*** *Skin prick test*

Table II: Comparison of patients with IgE-mediated and Mixed-Type (AD) Egg allergies

	IgE-mediated		Mixed (AD)		p†
	n	Values	n	Values	
Age at initial visit (month)*	35	12 (7-20)	35	7 (5-11)	<0.001
Age at symptom onset (month)	35	6 (4-9)	35	4 (2-6)	<0.001
Age at diagnosis (month)	35	10 (6-18)	35	7 (5-10)	0.001
Laboratory at admission					
Egg protein-specific IgE (kU/L)*	31	2.5 (0.66-6.97)	120	1.47 (0.42-4.71)	0.266
SPT (commercial egg antigen) (mm)*	24	5 (5-7)	106	5 (4-7)	0.457
SPT (egg) (mm)*	24	7.5 (5-9)	105	7 (5-9)	0.451
Eosinophilia (%)*	30	4.75 (3.3-7.7)	101	5.4 (3.3-8.2)	0.543
ANE (/mm^3)*	30	550 (300-725	100	500 (300-800)	0.733
Total IgE (U/L)*	24	70.1 (29.9-140)	93	63.1 (10.4-141)	0.463

:** *median (IQR),* **†:** *Mann-Whitney U test,* ***AD: *Atopic dermatitis,* ***ANE:*** Absolute number of eosinophils ***IQR=*** *Interquartile range,* ***mo:*** *Months,* ***SPT:*** *Skin prick test*

Table III: Frequency of tolerance development of patients according to reaction type and age range

Age range	Age of tolerance*		IgE-mediated age of tolerance		Mixed (AD) age of tolerance	
	n	Values	n	Values	n	Values
<2 years	63	63(100%); 17(13-20)	8	8 (100%); 19 (14-21)	52	48 (92.3%); 17 (13-21)
2 to 3 years	110	42 (38.2%); 28 (25-33)	27	10 (37%); 27 (25-29)	81	32(39.5%); 29 (25-33)
3 to 4 years	61	21(34.4%); 40 (38-45)	17	2 (11.8%); 47	42	19 (45.2%); 39 (38-45)
4 to 5 years	34	10 (29.4%); 51 (50-53)	12	3 (25%); 50	20	7 (35%); 51 (48-52)
Total	173	144 (83.2%); 25 (18-38)	35	28 (80%); 27 (21-50)	133	113 (85%); 24 (17-36)

:** *Months,* **†:** *n(%); median (IQR),* ***AD: *Atopic dermatitis*

to three years of age, 21 (34.4%) developed tolerance between three and four years. Among the 34 patients followed up to four years of age, 10 (29.4%) developed tolerance between four and five years. Finally, of the 15 patients followed up to five years of age, 8 developed tolerance after the age of five. The frequencies of tolerance development according to allergy type are also presented in the Table III. Figure 1 illustrates that while both groups showed an increase in tolerance rates with age, the mixed-type group consistently exhibited slightly higher tolerance rates compared to the IgE-mediated group across all age ranges.

Finally, when comparing the groups of patients who developed tolerance and those whose EA persisted, the findings presented in Table 4 were obtained. A total of 168 patients were compared based on the persistence or resolution of EA. No significant differences were found between the groups regarding sex distribution, breastfeeding duration, maternal smoking during pregnancy, family history of allergy, eczema, anaphylaxis, coexistence of asthma or allergic rhinitis, aeroallergen sensitivity, or coexisting food allergies (all p>0.050).

However, several factors were significantly associated with persistent EA. Patients with persistent allergy had a significantly higher prevalence of nut allergy (6 [22.2%] vs. 8 [5.7%], p= 0.004) and legume allergy (5 [18.5%] vs. 9 [6.4%], p=0.037) compared to those who developed tolerance.

In terms of laboratory findings at the time of admission, patients with persistent allergy exhibited significantly higher median egg protein-specific IgE levels (5.34 kU/L [IQR=0.42-3.74] vs. 1.27 kU/L [IQR=0.42-3.74], p=0.002) and larger wheal diameters in SPT performed with raw egg (9 mm [IQR=6-14] vs. 6 mm [IQR=5-9], p=0.008).

Similarly, at the final follow-up, egg-specific IgE levels remained significantly elevated in the persistent group compared to the tolerance group (8.56 kU/L [IQR=1.18-40.4] vs. 0.96 kU/L [IQR= 0.29 - 3.30], p<0.001), and the wheal sizes in SPT with raw egg continued to be larger (9 mm [IQR=5-12] vs. 5 mm [IQR=0-10], p=0.034).

These findings suggest that higher initial and persistent egg-specific IgE levels, larger SPT reactions, and the coexistence of nut and legume allergies are associated with a greater likelihood of persistent EA.

DISCUSSION

The present study investigated the clinical course and determinants of tolerance development in children with egg allergy. Our findings demonstrated that the majority of patients developed tolerance during follow-up, while higher egg-specific IgE levels and larger skin prick test responses were associated with persistence. In addition, having concomitant nut and legume allergies was also found to be associated with the persistence of egg allergy. These results support previous reports while also providing new insights into the predictive factors of disease outcome.

Table IV: Comparison of characteristics of patients with persistent allergies and those who developed tolerance

	Persistent allergy		Tolerance		p
	n	Values	n	Values	
Demographic factors					
Sex (male)*	27	19 (70.4)	141	99 (70.2)	0.990†
Breastfeeding duration‡(month)	27	20 (9-24)	141	19 (10-24)	0.960†
Pregnant smokers*	13	1(7.7)	100	11 (11)	0.720†
Family history of food allergy*	17	1 (5.9)	106	2 (1.9)	0.363†
Family history of any allergy*	17	9 (52.9)	107	39 (36.4)	0.195†
Clinical factors*					
Eczema (AD)	27	21 (77.8)	141	118 (83.7)	0.419†
Skin	27	11 (40.7)	141	34 (24.1)	0.740†
Anaphylaxis	27	3 (11.1)	141	3 (2.1)	0.053†
Coexistence of asthma	27	5 (18.5)	141	46 (32.6)	0.144†
Coexistence of allergic rhinitis	27	2 (7.4)	141	5 (3.5)	0.313†
Coexistence of aeroallergen sensitivity	23	1 (4.3)	119	15 (12.6)	0.473†
Any food allergy besides egg	27	19 (70.4)	141	71 (50.4)	0.056†
Allergies to			141		
Cow's milk	27	16 (59.3)	141	61 (43.3)	0.126†
Nuts	27	6 (22.2)	141	8 (5.7)	0.004†
Wheat	27	3 (11.1)	141	8 (5.7)	0.384†
Legumes	27	5 (18.5)	141	9 (6.4)	0.037
Fish	27	1 (3.7)	141	5 (3.5)	1.000†
Laboratory parameters‡,(n)					
At admission					
Egg protein-specific IgE (kU/L)	25	5.34 (0.42-3.74)	126	1.27 (0.42-3.74)	0.002‖
SPT (commercial egg antigen) (mm)	19	6 (5-9)	111	5 (4-7)	0.211‖
SPT (raw egg) (mm)	19	9 (6-14)	110	6 (5-9)	0.008‖
Eosinophilia (%)	19	7.2 (4.4-10.9)	112	5.1 (3.3-7.6)	0.076‖
ANE (/mm^3)	19	600 (400-1200)	111	500 (300-800)	0.189‖
Total IgE (U/L)	17	89 (53-368)	97	57 (11-124)	0.069‖
Final control					
Egg-specific IgE (kU/L)	22	8.56 (1.18-40.4)	79	0.96 (0.29-3.30)	<0.001‖
SPT test (commercial egg antigen)(mm)	15	6 (4-7)	81	4 (0-7)	0.087‖
SPT test (egg) (mm)	15	9 (5-12)	80	5 (0-10)	0.034‖
Eosinophilia (%)	18	4.2 (2.7-6)	54	3.7 (2.2-6.4)	0.474‖
ANE (/mm^3)	18	400 (200-500)	54	300 (200-500)	0.793‖
Total IgE (U/L)	12	249 (107-828)	33	169 (25-243)	0.151‖

:** *n(%),* **†:** *Chi-square,* **‡:** *median (IQR),* **‖:** *Mann-Whitney U test,* ***AD: *Atopic dermatitis,* ***ANE:*** Absolute number of eosinophils, ***IQR=*** *Interquartile range,* ***mo:*** *Months,* ***SPT:*** *Skin prick test*

A review of the literature on the prognosis of EA. reveals that similar estimates have been reported regarding the age of tolerance development. Several studies in the literature have reported comparable ages for the development of tolerance in patients with EA, supporting the general understanding of its natural resolution. Sicherer et al. (8) reported that 50% of patients developed tolerance by age 6, while Ohtani et al. (9) demonstrated age-specific tolerance rates of 30% of children by 3 years of age, 59% by 5 years of age, and 73% by 6 years of age. In our study, tolerance developed at a younger age compared with that reported in previous studies. One possible explanation for this difference may be the variation in median egg-specific IgE levels. In the study by Sicherer et al.(8), higher egg-specific IgE levels (37% had levels of 2 kU/L, 34% had levels between 2–10 kU/L, and 28% had levels ≥10 kU/L) were reported, whereas lower levels were observed in our study. This discrepancy may be attributed to the higher proportion of patients with mixed-type allergic reactions in our cohort.

It is known that elevated egg-specific IgE levels and SPT results at the time of diagnosis are associated with the persistence of EA (20–22). In the study by Peters et al. (23), higher egg-specific IgE levels at both diagnosis and follow-up, as well as elevated SPT wheal sizes, were associated with persistent allergy. A similar relationship was reported by Sicherer et al. (8). In the study conducted by Yilmaz et al. (16) demonstrated a significant association between egg-specific IgE levels and persistent allergy, but no such association was found with SPT results. In our study, higher egg-specific IgE levels at admission were observed in patients with persistent allergy compared to those who developed tolerance, indicating a potential role in predicting disease course. In addition, patients with higher SPT results with raw egg at the initial visit were found to have a higher frequency of persistent allergy. These findings are consistent with previous reports in the literature.

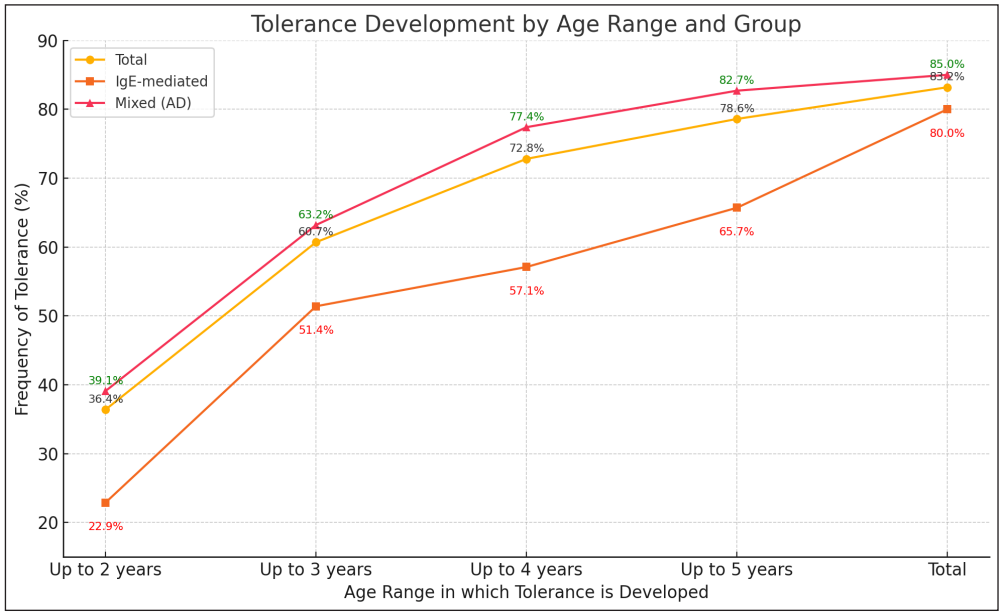

Figure 1: Tolerance development by age range and allergy type

In a population-based study, infants with eczema were found to be 5.8 times more likely to have hen's EA compared to healthy infants (24). There are few studies investigating the relationship between EA and AD. In a study by Kim et al. (25), moderate-to-severe AD was identified as a prognostic factor for persistent egg allergy and similar associations have been demonstrated in other studies (20,26). In another study which included 106 children with both AD and EA, 41% of patients developed tolerance by the age of 3, and 60% by the age of 5 and in infants with atopic dermatitis, and it was demonstrated that egg sensitization in infants with atopic dermatitis is frequently associated with a more prolonged or persistent course of egg allergy (27). In contrast to some studies suggesting that atopic dermatitis may be associated with a more persistent course of egg allergy, other reports have not confirmed this relationship. Peters et al. (4) reported that eczema was not a risk factor for persistent egg allergy. Similarly, Yilmaz et al.(16) found no association between the presence of skin symptoms and the development of tolerance. In our study, the presence of atopic dermatitis also had no significant impact on the development of tolerance.

Previous studies have demonstrated that a history of anaphylaxis is associated with a more persistent course of egg allergy (5,16). In our study, the number of patients with a history of anaphylaxis was limited; therefore, a definitive evaluation regarding its association with the persistence of egg allergy could not be made.

EA may occur in isolation or in combination with other FAs. Savage et al. (28) reported that 93% of 881 patients diagnosed with EA also had other concomitant FAs, and that these patients developed tolerance at a later age. In a study by Sicherer et al. (8) involving 213 patients with EA, 46.4% of patients who developed tolerance and 53.6% of those with persistent EA had additional FAs. Similarly, Peters et al. (23) found that 13% of patients who developed tolerance and 35% of those with persistent EA had multiple FAs, indicating a significantly higher rate of coexisting FAs in the persistent group. In our study, the presence of additional FAs was not significantly associated with tolerance development.

The major strengths of our study include the identification of key factors influencing the natural course of egg allergy through a comprehensive review of longitudinal patient data, and the ability to highlight critical considerations for clinical follow-up and management. However, the retrospective design, variability in follow-up durations, and inconsistency in the timing and frequency of control visits represent notable limitations that may affect the uniformity and generalizability of the results. In addition, the fact that the majority of the patients had atopic dermatitis and that the number of patients with IgE-mediated food allergy was very limited constitutes one of the major limitations of the study. Furthermore, the use of two different methods (UniCAP until April 2015 and IMMULITE after April 2015) for measuring egg-specific IgE levels during the study period can also be considered a limitation.

In conclusion, our study demonstrated that a higher egg-specific IgE level at the time of admission is a significant risk factor for the persistence of EA. These findings suggest that egg-specific IgE levels measured at diagnosis and during follow-up may serve as useful predictors of clinical prognosis. Additionally, when evaluating the age distribution of tolerance development, our results indicated an earlier resolution of EA compared to previous studies in the literature. This discrepancy may reflect differences in the natural course of EA across populations, potentially influenced by the type of allergic reaction.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Ankara Children's Hematology Oncology Education and Research Hospital (05.06.2017, reference number: 2017-051).

Contribution of the authors

Study conception and design: HY, EDM; data collection: HY, HG, İKÇ, TG; analysis and interpretation of results: HY, EDM, BB, EC; draft manuscript preparation: HY, EDB, MT, CNK, İKÇ; Reviewing the article before submission scientifically besides spelling and grammar: İKÇ, MT, EDM. 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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Original Article

Etiology and clinical features of hypertransaminasemia in children: A retrospective study from a tertiary care center in Türkiye

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ABSTRACT

Objective: This study aimed to investigate the etiology of hypertransaminasemia in children and to evaluate the clinical characteristics of patients based on age and underlying causes.

Material and Methods: A total of 210 pediatric patients aged between 1 month and 18 years who presented to the Pediatric Gastroenterology Outpatient Clinic with hypertransaminasemia were retrospectively analyzed. Hypertransaminasemia was defined as AST >50 IU/L and ALT >45 IU/L on at least two separate occasions within two months.

Results: The mean age of the patients was 5.36±5.30 years and 50.5% were female. At presentation, 30.5% were asymptomatic, with fever being the most common symptom (23.4%). Physical examination findings were normal in 53.8% of cases. Mean AST and ALT values were significantly higher in symptomatic patients compared to asymptomatic ones ($p<0.001$). No significant difference were observed between age groups in terms of mean ALT and AST values ($p=0.290$, $p=0.190$). Hypertransaminasemia was mild in 55.7% of patients, moderate in 20.5%, and severe in 23.8%. An underlying etiology was identified in 61% of cases. The most common cause was infectious diseases, followed by metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic/genetic disorders. Severe hypertransaminasemia was significantly more frequent in infectious diseases than in idiopathic cases or MASLD, whereas mild hypertransaminasemia was more common in MASLD and idiopathic cases compared to infections ($p<0.001$).

Conclusion: Infectious diseases and MASLD remain the leading causes of hypertransaminasemia in children. Infectious etiologies contribute across all age groups, MASLD is strongly linked to obesity and adolescence. As elevated transaminase levels may be the only clinical clue, especially in asymptomatic patients with normal physical examinations, careful follow-up and comprehensive evaluation are essential to avoid potential complications.

Keywords: ALT, AST, infectious diseases, NAFLD, pediatric, transaminases

INTRODUCTION

Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are intracellular enzymes found in hepatocytes and other cells and are called transaminases. AST is found not only in the liver but also in various extrahepatic tissues such as heart muscle, skeletal muscle, kidneys, pancreas, lungs, brain, erythrocytes, and leukocytes. ALT, on the other hand, is present in low concentrations in extrahepatic tissues and is considered more specific to hepatocellular damage (1, 2). Hypertransaminasemia occurs when these enzymes leak into the serum due to cellular injury or increased cell membrane permeability in affected tissues (1).

The degree of transaminase elevation does not always correlate with the severity of liver damage or prognosis (1). However, markedly elevated levels are typically associated with significant hepatocellular injury (1). For clinical interpretation, hypertransaminasemia is commonly classified into three categories: mild (<5× the upper limit of normal [ULN]), moderate (5-10×ULN), and severe (>10×ULN) (1). Mild to moderate elevations are often linked to chronic liver diseases such as chronic viral hepatitis, metabolic dysfunction-associated steatotic liver disease (MASLD), haemochromatosis, autoimmune hepatitis, alpha1-antitrypsin deficiency, Wilson's disease and celiac disease. Additionally drugs or non-hepatic causes including haemolysis, myopathy, thyroid disease, may contribute to hypertransaminasemia. Severe elevations ara

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often associated with acute viral hepatitis (e.g., A-E, herpes, EBV, CMV), drug or toxin induced liver injury, ischaemic hepatitis, autoimmune hepatitis, Wilson's disease, acute biliary obstruction, or acute Budd-Chiari syndrome (3,4).

In adults, the prevalence of elevated transaminase levels has been reported to be approximately 7.9%, with no identifiable etiology in many cases (5). Among asymptomatic adolescents, the prevalence ranges from 3.5% to 12.4% (3). However, the prevalence and etiology of hypertransaminasemia in children of all ages are not well defined, probably due to underestimation of the condition (3,5).

This study aimed to investigate the etiological spectrum and clinical characteristics of children who presented with hypertransaminasemia at a pediatric gastroenterology outpatient clinic.

MATERIALS and METHODS

This retrospective study included 210 pediatric patients aged between 1 month and 18 years who were admitted to the Pediatric Gastroenterology Outpatient Clinic of Kahramanmaraş City Hospital between June 2023 and December 2024 with hypertransaminasemia and who had elevated transaminases in at least two different measurements in the last two months. Patients with known chronic comorbidities such as chronic liver disease, chronic renal failure, congenital heart disease, type 1 diabetes mellitus, known genetic syndromes (e.g., Down syndrome), and myopathies were excluded from the study. For the purpose of statistical analysis, the highest recorded ALT and AST values were used.

Demographic data, presenting symptoms, clinical findings, laboratory results, imaging results and histopathological evaluations were collected from hospital electronic medical records and patient files. Hypertransaminasemia was defined as AST >50 IU/L and/or ALT >45 IU/L, in accordance with previously published national pediatric data (6,7). These fixed cut-off values were applied uniformly across all four age groups studied (1 month–2 years, 2–6 years, 6–12 years, and >12 years). Hypertransaminasemia was classified according to severity as mild (<5× upper limit of normal [ULN]), moderate (5–10× ULN), or severe (>10× ULN) (1).

Asymptomatic patients were identified incidentally, most often during routine laboratory evaluations such as preoperative evaluation, or general health checks. In some patients with non-specific complaints (e.g., sore throat, diarrhea), liver function tests were ordered as part of a broader evaluation for febrile or systemic illness. In cases with constipation or epistaxis, elevated transaminases were discovered incidentally, as these tests were performed as part of extended laboratory panels rather than targeted investigations.

Metabolic dysfunction associated steatotic liver disease (MASLD), the updated term for nonalcoholic fatty liver disease (NAFLD). The updated definition requires evidence of hepatic steatosis via imaging or biopsy along with at least one cardiometabolic risk factor. In this study, MASLD was diagnosed in patients with a body mass index (BMI) above the 85th percentile for age and sex (BMI z-score > +1), radiologic evidence of steatosis, and absence of other chronic liver diseases known to cause steatosis (8).

Drug-induced liver injury (DILI) was diagnosed according to the 2019 European Association for the Study of the Liver (EASL) Clinical Practice Guidelines, based on exclusion of other etiologies and at least one of the following criteria in patients with a relevant drug exposure history: (1) ALT ≥5×ULN; (2) ALP ≥2×ULN with elevated GGT and no bone disease; (3) ALT ≥3×ULN and total bilirubin >2×ULN (9).

The diagnosis of autoimmune hepatitis was based on the presence of interphase hepatitis, ALT, AST and serum IgG elevations and specific autoantibodies (10).

BMI Z-scores were calculated based on WHO growth standards. For children aged 0–5 years, malnutrition was defined as BMI Z-score < –2 SDS, overweight as > +2 SDS, and obesity as > +3 SDS. For those aged 5–19 years, malnutrition was defined as BMI Z-score < –2 SDS, overweight as > +1 SDS, and obesity as > +2 SDS. Values between these ranges were considered normal (11).

Statistical analysis

Statistical analyses were performed using IBM Statistical Package for the Social Sciences, version 21.0 (SPSS Inc., Armonk, NY, IBM Corp., USA). Categorical variables were expressed as numbers and percentages, while continuous variables were presented as mean±standard deviation. Normality of numerical data was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Categorical variables were compared using the Chi-square test when applicable, and the Mann-Whitney U test was used for non-normally distributed data. When significant differences were observed in Chi-square analyses involving more than two groups, post-hoc pairwise comparisons with Bonferroni correction were applied. Statistical significance was defined as a p-value of <0.050.

RESULTS

The mean age of the patients was 5.36±5.30 years (range:1 month-18 years), and 106 (50.5%) were female. At presentation, 30.5% of the patients were asymptomatic. The most common presenting complaint was fever (23.4%). Physical examination was normal in 113 patients (53.8%), while some had findings such as hepatomegaly, jaundice, or splenomegaly. Nutritional status varied, with both overweight/obesity and malnutrition observed (details in Table I).

Table I: Demographic and clinical characteristics of children with hypertransaminasemia n(%)

Age	
1 months-2 years	91 (43.3)
2-6 years	37(17.6)
6-12 years	51 (24.3)
>12 years	31 (14.8)
Gender	
Female	106 (50.5)
Male	104 (49.59
BMI z-score	
Normal	138 (65.7)
Malnourished	40 (19)
Overweight	19 (99
Obese	13 (6.2)
Complaints	
Fever	49 (23.4)
Sore throat	19 (9)
Jaundice	16 (7.6)
Diarrhea	13 (6.3)
Presentation due to overweight/obesity	12 (5.7)
Fatigue	11 (5.2)
Vomiting	11 (5.2)
Others (swelling in the neck, abdominal pain, constipation, failure to thrive, epistaxis, trauma, toxic ingestion, joint pain)	15 (7.1)
Asymptomatic	64 (30.5)
Physical examination findings	
Normal physical examinations	113 (53.8)
Upper respiratory and/or lower respiratory tract infection findings	43 (20.5)
Hepatomegaly	25 811.9)
Jaundice	16 (7.6)
Splenomegaly	13 (6.2)
Severity of hypertransaminasemia	
Mild	117 (55.7)
Moderate	43 (20.5)
Severe	50 (23.8)

Table II: Laboratory characteristics of children with hypertransaminasemia

	Asymptomatic	Symptomatic	p†
AST (IU/L)*	154.9±107.0	443.7±575.3	<0.001
ALT (IU/L)*	158.1±104.6	418.3±483.9	<0.001

**: (Mean±SD), †: Non parametric test*

Table III: Etiologies of Hypertransaminasemia in Children

Etiology	n (%)
Idiopathic	82 (39)
Infectious diseases	62 (29.5)
EBV	23 (29.5)
CMV	19 (29.5)
Sepsis	7 (29.5)
HAV	5 (29.5)
Rubella	3 (29.5)
Toxoplasma	2 (29.5)
Brucella	2 (29.5)
Influenza	1 (29.5)
MASLD	19 (9)
Metabolic/Genetic diseases	13 (6.2)
Wilson's disease	2 (6.2)
PFIC 8	1 (6.2)
SCYL 1 mutation	1 (6.2)
Johanson Blizzard syndrome	1 (6.2)
Glycogen storage type 3 disease	2 (6.2)
X-linked liver glycogenosis	1 (6.2)
Tyrosinemia type 1	1 (6.2)
Ornithine transcarbamylase deficiency	1 (6.2)
Hemachromatosis	1 (6.2)
Biotinidase deficiency	1 (6.2)
Alpha 1 antitrypsin deficiency	1 (6.2)
Autoimmune hepatitis	9 (4.3)
Muscular dystrophy	9 (4.3)
DILI (Pyrantel pamoate, sulfadiazine, isotretinoin, valproic acid, levetiracetam)	6 (2.9)
Celiac disease	4 (1.9)
Other (Trauma, mauriac syndrome, Maraş powder intake, mushroom poisoning)	4 (1.9)
Cholelithiasis and cholecystitis	2 (1)

Table IV: Severity of hypertransaminasemia classified by etiology

Etiology	Mild*	Moderate*	Severe*	Total (n)
Infectious diseases	20 (32.2)	15 (24.2)	27 (43.6)	62
MASLD	17 (89.5)	2 (10.5)	0 (0)	19
Metabolic/genetic disorders	8 (61.5)	0 (0)	5(38.6)	13
Idiopathic	43 (52.4)	16 (19.5)	23 (28.1)	82

: n(%)

The severity of hypertransaminasemia was mild in 117 (55.7%), moderate in 43 (20.5%) and severe in 50 (23.8%) patients (Table I). The mean ALT level was 342±427 IU/L (range 36-2.386 IU/L), and the mean AST level was 359±504 IU/L (range 27-3.042 IU/L). Mean AST and ALT levels were significantly higher in symptomatic patients compared to asymptomatic ones (p<0.001) (Table II). No significant differences in transaminase levels were observed among different age groups (ALT: p=0.290, AST: p=0.190).

An etiologic cause was identified in 128 patients (61%), with infectious diseases (e.g., EBV, CMV, sepsis, HAV, rubella, toxoplasmosis, brucellosis, influenza) being the most frequent cause, followed by MASLD and metabolic/genetic disorders (Table III). Among the metabolic/genetic group, rare conditions such as biotinidase deficiency were also observed. Although not typically considered a hepatic disorder, biotinidase deficiency has been reported to cause elevated liver enzymes in some patients (12).

Among patients diagnosed with autoimmune hepatitis, 66.7% had mild elevations. Similarly, 55.6% of muscular dystrophy patients, all patients with celiac disease, and 89.5% of those with MASLD exhibited mild hypertransaminasemia. In contrast, 43.6% of patients with infectious etiologies showed severe enzyme elevations (Table IV). Severe hypertransaminasemia was

Table V: Comparison of transaminase serum levels among the most common etiologies of hypertransaminasemia in children

	Etiology				p
	Idiopathic	Infectious diseases	MASLD	Metabolic/ Genetic diseases	
AST(IU/L)*	260.7±390.9	573.0±679.5	84.8±49.5	334.9±369.7	<0.001[1,2,3]
ALT(IU/L)*	293.5±414.5	499.9±546.7	134.4±58.6	243.0±226.6	<0.001[1,3]

***:** *(Mean±SD),* ***MASLD:** *Metabolic Dysfunction-associated Steatotic Liver Disease,* [1]*idiopathic vs. infectious diseases,* [2]*idiopathic vs. MASLD,* [3]*infectious diseases vs. MASLD*

Table VI: Distribution of hypertransaminasemia etiologies in children according to age groups.

	Age				p
	1 months-2 years*	2-6 years*	6-12 years*	>12 years*	
Etiology					
Idiopathic	46 (56.1)[a]	16 (51.6)[a,b]	15 (38.5)[a,b]	5 (20.8)[b]	
Infectious diseases	30 (36.6)[a]	10 (32.3)[a]	15 (38.5)[a]	7 (29.2)[a]	<0.001
MASLD	0 (0.0)[a]	1 (3.2)[a,b]	8 (20.5)[b,c]	10 (41.7)[c]	
Metabolic/Genetic diseases	6 (7.3)[a]	4 (12.9)[a]	1 (2.6)[a]	2 (8.3)[a]	

***:** *n (%), Different superscript letters (a, b, c) indicate significant pairwise differences between age groups (p<0.050, post-hoc Bonferroni corrected Chi-square test).*

significantly higher in infectious diseases than in the idiopathic group and MASLD, and in metabolic/genetic diseases than in MASLD. Mild hypertransaminasemia was significantly higher in MASLD and idiopathic group compared to infectious diseases (p<0.001). In infectious diseases, both AST and ALT levels were found to be elevated while the lowest values were observed in the MASLD group (Table V).

Infectious diseases contributed to hypertransaminasemia across all age groups at similar rates (p=0.718). MASLD was rarely observed in younger children but showed a marked increase with age: 52.6% of all MASLD cases occurred in patients older than 12 years, and within the >12 year age group, 41.7% were diagnosed with MASLD. Metabolic/genetic disorders, while overall rare, were most frequently encountered in the 1 month–2 years age group (46.1%). The proportion of patients with idiopathic hypertransaminasemia was highest in the 1 month–2 years (56.1%) and 2–6 years (51.6%) groups and decreased with age (20.8% in >12 years). The most common etiologies were idiopathic in the youngest two age groups, idiopathic and infectious diseases in the 6–12 years group, and MASLD in adolescents over 12 years (Table VI). Additionally, MASLD was identified in 59.4% of patients classified as overweight or obese.

Abdominal ultrasonography was performed in all patients, and imaging was normal in 67.7% of children for liver parenchyma and bile ducts. Hepatomegaly was detected in 25 (11.9%) patients, hepatosteatosis in 21 (9.3%), splenomegaly in 13 (6.2%), heterogeneity in liver parenchyma in 8 (3.5%), cholelithiasis and cholecystitis in 2 (1%), and hepatic haemangioma in 1 (0.4%) patient. Liver biopsy was performed in 13 (6.2%) patients and histopathological results contributed to the diagnosis in 11 (84.6%) patients. Liver biopsy confirmed autoimmune hepatitis in nine patients and Wilson's disease in two patients. In two other patients—one with SCYL1 mutation and one with ornithine transcarbamylase (OTC) deficiency—the biopsy revealed nonspecific and nondiagnostic histological changes, including macrovesicular steatosis, pericellular fibrosis, hydropic degeneration and atrophic changes in hepatocytes, moderate lymphocytic infiltration in portal areas, and mild bile duct injury.

DISCUSSION

The increased use of routine biochemical testing has led to a rise in incidental findings of hypertransaminasemia. The symptoms accompanying hypertransaminasemia are highly variable (13). While Sanrı et al. (7) reported obesity as the most common presenting complaint (29.1%), and Serdaroğlu et al. (8) found fatigue in 53.4% of cases, this study showed that 30.5% of patients were asymptomatic. Fever was the most frequent presenting symptom (23.4%), and physical examination was unremarkable in 53.8% of patients. This highlights that hypertransaminasemia may remain clinically silent and the importance of routine monitoring for laboratory abnormalities even in the absence of symptoms or abnormal physical findings.

The prevalence of idiopathic hypertransaminasemia varies among studies. Serdaroğlu et al. (7) reported idiopathic hypertransaminasemia in 6.4% of cases. In the cohort by Iorio et al. (13), idiopathic hypertransaminasemia was observed in 135 out of 425 patients (31.7%), including both those with transient (<6 months) and persistent (>6 months) enzyme elevation. Çeltik et al. (15) reported a rate of 27.1% in the neonatal period, with 12% in their overall cohort. In our study, no etiological cause was identified in 39% of patients.

In underdeveloped countries, hepatitis A virus (HAV) infection remains the leading cause of hypertransaminasemia in children.

Conversely, in developed countries, MASLD is the primary cause, followed by hepatobiliary, genetic and autoimmune diseases (3). The etiological spectrum of hypertransaminasemia in our cohort largely reflects both local epidemiology and global trends. Infectious diseases emerged as the most common cause (29.5%), consistent with previous studies from Türkiye reporting similar rates 34% in Serdaroğlu et al. (7) and 34.4% in Çeltik et al. (15). MASLD was the second leading cause in our study (9%), in line with global data showing its rising prevalence in children and adolescents.

Hepatotropic viruses (hepatitis A, B, C, E, and non-A-E viruses) and systemic febrile infections such as EBV and CMV frequently cause moderate to severe elevations in aminotransferase levels (3,4,16). In addition to viral infection, bacterial sepsis or parasite infections may also lead to hepatitis (17). In our study, the leading etiological infectious cause was EBV infection (11%), followed by CMV infection (9%) and bacterial sepsis (3.4%). HAV infection was observed less frequently (2.4%) because hepatitis A vaccination in the national immunization program since 2012. Among patients with infectious etiologies, 43.6% exhibited severe and 24.2% moderate hypertransaminasemia. Interestingly, infectious etiologies were observed at similar frequencies across all age groups in our study. This suggests that infectious diseases remain a substantial and age-independent contributor to pediatric hypertransaminasemia in our population, despite improvements in vaccination coverage and public health measures.

MASLD has become an increasingly prevalent cause of hypertransaminasemia in children and adolescents (8). This trend has been underscored by recent consensus statements and pediatric guidelines, which highlight MASLD as one of the most significant chronic liver diseases of childhood (8,18,19). A global meta-analysis estimated MASLD prevalence at 7.6% in the general pediatric population and approximately 36% among children with obesity (20). An autopsy study revealed that histological MASLD prevalence ranges from 0.7% in 2-4 year olds to 17.3% in 15-19 year olds (21). Mild to moderate hypertransaminasemia is commonly observed in MASLD (22). In our study, similar to the literature, 89.5% of the MASLD group had mild hypertransaminasemia and 52.6% were >12 years of age. MASLD was present in 59.4% of our overweight/obese patients. Recent meta-analyses indicate that the prevalence of MASLD among children with obesity is approximately one-third (around 34.2%), though this varies across regions. This condition is now recognized as a significant public health concern. Particularly worrisome is the pediatric-onset form, since early manifestation leads to a longer duration of exposure to metabolic risk factors and thereby increases the likelihood of lifelong complications (19).

Congenital metabolic and genetic diseases are more prevalent in pediatric patients compared to adults, accounting for 20–30% of liver diseases in infancy and childhood (3). Iorio et al. (13) reported a 12% prevalence of genetic diseases among children with isolated hypertransaminasemia. In our study, metabolic/genetic diseases were responsible for 6.2% of children with hypertransaminasemia and were mostly observed in the 1 month-2 years age group (46.1%), similar to the literature.

Autoimmune hepatitis has a lower prevalence than viral hepatitis and MASLD (4, 23). The most common non-hepatic cause of transaminase elevation is muscle diseases. In case of muscle disease, ALT and AST elevation is accompanied by creatine kinase (CK) elevation, which indicates muscle destruction (3). The prevalence of autoimmune hepatitis was 4.3%, and the prevalence of muscular dystrophy in our study was also 4.3%.

Drug-induced liver injury (DILI) is an important but often unrecognised cause of hypertransaminasemia in children. The true incidence of pediatric DILI is unknown, but children are estimated to account for approximately 10% of all reported cases. Most cases are subclinical, presenting only with laboratory abnormalities. The most frequently implicated hepatotoxic drugs in children are antibiotics and antiepileptics (24,25). In our study, DILI was rare (2.9%) and most often related to antiepileptic drugs.

The limitations of our study are that it is retrospective in design, macro AST was not studied, and transaminase cut-off values reflecting our population are not known. In addition, we used fixed cut-off values (AST >50 IU/L and ALT >45 IU/L) rather than age- and sex-specific thresholds.

CONCLUSION

This study highlights that infectious diseases and MASLD remain the leading causes of pediatric hypertransaminasemia in Türkiye. The age-independent role of infections, the strong association of MASLD with adolescent obesity, and the high proportion of asymptomatic cases represent the distinctive contributions of this study. These results emphasize the need for clinicians to remain vigilant even in asymptomatic children and support public health strategies that combine infection control with urgent efforts to prevent and manage childhood obesity.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Kahramanmaras Sutcu Imam University Medical Research (16.12.2024, reference number: 34/05).

Contribution of the authors

Study conception and design: Dr. Melike Arslan; data collection: Dr. Melike Arslan; analysis and interpretation of results: Dr. Melike Arslan; draft manuscript preparation: Dr. Melike Arslan

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Clinical characteristics and outcomes of invasive pneumococcal disease in neonates: A retrospective study

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ABSTRACT

Objective: Invasive pneumococcal disease (IPD) is a rare but serious cause of neonatal sepsis associated with significant morbidity and mortality. Despite widespread pneumococcal conjugate vaccine (PCV) use in infants, neonates remain vulnerable due to lack of direct vaccination and potential vertical or horizontal transmission. This study aimed to characterize the clinical, laboratory, and microbiological features of neonatal IPD and to evaluate associated outcomes in this high-risk population.

Material and Methods: We conducted a retrospective cross-sectional study of neonates (0–30 days old) diagnosed with IPD between September 2019 and April 2025. Diagnosis was confirmed by isolation of *Streptococcus pneumoniae* from sterile body fluids or PCR detection. Demographic, clinical, microbiological, and outcome data were analyzed.

Results: Among 68 IPD cases, 12 neonates with pneumococcal bacteremia were identified; no meningitis or focal infections were observed. The cohort had equal sex distribution, mean gestational age of 35±3.8 weeks, and 33.3% had comorbidities. Early-onset sepsis (≤72 hours) accounted for 25% of cases, with the remainder presenting as late-onset sepsis (>72 hours). One neonate had concurrent SARS-CoV-2 infection. All patients survived; one preterm infant developed neurological sequelae attributable to pre-existing conditions. Antibiotic susceptibility testing showed reduced sensitivity to penicillin (20%) and ceftriaxone (16.7%), while vancomycin and linezolid remained highly effective.

Conclusion: Neonatal invasive pneumococcal bacteremia, although uncommon, continues to pose clinical challenges, particularly due to evolving antimicrobial resistance. Our findings emphasize the importance of vigilant clinical monitoring and tailored antimicrobial therapy in this vulnerable population. Continued surveillance and prospective studies are warranted to assess the impact of maternal and early infant vaccination strategies on neonatal IPD prevention.

Keywords: Antibiotic resistance, bacteremia, pneumococcal infections, sepsis, *Streptococcus pneumoniae*

INTRODUCTION

Streptococcus pneumoniae is a Gram-positive diplococcus and the etiologic agent of invasive pneumococcal diseases (IPD), which include bacteremia, sepsis, and meningitis. Globally, IPD continues to pose a substantial health burden, particularly in children under five years of age, and remains associated with considerable morbidity and mortality despite the availability of effective vaccines. In 2015, pneumococcal infections were estimated to cause approximately 335.000 deaths in this age group, a decrease from 541.000 deaths in 2008 prior to the widespread implementation of conjugate vaccines in low-income countries (1). Although pneumococcal conjugate vaccines (PCVs) have reduced the incidence of severe infections and antibiotic resistance, the emergence of non-vaccine serotypes continues to pose challenges (2). In Türkiye, PCV13 was introduced into the national immunization program in April 2011 and has been administered in a 2+1 schedule (at 2, 4, and 12 months) since 2019 (3). The indirect protection conferred by pneumococcal conjugate vaccine

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(PCV) to neonates and infants too young to receive PCV—mediated through herd immunity— has been well documented in the literature. Studies report a 40% to 83% reduction in IPD incidence in this age group, along with an overall declining trend in IPD rates (4,5).

While *S. pneumoniae* infections are rare in neonates, they are associated with considerable mortality and morbidity (6). Transmission may occur via the birth canal, intrauterine spread, or horizontal contact with caregivers (7). Despite herd immunity achieved through childhood vaccination, neonates remain vulnerable to IPD via vertical or horizontal transmission. Pneumococcus accounts for 1–11.5% of neonatal sepsis cases, with reported mortality rates ranging from 14.3% to 60%, often manifesting as sepsis or early-onset pneumonia (8-10). Although neonatal cases are often described as early-onset sepsis, findings from the largest published series indicate that only 6.8% of cases developed symptoms within the first 48 hours, while the majority presented after the first week of life (6-8). These data highlight the variable timing of disease onset and underscore the importance of clinical vigilance throughout the neonatal period.

Given the limited recent data on neonatal pneumococcal infections, this study aimed to characterize the clinical and microbiological features of invasive pneumococcal disease in this unvaccinated population.

MATERIALS and METHODS

This retrospective cross-sectional study evaluated a total of 68 invasive pneumococcal disease (IPD) cases identified in children aged 0–18 years between September 1, 2019, and April 1, 2025. Among these, 12 neonates (postnatal age 0–30 days) with culture-confirmed Streptococcus pneumoniae bacteremia were included as the study sample. Data were obtained from the hospital information system. For each case, demographic characteristics (gender, age, date and type of specimen), risk factors, clinical and laboratory findings, antibiotic susceptibility, and outcomes were recorded.

IPD was confirmed by isolating *Streptococcus pneumoniae* from sterile body fluids (blood, cerebrospinal fluid, synovial/bone, pleural, or middle ear fluid) or by detecting pneumococcal DNA via polymerase chain reaction (PCR) in blood or cerebrospinal fluid samples. All microbiological procedures followed standardized protocols.

Neonatal sepsis was classified according to the timing of symptom onset. Early-onset neonatal sepsis (EONS) was defined as the occurrence of clinical manifestations within the first 72 hours after birth, most frequently resulting from vertical transmission of pathogens from the maternal genital tract during labor or delivery (11). Late-onset neonatal sepsis (LONS) was defined as symptom onset beyond 72 hours of life, generally associated with horizontal acquisition of pathogens from the postnatal environment, including community or healthcare-associated sources (12).

Gram-stained preparations were assessed under 100× magnification for polymorphonuclear leukocytes and Gram-positive diplococci using a BioMérieux device (France). Clinical samples were inoculated onto appropriate culture media and incubated using the WASPLab® system (Copan, Italy), with conditions tailored to the sample type. Blood samples were processed in BACT/ALERT bottles (bioMérieux, France) and incubated for 120 hours in the BACT/ALERT 3D system. Positive signals prompted Gram staining and subcultures, which were incubated for 24–48 hours. Suspicious colonies—alpha-hemolytic, small, gray, mucoid, or button-like with central depression—were identified using MALDI-TOF MS (VITEK® MS, bioMérieux, France). Colonies were transferred to metal slides, overlaid with 1 µL of α-cyano-4-hydroxycinnamic acid matrix solution, air-dried for ~15 minutes, and analyzed.

Antibiotic susceptibility testing was performed using the VITEK® 2 Compact system (bioMérieux, France), and results were interpreted according to EUCAST guidelines. Bacterial inocula were adjusted to 0.5 McFarland standard. A 280 µL aliquot was added to sterile saline (0.45%) in transparent tubes, vortexed, and loaded with AST-ST03 cards into the system. Minimum inhibitory concentrations (MICs) were determined automatically for each antimicrobial agent. As all cases in our cohort represented bacteremia without meningitis, EUCAST non-meningitis breakpoints were applied. Results are presented as susceptible (S), intermediate (I), or resistant (R), expressed as n/N (%), to enhance clarity and minimize misinterpretation in the context of a small sample size.

Statistical analysis

Descriptive statistical analyses were conducted using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). Categorical variables, including sex, prematurity, comorbidities, clinical presentation, and antimicrobial susceptibility patterns, were summarized as frequencies and percentages. Continuous variables, such as gestational age and postnatal age at diagnosis, were assessed for normality and presented as means with standard deviations. Owing to the small sample size and the rarity of neonatal IPD, no inferential statistical analyses or group comparisons were performed. Antibiotic susceptibility rates were calculated based on the proportion of isolates meeting EUCAST-defined sensitivity thresholds. This approach ensured an accurate and transparent representation of clinical and microbiological characteristics within the neonatal IPD cohort.

RESULTS

Among the 68 patients aged 0–18 years who were diagnosed and followed with IPD during the study period, 12 were identified in the neonatal period. In these 12 neonates, Streptococcus

Table I: Clinical characteristics of neonates with invasive pneumococcal disease (n = 12)*	
Prematurity	5 (41.7)
Comorbid conditions	4 (33.3)
Nutrition	
Exclusive breastfeeding	6 (50.0)
Breast milk + formula	6 (50.0)
Respiratory and circulatory support	
Mechanical ventilation	3 (25.0)
Non-invasive ventilation	4 (33.3)
Inotropic support	1 (8.3)

**: n(%), Prematurity is defined as gestational age <37 weeks. Comorbid conditions include congenital anomalies and other significant underlying diseases*

Table II: Laboratory characteristics of neonates with invasive pneumococcal disease (n = 12)	
White Blood Cell count*	11.717±2.446
Absolute Neutrophil Count*	4.996±1.861
Absolute Lymphocyte Count*	4.434±1.822
Hemoglobin *	12.3±1.9
Platelet count*	373.333±143.281
C-reactive Protein†	6.5 (0–46)
Sodium*	138.8±3.6
Potassium*	5.4±1.0
Aspartate Aminotransferase*	36±30
Alanine Aminotransferase*	19±11.5

**: mean ± SD, †: Median (range)*

pneumoniae was isolated exclusively from blood cultures; no growth was detected in cerebrospinal fluid or other sterile body sites, and multiplex PCR panels for sepsis or meningitis/encephalitis were negative in all cases. A detailed overview of demographic features, clinical presentations, comorbidities, and timing of sepsis onset for all neonates is provided in Table I.

Of the 12 included patients, 6 were female and 6 were male. The mean gestational age was 35±3.8 weeks; 5 were born preterm (gestational ages: 36+6, 32+6, 28+5, 32, 30+1, 33+4 weeks). All infants were delivered via cesarean section.

Four patients (33.3%) had underlying comorbidities, including meningomyelocele, tracheoesophageal fistula, gastroschisis, and liver abscess; one of these patients was also small for gestational age (SGA) due to intrauterine growth restriction.

Admission diagnoses were early-onset sepsis in 4 cases (33.3%), late-onset sepsis in 4 (33.3%), and respiratory distress in 4 (33.3%). Based on timing of blood culture positivity, 4 patients had early-onset bacteremia (≤3 days of life), while 8 had late-onset bacteremia (>3 days). Laboratory parameters, including complete blood count and inflammatory markers at admission, are summarized in Table II.

One patient was born to a COVID-19 positive mother. The infant, delivered at 39+1 weeks via cesarean section, presented with fever on postnatal day 4. The infant's nasopharyngeal PCR was also positive for SARS-CoV-2. *S. pneumoniae* was isolated from the initial blood culture, and empiric ampicillin-gentamicin was escalated to vancomycin. The infant completed 10 days of antibiotics and was discharged without sequelae. No other patients had viral coinfections or positive PCR panel results.

One neonate, born at 30 weeks of gestation following preterm premature rupture of membranes (PPROM) and fetal distress, developed IPD manifesting as isolated bacteremia on postnatal day 30. The patient had pre-existing comorbidities, including respiratory distress syndrome, grade 4 intraventricular hemorrhage, posthemorrhagic hydrocephalus, and hepatic hematoma, and subsequently required ventriculoperitoneal (VP) shunt placement. The long-term neurological sequelae observed in this case were attributable to the underlying conditions rather than pneumococcal infection; all other patients recovered without complications.

Antibiotic susceptibility rates for *S. pneumoniae* isolates were as follows: penicillin 20%, ampicillin 16.7%, clindamycin 18.2%, erythromycin 16.7%, ceftriaxone 16.7%, levofloxacin 75%, moxifloxacin 80%, linezolid 100%, tetracycline 9.1%, vancomycin 91.7%, and trimethoprim-sulfamethoxazole 100%.

DISCUSSION

In this 5.5-year retrospective analysis, 12 neonates with invasive pneumococcal disease were identified, all presenting with Streptococcus pneumoniae bacteremia. No cases of meningitis or other focal infections were detected, as cerebrospinal fluid cultures and multiplex PCR panels were uniformly negative. The cohort had equal sex distribution and a mean gestational age of 35 ± 3.8 weeks, with nearly half born preterm; all infants were delivered by cesarean section. One-third had notable comorbidities, including congenital anomalies or intrauterine growth restriction. Clinical presentations were evenly divided among early-onset sepsis, late-onset sepsis, and respiratory distress. Only one infant experienced long-term neurological sequelae, attributed to severe pre-existing conditions rather than pneumococcal infection. All remaining neonates recovered without complications. Overall, IPD in this cohort manifested exclusively as isolated bacteremia, with favorable outcomes following timely management.

Streptococcus pneumoniae is a rare but well-recognized cause of neonatal sepsis, associated with considerable morbidity and mortality (7). Most published data consist of case reports or small series. The largest to date, by Hoffmann et al. (8), included 29 neonatal IPD cases and reported a mortality rate of 14.3%, with most cases presenting as late-onset sepsis. In contrast, Malhotra et al.(7), and Gomez et al.(13) found earlier presentations in 69% and 100% of their small case series, respectively, though sample sizes were limited to five and four cases. Gomez et al. (13), also reported a mortality rate of 50%, while a more recent study reported 39%, with the highest rates

in meningitis cases (14). In our series of 12 neonates with confirmed pneumococcal bacteremia, 25% presented with early-onset sepsis, whereas the majority (75%) were diagnosed with late-onset sepsis. No deaths occurred. The favorable outcomes observed in our cohort could be attributed to advanced supportive care practices, such as early recognition of sepsis, optimized antimicrobial use, and intensive neonatal monitoring. Furthermore, our study represents a post-vaccine era cohort, which may explain lower mortality compared to earlier reports. Notably, no cases of pneumococcal meningitis were observed, a condition historically linked with higher fatality (13,15).

Infants can become colonized with *S. pneumoniae* soon after birth, and the prevalence of colonization tends to rise as they get older. Colonization rates of approximately 0.3%, 7%, 4%, and 10% have been observed at 0, 4, 8, and 12 months of age, respectively (16). Although *S. pneumoniae* is an uncommon cause of neonatal sepsis, infections due to this pathogen have been described as having a more severe clinical course. Interestingly, some studies have reported that *S. pneumoniae* was identified more frequently than Group B Streptococcus (15%) in cases of early-onset sepsis. This suggests that *S. pneumoniae* may represent a more significant pathogen in early neonatal sepsis than previously appreciated (17). In our study, four patients presented with early-onset and four with late-onset neonatal sepsis. Although national data on the incidence of neonatal IPD in Türkiye are limited, the rate appears to be markedly reduced following widespread implementation of pneumococcal conjugate vaccines. Consistent with this, only a small number of neonatal IPD cases were identified over a 5.5-year period at our institution, one of the largest pediatric centers in the country, underscoring the rarity of this condition in the current post-vaccination era.

Maternal factors are thought to play a critical role in the pathogenesis of neonatal IPD, particularly in early-onset disease. Several reports have suggested that vertical transmission during labor or colonization of the maternal genital tract may contribute to infection in neonates (18,19). Other potential risk factors include maternal chorioamnionitis, premature rupture of membranes, and preterm delivery, all of which may facilitate perinatal acquisition of *S. pneumoniae* (20). Despite the biological plausibility of these associations, robust data remain limited, as maternal screening for pneumococcal carriage is not routinely performed in most settings. In our study, detailed obstetric histories and maternal colonization status could not be retrieved due to the retrospective design and incomplete clinical documentation. This gap highlights the importance of prospective surveillance incorporating maternal data to better delineate risk factors for neonatal IPD and inform preventive strategies.

Increasing antimicrobial non-susceptibility among *Streptococcus pneumoniae* isolates has been documented in recent regional reports and mirrors the low penicillin and ceftriaxone susceptibilities observed in our cohort. A recent Turkish surveillance analysis reported a significant rise in penicillin non-susceptibility from 1.9% (2017–2019) to 20.3% (2020–2022), with appreciable ceftriaxone non-susceptibility noted in some periods, underscoring an emerging local trend toward reduced β-lactam susceptibility (21). A two-decade analysis of invasive pneumococcal isolates from Türkiye similarly documented increasing non-susceptibility to penicillin and macrolides over time, suggesting that these trends are not isolated to a single center. More recent multicenter surveillance in neighboring regions and broader analyses report variable but notable rates of reduced susceptibility to penicillins and third-generation cephalosporins, reinforcing the need for ongoing regional monitoring to guide empiric therapy (22). Compared with these regional data, our finding of low penicillin (20%) and ceftriaxone (16.7%) sensitivity likely reflects local epidemiology and the impact of serotype replacement and antimicrobial selection pressure in the post-PCV era. These observations support empiric coverage that includes agents active against resistant pneumococci (e.g., vancomycin), particularly in severe neonatal infections or where initial therapy fails, while underlining the imperative for routine, up-to-date susceptibility surveillance and incorporation of serotype data in future studies to better correlate resistance patterns with vaccine-driven serotype shifts.

Over the years, the introduction of PCVs with broader serotype coverage has led to a marked decline in the incidence of IPD in children. Studies have consistently demonstrated this reduction across vaccine-included serotypes (23,24). Following the implementation of PCV7, a significant decrease was observed in the covered serotypes, which subsequently created the need for vaccines with expanded serotype coverage. In our country, PCV13 is currently in use as the latest formulation. However, due to the retrospective design of our study, we were unable to capture temporal trends in serotype distribution. Nevertheless, we believe that the low number of positive cases observed in our cohort likely reflects the impact of widespread vaccination. Furthermore, the low case count, absence of mortality, and the presence of sequelae only in an infant with significant pre-existing comorbidities suggest that the favorable outcomes observed in our cohort may, in part, reflect the impact of high pneumococcal vaccine coverage on reducing disease severity in the neonatal population.

Historically, neonatal IPD case series have contributed significantly to understanding disease progression. However, older reports may not reflect current trends due to improvements in healthcare and neonatal outcomes. To our knowledge, recent large-scale analyses focusing on post-vaccine era neonatal IPD remain scarce. We believe our study offers updated insights into this rare but serious condition.

Infant immunization at two months contributes to herd immunity, indirectly protecting neonates (25). Maternal vaccination could offer additional protection via transplacental antibodies, though

it is not currently recommended in pregnancy (26). To strengthen prevention strategies, prospective studies should evaluate the safety and efficacy of maternal pneumococcal vaccination, particularly in high-risk populations such as preterm infants or those with underlying comorbidities. Enhanced perinatal screening and surveillance programs, including monitoring of maternal colonization, may further guide targeted interventions. In addition, integration of pneumococcal vaccination into broader maternal immunization platforms—such as those for pertussis and influenza—could improve uptake and provide dual maternal–infant benefits. From a health systems perspective, reinforcing vaccine outreach, ensuring equitable access, and maintaining robust antimicrobial stewardship are essential complementary measures to reduce the burden of neonatal IPD.

Limitations:

This study has several limitations. The small sample size and the absence of a non-pneumococcal control group restrict the generalizability of the findings. The retrospective design also limited access to complete obstetric histories, which may have provided additional insights. Furthermore, incidence rates and pneumococcal serotype data were not analyzed, precluding a broader epidemiological interpretation of the results. Although our study provides valuable clinical insights, the lack of pneumococcal serotype data limits the ability to assess serotype-specific epidemiology and clinical outcomes. This is particularly relevant in the post-vaccine era, as shifts in circulating serotypes may influence both disease severity and antimicrobial susceptibility patterns. Future studies incorporating serotyping are warranted to better characterize the evolving epidemiology of neonatal invasive pneumococcal disease and to guide targeted prevention strategies.

CONCLUSION

Despite widespread infant immunization, pneumococcal infections continue to pose a clinically significant risk in neonates. The presence of unvaccinated and vulnerable populations underscores the importance of strengthening vaccine outreach and ensuring equitable access to neonatal intensive care. Although current vaccines have reduced the overall disease burden, the emergence of non-vaccine serotypes highlights the need for continued epidemiological surveillance and microbiological monitoring. From a clinical perspective, neonates presenting with sepsis should be considered at risk for *Streptococcus pneumoniae*, particularly when unresponsive to standard first-line regimens. In such scenarios, empiric coverage with agents active against resistant strains, including a glycopeptide when meningitis is suspected or devices such as ventricular shunts are present, should be considered until susceptibility results are available. De-escalation to the narrowest effective antibiotic and adherence to evidence-based treatment durations (10–14 days for bacteremia, up to 21 days for meningitis or focal infection) are recommended. Future research should adopt a multicenter design incorporating systematic serotyping and comprehensive incidence estimation to better define the epidemiology of neonatal IPD. Such studies would allow correlation of circulating serotypes with antimicrobial resistance patterns, evaluate vaccine impact across diverse populations, and inform evidence-based strategies for prevention, empiric therapy, and maternal-infant vaccination programs.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Ankara Bilkent City Hospital (12.03.2025, reference number: TABED 1-25-1112).

Contribution of the authors

Conceived and designed the study, collected and analyzed the data, and drafted the manuscript;BD, is contributed to data acquisition, the statistical analysis and interpretation of data, laboratory analysis, and interpretation of microbiological findings; GİB, provided critical revisions of the manuscript and contributed to the study design. All authors reviewed and approved the final version of the manuscript; AY,SÖ,TE,AYB,DÇ,BD,ŞSO.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Original Article

Evaluation of awareness and knowledge levels of pediatric residents on brucellosis

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ABSTRACT

Objective: Brucellosis, endemic in Türkiye, requires physicians' awareness for early recognition, diagnosis, and treatment. This study aimed to assess pediatric residents' knowledge and awareness of brucellosis.

Material and Methods: Between August and September 2023, pediatric residents with 0–48 months of training at Ankara Bilkent City Hospital were surveyed using an online 15-item, cross-sectional, multiple-choice questionnaire covering demographics, clinical findings, diagnosis, treatment, and prophylaxis. Each item included four response options reflecting different diagnostic or therapeutic approaches. Incomplete or unsubmitted forms were excluded.

Results: A total of 174 residents participated (73% female). Of these, 84 (48.3%) were senior and 90 (51.7%) junior. Senior residents had significantly higher correct response rates than juniors regarding complications (88.1% vs. 83.3%), clinical symptoms (91.1% vs. 70.2%), laboratory findings (77.8% vs. 58.3%), diagnostic serology (52.2% vs. 28.6%), magnetic resonance imaging (MRI) for sacroiliitis (83.3% vs. 65.5%), antibiotic combinations (72.2% vs. 50.0%), and treatment of spondylitis (47.8% vs. 23.8%) ($p<0.050$ for all). Knowledge improved progressively with residency year (linear-by-linear association, $p<0.001$).

Conclusion: Senior residents demonstrated significantly greater knowledge of brucellosis compared to juniors. These results emphasize the importance of structured, continuous education that begins early in residency and is reinforced periodically. Given the endemic nature of brucellosis in Türkiye, targeted and regularly updated training programs for pediatric residents may improve recognition, diagnostic accuracy, appropriate treatment, and clinical outcomes. Future multi-center studies may better reflect regional differences in awareness and training.

Keywords: Awareness, brucellosis, children, knowledge, residents

INTRODUCTION

Brucellosis is a widespread and re-emerging zoonotic disease that continues to pose a significant public health challenge worldwide. In Türkiye, brucellosis remains endemic, particularly in the Central, Eastern, and Southeastern Anatolia regions (1). The disease is caused by Gram-negative coccobacilli of the genus *Brucella*, most commonly *B. melitensis*, *B. abortus, B. suis, and B. canis* (2). Transmission occurs primarily through the consumption of unpasteurized dairy products, direct contact with infected animals or their secretions, and inhalation of contaminated aerosols, while congenital transmission is rare (1). Clinical manifestations are variable and may include fever, night sweats, malaise, fatigue, arthralgia, and hepatosplenomegaly. In children, growth retardation, weight loss, and anorexia may also be observed (3). Brucellosis can mimic other zoonotic or febrile diseases, such as Crimean-Congo hemorrhagic fever or malaria, which may lead to delayed diagnosis (4). Osteoarticular involvement is among the most common complications, including sacroiliitis and spondylitis (5). Culture remains the diagnostic gold standard; however, serologic methods are more practical in routine clinical settings. The Rose Bengal test (RBT) is commonly used for screening, while the Standard Agglutination Test (SAT) is employed for diagnosis. In endemic

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regions, a SAT titer of ≥1:160 is considered diagnostic, although false-positive or false-negative results may occur due to cross-reactions or the prozone phenomenon (6). Magnetic resonance imaging (MRI) is valuable for detecting complications such as spondylitis or sacroiliitis. Treatment requires combination antibiotic therapy effective against intracellular bacteria, typically doxycycline plus rifampin for children older than eight years, or rifampin plus trimethoprim-sulfamethoxazole for younger children. The minimum treatment duration is six weeks, and an aminoglycoside may be added for focal or complicated cases (1). Prevention includes avoiding unpasteurized dairy consumption, strengthening veterinary control programs, and using protective measures for high-risk occupational groups (7). Beyond prevention, physician knowledge and awareness are crucial for early recognition, accurate diagnosis, and appropriate management. Studies from Yemen, Namibia, Saudi Arabia, Uganda, and Tanzania have shown that insufficient knowledge among healthcare workers—particularly in exposure history taking, serological testing, and recognition of clinical findings—contributes to underdiagnosis and underreporting of brucellosis (8–12).

However, studies specifically evaluating pediatric residents' awareness and knowledge are scarce. Considering that pediatric residents are on the frontline in diagnosing, treating, and following up pediatric brucellosis, evaluating their level of knowledge is essential to design targeted educational interventions. This study therefore aimed to assess the awareness and knowledge of pediatric residents regarding brucellosis and to identify areas requiring further training to improve early diagnosis, appropriate treatment, and effective prevention strategies.

MATERIALS and METHODS

Study design and participants

This cross-sectional descriptive study was conducted among 174 pediatric residents under training for 0–48 months at Ankara Bilkent City Hospital between August and September 2023. Inclusion criteria were voluntary participation and complete submission of the questionnaire form. Residents who declined participation or submitted incomplete responses were excluded from the analysis.

Questionnaire (instrument)

A 15-item multiple-choice questionnaire, designed and administered via Google Forms, evaluated demographic characteristics, clinical manifestations of pediatric brucellosis, diagnostic approaches (including serological and imaging methods), treatment regimens, and prophylaxis practices.

Procedures (recruitment and consent)

The survey link was distributed through official departmental communication channels and closed social media groups after obtaining administrative approval. Before accessing the questionnaire, participants viewed an information and consent statement explaining the study purpose, voluntary nature, and confidentiality of responses. Electronic informed consent was obtained prior to participation. To prevent response bias, the correct answers were shared only after participants had submitted their responses.

Seniority status of pediatric residents

In Ankara City Hospital's Department of Pediatrics, residents take a seniority examination at the 24th month of training. Those who pass are designated senior pediatric residents. First and second-year residents are considered juniors, whereas third and fourth-year residents are classified as seniors.

Resident rotation structure

At Ankara Bilkent City Hospital, pediatric residents in the Department of Pediatrics rotate regularly through inpatient and outpatient services of the Pediatric Infectious Diseases Unit. Each of the two inpatient wards hosts two senior and two junior pediatric residents on rotation every month. In addition, two senior residents and one to two junior residents are assigned monthly to the two Pediatric Infectious Diseases outpatient clinics.

This rotation structure ensures that both junior and senior residents are continuously exposed to the diagnosis, management, and follow-up of pediatric infectious diseases, including brucellosis, during their residency training.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, USA). Categorical variables were presented as numbers and percentages and compared using the chi-square test. Continuous variables were expressed as mean and standard deviation (SD) or median (minimum–maximum), as appropriate. Linear-by-linear association tests were used to evaluate trends between residency year and correct response rates. Statistical significance was defined as two-tailed $p<0.050$. A target sample size of 170 participants was estimated to achieve 80% power at a 95% confidence level, assuming an expected response rate of 80%.

RESULTS

A total of 174 pediatric residents (73% female) completed the survey. Of these, 84 (48.3%) were junior residents (1st year: n = 40; 2nd year: n=44) and 90 (51.7%) were senior residents (3rd year: n=43; 4th year: n=47).

Responses to questions on clinical manifestations

Correct-response rates for questions addressing the clinical symptoms and complications of brucellosis are presented in

Table I: Comparison of the correct response rates of pediatric residents according to seniority status to the survey questions related to clinical symptoms and signs of brucellosis in children

	Junior residents* (n=84)	Senior residents* (n=90)	Total* (n=174)	p
Which of the following is the most common route of transmission of brucellosis?	74 (88.09)	84 (93.33)	158 (90.80)	0.232
Which of the following is not one of the complications of brucellosis?	59 (70.23)	75 (83.33)	134 (77.01)	0.034
Which is one of the frequently seen clinical symptoms and signs of brucellosis?	60 (71.42)	82 (91.11)	142 (81.61)	0.001

**: n(%)*

Table II: Comparison of correct response rates of pediatric residents according to seniority status to the survey questions related to laboratory-imaging findings of brucellosis

	Junior residents* (n=84)	Senior residents* (n=90)	Total* (n=174)	p
Which of the following is/are not one of the laboratory findings of brucellosis?	49 (58.33)	70 (77.77)	119 (68.39)	0.006
Which serologic test is used to diagnose brucellosis in clinical practice?	24 (28.57)	47 (52.22)	71 (40.80)	0.004
What titers are considered significant in non-endemic and endemic areas in the standard tube agglutination test?	23 (27.38)	53 (58.88)	76 (43.67)	0.239
Which screening test is used to detect brucellosis?	59 (70.23)	70 (77.77)	129 (74.13)	0.911
What is one of the factors that causes cross-reaction in the standard tube agglutination test?	42 (50.00)	48 (53.33)	90 (51.72)	0.660
Inhibition of agglutination at low dilutions due to excess antibodies or nonspecific serum factors is defined by which of the following and can result in a false negative result?	44 (53.57)	55 (61.11)	99 (56.89)	0.245
Which imaging modality is preferred in the diagnosis of sacroiliitis secondary to brucellosis?	55 (65.47)	75 (83.33)	130 (74.71)	0.012

**: n(%)*

Table I. Senior residents achieved significantly higher correct-response rates than juniors for the item "Which of the following is not one of the complications of brucellosis?" (88.1% vs. 83.3%; p=0.034) and for "Which of the following is a common clinical symptom/sign of brucellosis?" (91.1% vs. 71.4%; p=0.001). There was no statistically significant difference between groups for the item "Which of the following is the most common route of transmission of brucellosis?" (p=0.232). As the residency year increased, the rate of correct responses to clinical-symptom-related questions also increased (linear-by-linear association test, p<0.001).

Responses to questions on laboratory findings and diagnosis

Correct responses to items assessing diagnostic approaches and laboratory tests are summarized in Table II. Senior residents demonstrated higher accuracy for the item "Which of the following is not a laboratory finding of brucellosis?" (77.8% vs 58.3%; p=0.006) and for "Which serological test is used in the diagnosis of brucellosis in clinical practice?" (52.2% vs 28.6%; p=0.004). Similarly, for the question "Which of the following imaging modalities is preferred for the diagnosis of sacroiliitis secondary to brucellosis?", senior residents provided more correct answers (83.3% vs. 65.5%; p=0.012). These results indicate that senior residents possess stronger diagnostic knowledge and familiarity with both serologic and imaging-based evaluation of brucellosis.

Responses to questions on treatment and prophylaxis

Responses to items on treatment regimens and prophylactic measures are displayed in Table III. Senior residents outperformed juniors on the question "Which antibacterial combination is commonly used in the treatment of brucellosis?" (72.2% vs. 50.0%; p=0.003) and on "Which antibiotic is commonly added to the combination therapy in Brucella spondylitis?" (47.8% vs. 23.8%; p=0.001). Overall, senior residents demonstrated a significantly higher understanding of appropriate antibiotic combinations and adjunctive therapy for complicated cases.

Trend by residency year

When analyzed by residency year, knowledge scores improved progressively from first-year to fourth-year residents, while the proportion of incorrect responses declined correspondingly (linear-by-linear association, p<0.001).

Table III: Comparison of correct response rates of pediatric residents according to seniority status to the survey questions related to treatment and prophylaxis in cases of brucellosis

	Junior residents* (n=84)	Senior residents* (n=90)	Total* (n=174)	p
Which combination of the following is commonly used in clinical practice in the treatment of brucellosis	42 (50.00)	65 (72.22)	107 (61.49)	0.003
Which of the following antibiotics is commonly added to the combined treatment of brucella spondylitis in clinical practice?	20 (23.80)	43 (47.77)	63 (36.20)	0.001
Which agents are used and for how long after high-risk exposure to brucellosis?	29 (34.52)	41 (45.55)	70 (40.23)	0.138

***:** *n(%)*

DISCUSSION

This study is one of the first to evaluate the awareness and knowledge levels of pediatric residents regarding the diagnosis, treatment, and follow-up of brucellosis in children. Brucellosis remains a major zoonotic infection with significant implications for child health, particularly in endemic regions such as Türkiye, where timely diagnosis and appropriate management are essential for reducing morbidity (1). The present findings demonstrated that senior pediatric residents had significantly higher knowledge and awareness scores than junior residents, reflecting the positive impact of cumulative clinical exposure and residency-based infectious diseases training. This trend aligns with prior literature showing that physicians' diagnostic accuracy and confidence in managing brucellosis improve with experience and targeted education (8–10). However, most earlier studies have focused on general practitioners or primary healthcare physicians, while data on pediatric residents remain scarce (11,12). Therefore, our study fills an important gap by specifically assessing knowledge within a pediatric training context, where early recognition and management of brucellosis are vital for preventing complications and long-term sequelae in children.

An important finding of our study was that senior pediatric residents demonstrated greater awareness of the clinical manifestations of brucellosis than junior residents. Previous studies from endemic regions have reported similar challenges in clinical recognition among healthcare providers. In Yemen, physicians had high theoretical awareness but frequently failed to inquire about exposure or consider brucellosis in cases of prolonged fever (8). In Namibia, nearly all physicians (98.4%) did not include brucellosis in the differential diagnosis of persistent fever (9). Significant deficiencies in case recognition were also noted among Saudi primary care physicians, while only 15.3% of Ugandan medical workers demonstrated adequate knowledge of transmission and symptoms (10,11). In Tanzania, insufficient understanding among practitioners contributed to underdiagnosis and underreporting (12). Moreover, inadequate familiarity with diagnostic algorithms and limited awareness of serologic interpretation have been highlighted as contributing factors to delayed or missed diagnoses (13,14). Compared with these studies, our cohort—particularly senior residents—showed higher recognition rates of clinical features (91.1% vs 70.2%), reflecting the potential benefit of structured pediatric residency curricula that emphasize infectious diseases training. This suggests that clinical experience and formal instruction during residency play key roles in improving disease recognition. Consistent with our findings, a previous study among Saudi primary healthcare physicians also demonstrated that awareness of clinical symptoms increased with professional experience (15). However, several reports have highlighted that nonspecific and diverse presentations of brucellosis often lead to delayed or missed diagnoses (16).

Laboratory investigations are fundamental to the diagnosis of brucellosis. In our study, senior pediatric residents demonstrated significantly higher accuracy than junior residents in laboratory-related questions, particularly those concerning serologic screening and cross-reaction mechanisms. Previous studies have confirmed that adequate physician knowledge of serologic testing is essential for diagnostic precision (14,17,18). In Yemen, only one-third of physicians routinely employed serologic testing for prolonged fever cases, while similar underutilization was observed among physicians in Namibia (8,9). Significant deficiencies in confirmatory test requests were also reported among Saudi primary care physicians (10). In Uganda, despite positive attitudes, only 13.6% of medical workers performed routine serologic testing, and comparable diagnostic gaps were observed in Tanzania (11,12). Compared with these reports, our senior residents achieved notably higher correct response rates for serologic screening (52.22% vs. 28.57%) and recognition of cross-reactions (77.77% vs. 58.33% for juniors). These findings suggest that structured pediatric residency training, with its emphasis on infectious disease diagnostics, may enhance both conceptual understanding and practical application. However, several studies have indicated persistent deficiencies in the interpretation of serologic results and recognition of diagnostic pitfalls—particularly the prozone phenomenon—which may still lead to misdiagnosis or delayed treatment (19).

The use of correct antibiotic combinations is crucial for the effective treatment of brucellosis. In our study, senior

pediatric residents demonstrated higher accuracy in identifying appropriate antimicrobial regimens and adjunctive agents for focal disease compared to junior residents (72.22% vs. 50.00% and 47.77% vs. 23.80%, respectively). Previous studies from endemic countries have revealed considerable variability in adherence to guideline-based therapy. In Yemen, 72% of physicians recognized the doxycycline–rifampin regimen, but only half were aware of the recommended duration (8). In Namibia, poor compliance with standardized treatment protocols was reported, and inconsistent prescribing patterns were observed among Saudi primary care physicians (9,10). Similarly, in Uganda, although general attitudes were positive, actual treatment practices were suboptimal (11). Comparable deficiencies in antimicrobial knowledge and application have also been documented among healthcare professionals in other endemic settings (14). These discrepancies may be attributed to differences in structured training exposure. Pediatric residents benefit from systematic guideline-based instruction, whereas practicing physicians often rely on experiential learning and may lack regular educational updates. Our findings thus reinforce that structured residency programs incorporating evidence-based infectious disease management can improve both theoretical and practical competence. Consistent with prior studies, inappropriate or incomplete antimicrobial use remains a key contributor to treatment failure and relapse (20). In pediatric cases, it has been further emphasized that antibiotic combinations and treatment duration should be individualized according to disease course and clinical response (21,22).

Awareness of brucellosis management among pediatric residents is critical to reducing disease burden in endemic regions. Insufficient awareness and diagnostic delays have been widely reported among primary healthcare workers and general physicians (23). Our findings indicate that knowledge gaps persist even within pediatric training programs, particularly in early diagnosis and treatment decision-making. Previous studies have consistently emphasized the necessity of continuous education and professional development for healthcare providers (24,25). Evidence from endemic countries demonstrates that limited familiarity with diagnostic protocols, poor case reporting, and inadequate clinical suspicion remain major barriers to disease control (8–12). Our results, showing stepwise improvement in knowledge with increasing residency seniority, complement these observations by highlighting the positive impact of structured, guideline-based education. Taken together, these data underscore that sustained, repetitive, and standardized training interventions are essential not only within pediatric residency curricula but also across broader healthcare systems in endemic regions.

This study has certain limitations. First, it was conducted among pediatric residents from a single tertiary center, which may limit the generalizability of the findings. Second, the online survey format may have allowed some participants to consult additional resources, potentially inflating accuracy rates. Nevertheless, this work represents one of the first focused evaluations of pediatric residents' knowledge and awareness of brucellosis.

To enhance early recognition, accurate diagnosis, and evidence-based management of brucellosis, structured and regularly reinforced educational modules should be integrated into pediatric residency curricula. Considering Türkiye's endemic status, implementing targeted, case-based learning and refresher programs from the early years of training may significantly improve diagnostic precision, guideline adherence, and clinical outcomes.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Ankara Bilkent City Hospital (16.08.2023, reference number: E2-23-4862).

Contribution of the authors

Concept;ÖG, AÖP; Design: ÖG, AÖP, Data Collection or Processing: AYG, SKY, BG; Analysis or Interpretation: FÜ, AYG; Database and Informatics Support: FÜ, AYG; Literature Search: ÖG, AYG, SKY, BG; Writing – Original Draft: ÖG, AÖP, AYG; Writing – Review & Editing: ÖG, AÖP, AYG, FÜ, BG, SKY

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Conflict of interest

The authors declare that there is no conflict of interest.

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Case Reports

Atypical presentation of the Azerbaijani infant with pycnodysostosis: A case report with a de novo mutation

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ABSTRACT

Pycnodysostosis is a rare, autosomal recessive illness that is generally pathognomonic. It is characterized by the postnatal onset of short limbs, small stature, and global hyperostosis, as well as acro-osteolysis with sclerosis of the terminal phalanges. It has been shown that approximately 30% of patients have parental consanguinity. This condition is brought on by a mutation in the cathepsin K (CTSK) gene. To date, 34 distinct CTSK mutations have been found in patients. This lysosomal enzyme helps break down bone matrix proteins, including some forms of collagen, and is mostly present in osteoclasts. Between 90 and 95 percent of all organic bone matrix is made up of type 1 collagen, which is still uncleaved. Unusual bone and dental development results from the accumulation of undigested collagen fibrils by these patients' fibroblasts. Pycnodysostosis is a clinical characteristic that only occurs when cathepsin K is completely lost. About 10% of patients are found to have mental impairment. We present an infant with pycnodysostosis, undiagnosed before presentation at birth.

Keywords: Cathepsin K, infant, pycnodysostosis

INTRODUCTION

Pycnodysostosis is a rare, autosomal recessive illness that is generally pathognomonic. It is characterized by the postnatal onset of short limbs, small stature, and global hyperostosis, as well as acro-osteolysis with sclerosis of the terminal phalanges. It has been shown that approximately 30% of patients have parental consanguinity. This condition is brought on by a mutation in the cathepsin K (CTSK) gene (1). To date, 34 distinct CTSK mutations have been found in patients. This lysosomal enzyme helps break down bone matrix proteins, including some forms of collagen, and is mostly present in osteoclasts. Between 90 and 95 percent of all organic bone matrix is made up of type 1 collagen, which is still uncleaved. Unusual bone and dental development results from the accumulation of undigested collagen fibrils by these patients' fibroblasts. Pycnodysostosis is a clinical characteristic that only occurs when cathepsin K is completely lost. About 10% of patients are found to have mental impairment (2). We present an infant with pycnodysostosis, undiagnosed before presentation at birth.

CASE REPORTS

A 40-day-old boy was presented to the clinic with concerns regarding inadequate weight gain, respiratory difficulty, and chest deformity. The infant was born at 38 weeks of gestation via cesarean section, following a consanguineous marriage, due to premature rupture of membranes. At birth, the infant's APGAR scores were 7/8 at the 1st and 5th minutes, with a weight of 3070 g, a length of 53 cm, and a head circumference of 35 cm. Immediately after birth, the child exhibited signs of respiratory distress, including chest retraction, tachypnea, and nasal flaring, necessitating intubation due to the severity of the condition. The infant underwent mechanical ventilation for the first 24 hours of life and received a 10-day course of treatment for early-onset gram-negative bacteremia. Neurosonography revealed a grade 2 intraventricular hemorrhage. The infant was discharged home in stable condition on day 10 of life. Upon examination, the child was found to be underweight (3150 gr/5th percentile), exhibited craniofacial abnormalities and snoring. Additional findings included short stature, frontal and parietal bossing, beaked nose, hypoplastic midface,

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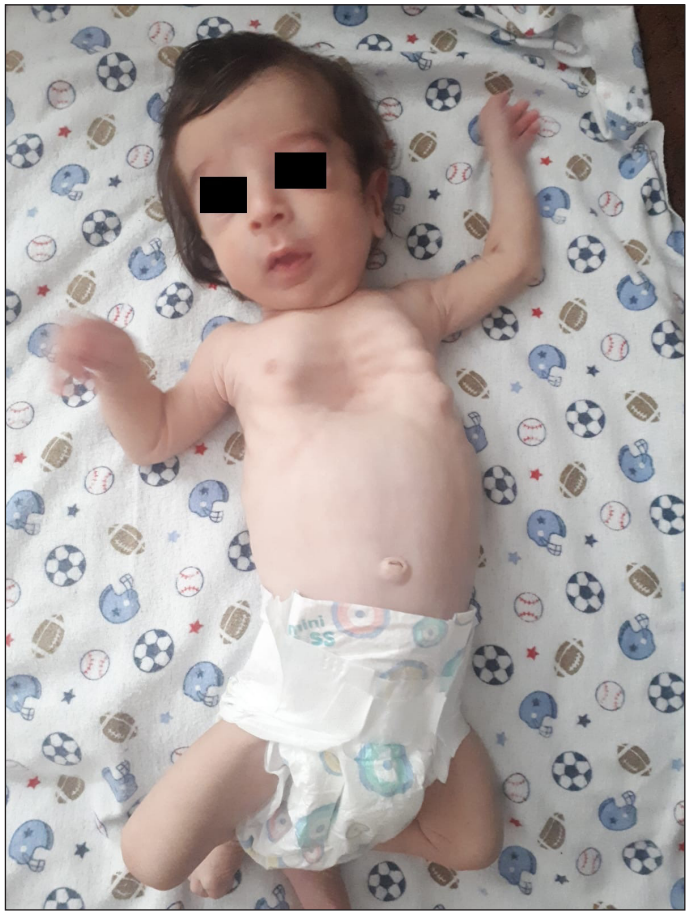

Figure 1: The patient's physical appearance

micrognathia, brachydactyly with broad thumbs and spoon-shaped fingernails, wrinkled skin over the fingertips and chest deformities in the form of pectus excavatum (Figure 1). Laboratory results indicated HGB-9.7 g/dL, Ca-9.74 mg/dL, P-6.08 mg/dL, and ALP-201 IU/L. The child was referred to pediatric surgery, cardiology, neurology, and genetics due to the presence of dysmorphic facial features. The pediatric surgeon applied vacuum bell therapy, a nonoperative management of pectus excavatum, which led to an improvement in respiratory symptoms. During the neurological examination, the child presented with glossoptosis and micrognathia, suspected Pierre-Robin syndrome, and further diagnostic evaluation was recommended. EEG, neurosonography, echocardiography, abdominal USG, hip joint USG, and metabolic screening test results were all normal. Whole exome sequencing showed that the patient was homozygous for a pathogenic variant in the CTSK gene NM_000396.4 mutation c.830C>T /p. Ala277Val / rs74315304R associated with pycnodysostosis.

DISCUSSION

Pycnodysostosis is a systemic skeletal disorder. Disproportionately small stature, a large cranium, fronto-occipital prominence, proptosis, bluish sclerae, a beaked and pointed nose, a small face and chin, an obtuse mandibular angle, a high-arched palate, and dental malocclusion with primary tooth retention are all characteristics that are seen during infancy and early childhood (3). Cranial sutures remain open. Fingers are short and clubbed from acro-osteolysis or aplasia of the terminal phalanges, and the hands are small and square. Repeated fractures cause knock-knee deformity. Craniosynostosis, low-energy fractures, chronic pain, respiratory problems, and dental complications may cause significant morbidity and reduce quality of life (4).

A review of the literature revealed p.Ala277Val the mutation in our patient had previously been found in a 31-year-old woman with thyroid cancer and in a 1-year-7-month-old girl of Arab origin (5,6). Structural anomalies, including mandibular hypoplasia and a small and narrow palate that contributed to narrowing the airway, were found to be similar to the findings in our patient. Growth and developmental delays were noted, similar to this patient. However, unlike our patient, no fractures developed. We emphasize the importance of early recognition, genetic testing, and multidisciplinary care for effective treatment and support. The most reliable method for diagnosing pycnodysostosis is the detection of mutations in the CTSK gene. Genetic testing for early identification of pycnodysostosis can result in more immediate treatment and therapy (7). Clinicians can monitor patients for complications like fractures, scoliosis, and joint abnormalities and take preventive actions to reduce these risks by knowing the hereditary etiology. Diagnosis of pycnodysostosis is based on the clinical presentation, and medical treatment for the condition is symptomatic. The differential diagnoses of pycnodysostosis include osteopetrosis, acroosteolysis, mandibuloacral dysplasia, cleidocranial dysplasia, and osteogenesis imperfecta. There are no standardized treatment protocols or guidelines for affected individuals (8). Upon reviewing the literature, our case is the earliest diagnosed infant.

Contribution of the authors

Study conception and design: TI, SE; data collection: TI, SE; analysis and interpretation of results: TI, SE; draft manuscript preparation: TI, SE. 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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