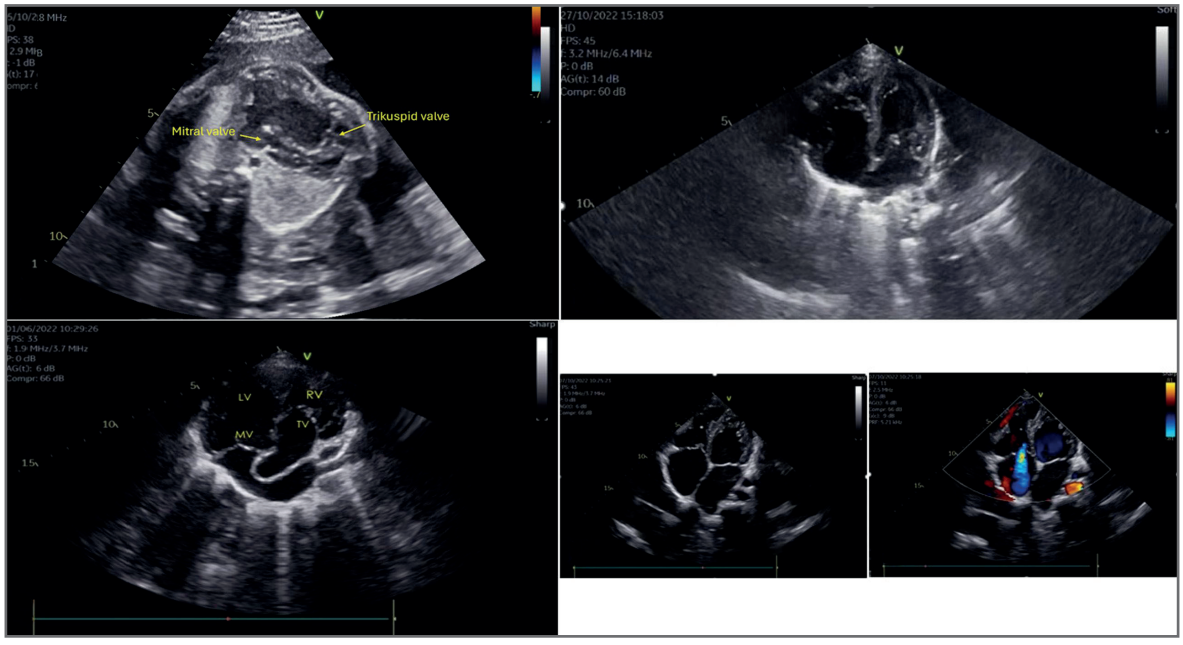
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Research Article

Psychosocial impact of continuous glucose monitoring on mothers of children with type 1 diabetes: A cross-sectional study

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ABSTRACT

Background: Mothers of children with type 1 diabetes (T1D) often experience heightened anxiety and caregiver burden due to continuous management tasks and vigilance for hypoglycemia, especially overnight. Continuous glucose monitoring (CGM), by providing real-time glucose information and alerts, may be associated with changes in these psychosocial outcomes beyond glycemic indices. We evaluated whether CGM use is associated with maternal anxiety and caregiver burden and examined its relationship with glycemic control.

Methods: In this single-center, comparative cross-sectional study, mothers of children aged 2–18 years with T1D were grouped as CGM users (≥3 months) or non-users (never). Maternal anxiety (STAI-S/T) and caregiver burden (ZBI) were assessed; children's HbA1c and change in HbA1c (ΔHbA1c) were recorded. Group differences and adjusted associations were examined.

Results: A total of 130 mothers were included (CGM n=65; non-CGM n=65); children were 49.2% girls, with a mean age of 11.66 ± 3.84 years. Groups were generally comparable in sociodemographic and clinical characteristics; paternal education differed and was adjusted for. Diabetes duration was similar between groups: median (IQR) 2.94 (1.87–6.64) vs. 2.96 (1.83–5.99) years, p=0.419. Among mothers of CGM users, mean caregiver burden, state anxiety, and trait anxiety scores were lower than among non-users, and these associations persisted after adjustment for prespecified sociodemographic and clinical covariates. Children using CGM had the lowest most recent HbA1c (7.57 ± 0.97 vs. 8.20 ± 1.47). In CGM users, longer use was associated with lower maternal anxiety, whereas caregiver burden did not vary with duration. Neither HbA1c nor ΔHbA1c independently explained maternal anxiety or burden.

Conclusion: Among mothers of children with T1D, CGM use was associated with lower anxiety and caregiver burden, with an inverse association between duration of CGM use and anxiety. These patterns suggest that processes beyond glycemic averages—such as perceived control, alarm management, and day-to-day caregiving demands—may shape maternal well-being. Clinically, CGM counselling may be optimized by tailoring alarm settings and integrating device use into family routines; further multicenter studies with longer follow-up and time-sensitive CGM/psychosocial measures are warranted.

Keywords: type 1 diabetes, continuous glucose monitoring, caregiver burden, anxiety, mothers, pediatric endocrinology

INTRODUCTION

Type 1 diabetes (T1D) is one of the most common chronic endocrine conditions in childhood and requires continuous, multidimensional self-management in daily life.[1,2] In younger children, day-to-day management responsibilities largely fall to primary caregivers—most often mothers—disrupting family routines and sleep.[2] Recurrent stressors—frequent glucose monitoring, insulin titration, fear of hypoglycemia (particularly nocturnal), and nighttime awakenings—are associated with heightened maternal

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anxiety and increased caregiving burden, and with elevated parental diabetes distress more broadly.[2,3]

Against this backdrop, continuous glucose monitoring (CGM) has become a key technology in T1D care with clear psychosocial implications for families.[4] Psychosocial theories help contextualize parental caregiving experiences: within stress–coping models, parents' appraisal of diabetes-related demands and available resources shapes caregiver adjustment and distress.[5,6] Within the uncertainty-in-illness framework, illness-related ambiguity, treatment complexity, informational gaps, and the unpredictability of the disease course undermine perceived control and elevate distress; in T1D specifically, higher parental illness uncertainty prospectively predicts greater long-term psychological distress.[7,8] Qualitative work further shows that parents manage uncertainty through information seeking, social support, and technology use—including CGM—yet family life, especially with young children, often remains in a vigilant state of chronic disruption.[4,9] Within this rationale, CGM may reduce informational uncertainty and enable timelier responses—potentially attenuating anxiety—while device demands and continuous data vigilance may conversely amplify stress in some families.[4,9]

Consistent with these frameworks, we quantified maternal outcomes using validated self-report instruments. The State–Trait Anxiety Inventory (STAI) differentiates momentary (STAI-S) from dispositional (STAI-T) anxiety (20 items each; total scores 20–80), with higher scores indicating greater anxiety.[10,11] The Zarit Burden Interview (ZBI; 22 items; item scores 0–4; total 0–88) assesses perceived caregiving burden, with higher scores reflecting greater burden.[12,13] Both scales have Turkish validations with adequate reliability; therefore, we analyze them as continuous outcomes and refrain from applying non-validated categorical thresholds.[11,13]

By providing near real-time glucose information, CGM can facilitate earlier recognition of hypo- and hyperglycemia and may attenuate parental anxiety—particularly around nocturnal events.[14,15] Consistent with this rationale, studies report associations between CGM use and lower parental stress and fewer sleep disruptions. However, alarm notifications and continuous data visibility have also been linked to heightened vigilance and stress in some families.[14-17] Persistent parental diabetes distress is clinically relevant because it is associated with higher child HbA1c.[3]

Although CGM's effects on glycemic control have been extensively examined, caregiver-focused psychosocial impacts—particularly among mothers—remain less clearly characterized.[18] Much of the available evidence is qualitative or single-center observational, limiting precision and generalizability.[19,20] In middle-income settings such as Türkiye—where CGM access may be shaped by reimbursement policies, device availability, out-of-pocket costs, and variable health literacy and caregiving roles across socioeconomic strata—these psychosocial outcomes should be evaluated within their cultural and structural determinants.[2,21]

We aimed to assess the association between CGM use and maternal anxiety and caregiving burden—measured with STAI-S/T and ZBI—after adjustment for key sociodemographic covariates, and to explore associations with CGM duration and glycemic indices (HbA1c, ΔHbA1c).

METHODS

This single-center, comparative cross-sectional observational study examined the association between continuous glucose monitoring (CGM) use and maternal anxiety/caregiver burden among mothers of children with type 1 diabetes (T1D). The study was conducted jointly by the Departments of Psychiatry and Pediatric Endocrinology at Muğla Sıtkı Koçman University Faculty of Medicine. Data were collected between January and April 2025 in the Pediatric Endocrinology and Psychiatry outpatient clinics of Muğla Sıtkı Koçman University Training and Research Hospital.

Eligible participants were mothers of children aged 2–18 years with ≥1 year since a T1D diagnosis. Diabetes was confirmed per ISPAD 2022 pediatric criteria: laboratory plasma glucose meeting any of the following—random ≥200 mg/dL with classic symptoms; fasting ≥126 mg/dL after ≥8 h fast; or 2-h OGTT glucose ≥200 mg/dL; in asymptomatic presentations, diagnosis required confirmation on a separate sample. HbA1c ≥6.5% was considered diagnostic only when NGSP/DCCT-standardized assays were used, and no conditions affecting red-cell turnover were present. When clinical classification was uncertain, diabetes-associated autoantibodies (GAD, IA-2, IAA, ZnT8) supported T1D classification.[1]

Participants were classified as CGM users or non-users (never used). All CGM users employed the same flash CGM system (Abbott FreeStyle Libre 2; factory-calibrated; optional low/high-glucose alarms; no routine fingerstick calibration). To ensure exposure homogeneity, users of other CGM brands/models were excluded (noted as

a limitation for generalizability). No participants used continuous subcutaneous insulin infusion (CSII); all were on multiple daily injections (MDI), thereby reducing potential confounding from differential technology support and automation features.

Inclusion criteria were: (i) a child with T1D for ≥1 year, (ii) the mother's willingness to participate, and (iii) functional literacy sufficient to independently complete study questionnaires. Exclusion criteria were: (i) chronic comorbidities other than common T1D-associated autoimmune conditions (autoimmune thyroid disease, celiac disease), (ii) a self-reported or documented maternal psychiatric disorder, or (iii) a severe traumatic life event within the past 6 months. We did not conduct structured psychiatric interviews because the prespecified outcomes were self-reported anxiety and caregiving burden; validated questionnaires (STAI, ZBI) are feasible in routine clinical settings. Universal diagnostic interviews were not feasible within the clinic workflow and could introduce selection bias; undiagnosed conditions, therefore, cannot be ruled out. STAI/ZBI were analyzed as continuous, non-diagnostic indicators of symptom severity. STAI/ZBI were analyzed as continuous, non-diagnostic indicators of symptom severity.

Data were obtained via face-to-face interviews using three forms. The Sociodemographic Data Form recorded the mother's age, education, employment, marital status, family type, and income level; and the child's age, sex, diabetes duration, most recent HbA1c, and CGM status. For the CGM group, the initial HbA1c was defined as the most recent value prior to CGM initiation; for the non-CGM group, the initial HbA1c was obtained retrospectively from medical records approximately 3 months prior to study participation. For both groups, the second HbA1c was the most recent measurement at the time of participation. ΔHbA1c was calculated as (initial HbA1c − most recent HbA1c) so that positive values indicate improvement (reduction) and negative values indicate deterioration (increase).

Caregiver burden was assessed with the Zarit Burden Interview (ZBI; 22 items; item scores 0–4; total 0–88), with higher scores reflecting greater burden.[12] The Turkish validation reported excellent internal consistency (Cronbach's α ≈0.95).[13]

Maternal anxiety was assessed with the State–Trait Anxiety Inventory (STAI), comprising STAI-S and STAI-T subscales (20 items each; total scores 20–80), with higher scores indicating greater anxiety.[10,11]

The study was approved by the Clinical Research Ethics Committee of Muğla Sıtkı Koçman University (Approval Date: January 10, 2025; Decision No: 12). Written informed consent was obtained from all participants. The study adhered to the principles of the Declaration of Helsinki.

Because directly comparable prior studies using STAI or ZBI in parents of children with T1D were limited, we conducted an a priori power analysis for the primary between-group comparison (CGM vs. non-CGM) on STAI-T, assuming a conservative medium effect size (Cohen's d = 0.50) at a two-tailed α = 0.05. Using G*Power 3.1, this required approximately 64 participants per group for 80% power. Our realized sample (n = 65 per group; total 130) yielded an achieved power ≈0.81 for d = 0.50 under a two-sample t-test with equal allocation, meeting the target to detect clinically meaningful differences.

Analyses were performed in SPSS v22.0. Distributional assumptions were evaluated using Shapiro–Wilk/ Kolmogorov–Smirnov tests and visual inspection of histograms and Q–Q plots. Descriptive statistics are presented as mean ± SD for approximately normal variables, and median (IQR) for skewed variables; categorical variables are n (%).

Between-group comparisons used independent-samples t-tests or Mann–Whitney U tests as appropriate; categorical variables were compared with χ^2 or Fisher's exact tests. Within-group change in HbA1c was assessed with the Wilcoxon signed-rank test, and between-group differences in ΔHbA1c with the Mann–Whitney U test.

Multivariable linear regression models were fitted for STAI-S, STAI-T, and ZBI. Prespecified covariates included maternal age, education, employment status, and a proxy for family income; paternal education; and child age, sex, and diabetes duration; and clinical variables were CGM use (0 = no, 1 = yes) and ΔHbA1c. We report unstandardized β coefficients, 95% CIs, p values, and adjusted R^2. Model assumptions (linearity, normality of residuals, homoscedasticity) were checked via residual diagnostics; multicollinearity was low (all VIFs < 2), and influential observations were screened (Cook's distance < 1).

Among CGM users, potential associations between CGM duration (months) and STAI-S, STAI-T, and ZBI were examined using Spearman correlations and multivariable linear regression, adjusting for maternal age, education, employment, family income, child age, diabetes duration, and ΔHbA1c. A two-tailed α of 0.05 defined statistical

significance. We assessed completeness of exposure, outcomes, and covariates; no missing data were identified, and analyses were conducted on a complete-case dataset.

RESULTS

A total of 130 mothers of children with type 1 diabetes were included in the study. Of the participants, 49.2% were girls (n=64) and 50.8% were boys (n=66). The mean age of all children was 11.66±3.84 years. Sixty-five children (50%) were using a continuous glucose monitoring (CGM) device, while 65 (50%) were not. Although the groups were generally comparable in sociodemographic and clinical characteristics, paternal education differed ($p = 0.002$). All multivariable models were adjusted for this variable (Table 1).

The most recent HbA1c level was significantly lower in the CGM group (7.57±0.97) compared to the non-CGM group (8.20±1.47; p=0.004). For within-group change, ΔHbA1c was defined as (initial HbA1c − most recent HbA1c; positive = improvement). In the CGM group, ΔHbA1c indicated a significant improvement (median: 0.2 [0.1–0.4] p<0.001), whereas in the non-CGM group, the within-group change was not significant (median: -0.1 [-0.1–0.0]; within-group p = NS). Between groups, ΔHbA1c values were significantly different, favoring CGM (Mann–Whitney p<0.001) (Table 1).

Caregiver burden was significantly lower in the CGM group (37.19±10.21 vs. 44.61±14.05; p=0.001). Similarly, state anxiety (36.46±7.69 vs. 42.15±6.50; p<0.001) and trait anxiety scores (40.26±5.69 vs. 49.59±6.49; p<0.001) were significantly lower in the CGM group (Table 2).

Among CGM users, CGM duration correlated inversely with anxiety: STAI-S ($\rho = -0.388$, $p = 0.0017$) and STAI-T ($\rho = -0.676$, $p < 0.0001$), whereas no correlation was observed with ZBI ($\rho = -0.084$, $p = 0.511$) (Table 3). These patterns were consistent with multivariable regression findings.

In models restricted to CGM users, longer CGM duration (per month) was associated with lower anxiety after adjustment for maternal age, education, employment, family income proxy, child age, diabetes duration, and ΔHbA1c: STAI-T $\beta = -4.06$ (95% CI −5.20 to −2.92, $p < 0.001$; adjusted $R^2 = 0.473$) and STAI-S $\beta = -3.78$ (95% CI −5.67 to −1.89, $p < 0.001$; adjusted $R^2 = 0.183$). No association was observed for ZBI ($\beta = -0.38$; 95% CI −3.17 to 2.42; $p = 0.788$) (Table 4).

Multivariable models (all participants): In models including all mothers and adjusting for maternal age, maternal education, maternal employment, family income proxy, paternal education, child age, sex, diabetes duration, and ΔHbA1c, CGM use (yes/no) remained inversely associated with maternal anxiety and caregiver burden: STAI-T $\beta = -8.80$ (95% CI −11.58 to −6.02, $p < 0.001$; adjusted $R^2 = 0.348$), STAI-S $\beta = -6.54$ (95% CI −9.73 to −3.35, $p < 0.001$; adjusted $R^2 = 0.134$), and ZBI $\beta = -6.11$ (95% CI −11.31 to −0.91, $p = 0.022$; adjusted $R^2 = 0.170$). In these adjusted models, HbA1c and ΔHbA1c were not independent predictors of STAI-S, STAI-T, or ZBI (all $p > 0.05$) (Table 5).

DISCUSSION

In this single-center, comparative cross-sectional study of 130 mothers of children with type 1 diabetes, maternal anxiety levels, measured with the State–Trait Anxiety Inventory (STAI-S/T), and caregiver burden, assessed with the Zarit Burden Interview (ZBI), were found to be lower among continuous glucose monitoring (CGM) users compared with non-users. These differences remained significant after adjustment for prespecified sociodemographic and clinical covariates. Among CGM users, longer duration of use was associated with lower anxiety, whereas caregiver burden did not vary with duration. In children, CGM use was associated with lower most recent HbA1c values and greater ΔHbA1c improvements; however, neither HbA1c nor ΔHbA1c independently explained maternal outcomes. This suggests that mothers' reports of anxiety and burden may be shaped by processes beyond metabolic averages, such as perceived control, alarm management, and daily caregiving routines.

In our study, CGM use was associated with lower maternal anxiety (STAI-S/T), which aligns with previous reports showing reduced parental distress and fear of hypoglycemia (FOH) during nighttime in the context of CGM use.[15,22] Conversely, the literature also reports mixed effects on sleep and stress, suggesting that families may experience CGM differently.[17,23] Taken together, our findings indicate that while CGM use is generally linked to lower anxiety, simultaneous device demands and alarm burden may limit this benefit for some families.[17]

Among mothers using CGM, longer duration of use was associated with lower anxiety levels; however, caregiver burden was not related to duration. Qualitative studies have reported that, over time, families gain experience in device and alarm management, develop greater confidence in interpreting glucose trends, and integrate CGM more effectively into daily routines; these observations are consistent with the anxiety pattern we identified.[17,23] By

Table 1. Baseline sociodemographic and clinical characteristics by CGM use (CGM users n=65; non-users n=65)

Variables		CGM Users (n=65)	CGM non-users (n=65)	p-value
Age (years), mean ± SD		11.81 (3.65)	11.51 (4.05)	0.648
Gender, n (%)	Female	28 (43.1)	36 (55.4)	0.219
	Male	37 (56.9)	29 (44.6)	
Schooling Status, n (%)	Not attending	7 (10.8)	10 (15.4)	0.830
	Primary school	15 (23.1)	15 (23.1)	
	Middle school	27 (41.5)	23 (35.4)	
	High school	16 (24.6)	17 (26.2)	
Presence of Chronic Illness, n (%)	None	48 (73.8)	54 (83.1)	0.431
	Thyroid disorder	6 (9.2)	2 (3.1)	
	Celiac disease	6 (9.2)	4 (6.2)	
	Other	5 (7.7)	5 (7.7)	
Family Structure	Nuclear Family	50 (76.9)	49 (75.4)	0.845
	Extended Family	7 (10.8)	6 (9.2)	
	Divorced Parents	7 (10.8)	9 (13.8)	
Diabetes duration (years), median (IQR)		2.94 (1.87-6.64)	2.96 (1.83-5.99)	0.419
Recent HbA1c (%), mean ± SD		7.57 (0.97)	8.20 (1.47)	**0.004**
Pre-study HbA1c (%), mean ± SD		7.83 (0.84)	8.18 (1.47)	0.099
Change in HbA1c (%), median (IQR)		0.2 (0.1-0.4)	-0.1 (-0.1-0)	**<0.001**
Duration of CGM use (months), mean ± SD		3.82 (1.02)	-	NA
Maternal age (years), mean ± SD		39.81 (6.66)	38.55 (5.8)	0.259
Maternal education, n (%)	Primary School	15 (23.1)	28 (43.1)	0.076
	Middle School	9 (13.8)	10 (15.4)	
	High school	24 (36.9)	16 (24.6)	
	University	17 (26.2)	11 (16.9)	
Maternal employment status, n (%)	Employed	19 (29.2)	16 (24.6)	0.693
	Unemployed	46 (70.8)	49 (75.4)	
Paternal age (years), mean ± SD		43.52 (6.07)	43.22 (5.56)	0.765
Paternal education, n (%)	Primary School	11 (16.9)	26 (40)	**0.002**
	Middle School	11 (16.9)	15 (23.1)	
	High school	16 (24.6)	14 (21.5)	
	University	27 (41.5)	10 (15.4)	
Paternal employment status, n (%)	Employed	57 (87.7)	60 (92.3)	0.560
	Unemployed	8 (12.3)	5 (7.7)	
Family income status, n (%)	Income < expenses	26 (40)	31 (47.7)	0.628
	Income = expenses	33 (50.8)	28 (43.1)	
	Income > expenses	6 (9.2)	5 (7.7)	

CGM: continuous glucose monitoring; HbA1c: glycated hemoglobin; IQR: interquartile range; SD: standard deviation.
Data are presented as mean ± SD, median (IQR), or n (%). p-values were calculated using independent samples t-test, Mann–Whitney U test, or chi-square test, as appropriate. The duration of CGM use is applicable only for CGM users. ΔHbA1c = initial − most recent; positive values indicate improvement.

Table 2. Comparison of caregiver burden and anxiety scores between groups

	CGM Users (n=65)	CGM non-users (n=65)	p-value
Caregiver burden total score (ZBI), mean ± SD	37.19 (10.21)	44.61 (14.05)	**0.001**
State anxiety score (STAI-S), mean ± SD	36.46 (7.69)	42.15 (6.5)	**<0.001**
Trait anxiety score (STAI-T), mean ± SD	40.26 (5.69)	49.59 (6.49)	**<0.001**

ZBI: Zarit Burden Interview; STAI-S: State-Trait Anxiety Inventory – State; STAI-T: State-Trait Anxiety Inventory – Trait.
Data are presented as mean ± SD. p-values were calculated using independent samples t-test.

Table 3. Correlation between CGM duration and maternal outcomes among CGM users

	n	CGM duration
STAI-S	65	ρ=-0.388; p=0.0017
STAI-T	65	ρ=-0.676; p <0.0001
ZBI	65	ρ=-0.084; p=0.511

STAI-S: State-Trait Anxiety Inventory – State; STAI-T: State-Trait Anxiety Inventory – Trait; ZBI: Zarit Burden Interview. Values are two-tailed Spearman rho (ρ) with p-values. Negative coefficients indicate lower scores with longer CGM use. Analyses restricted to CGM users only. CGM duration expressed in months. The correlation results support the multivariable regression findings.

Table 4. Multivariable linear regression analysis of the association between CGM duration and maternal outcomes (CGM users only)

	Regression Coefficients					
	β	SE	t	p	95% CI for β	
					Lower Bound	Upper Bound
STAI-T	-4.06	0.58	-6.98	<0.001	-5.2	-2.92
STAI-S	-3.78	0.96	-3.92	<0.001	-5.67	-1.89
ZBI	-0.38	1.42	-0.27	0.788	-3.17	2.42

STAI-S: State-Trait Anxiety Inventory – State; STAI-T: State-Trait Anxiety Inventory – Trait; ZBI: Zarit Burden Interview. β = unstandardized regression coefficient; SE = standard error; CI = confidence interval. Models adjusted for maternal age, maternal education, maternal employment status, family income proxy, child age, diabetes duration, and ΔHbA1c. CGM duration in months; CGM users only (complete-case n = 65). Adjusted R^2: STAI-T 0.473; STAI-S 0.183; ZBI 0.000.

Table 5. Multivariable linear regression analysis of the association between CGM use (yes vs no) and maternal outcomes (All participants)

	Regression Coefficients					
	β	SE	t	p	95% CI for β	
					Lower Bound	Upper Bound
STAI-T	-8.8	1.42	-6.21	<0.001	-11.58	-6.02
STAI-S	-6.54	1.63	-4.02	<0.001	-9.73	-3.35
ZBI	-6.11	2.65	-2.30	0.022	-11.31	-0.91

STAI-S: State-Trait Anxiety Inventory – State; STAI-T: State-Trait Anxiety Inventory – Trait; ZBI: Zarit Burden Interview. β = unstandardized regression coefficient; SE = standard error; CI = confidence interval. Predictor: CGM use (yes vs no). Models adjusted for maternal age, maternal education, maternal employment status, family income proxy, paternal education, child age, sex, diabetes duration, and ΔHbA1c. Complete-case sample n = 130 per outcome. Adjusted R^2: STAI-T 0.348; STAI-S 0.134; ZBI 0.170. P-values reported in decimal format.

contrast, caregiver burden largely stems from broader and relatively stable demands (e.g., nighttime responsibilities, periods of illness, cumulative caregiving tasks). It is therefore less likely to change duration. This pattern underscores the multifactorial nature of caregiver burden and suggests that the psychosocial impact of CGM may differ across families.[19,24] Similarly, recent studies emphasize that caregiver burden is shaped by sociodemographic and clinical factors and persists as a multidimensional experience.[25,26]

Real-time glucose data and alarms may reduce uncertainty and enhance perceived control, thereby mitigating fear

of hypoglycemia (FOH) and nighttime hypervigilance; this framework aligns with models of uncertainty in illness and stress–coping.[7,8,14] Qualitative and quantitative findings suggest that CGM can reduce nighttime checks and FOH in some families, improve sleep quality, and strengthen feelings of safety.[15-17] However, alarm burden, constant data visibility, and practical challenges of sensor use may fragment sleep and increase stress for other families; such countervailing effects may explain heterogeneity across and within study samples.[17,23] Particularly in families with young children, daily life may evolve into a persistent state of vigilance, which may not be fully alleviated even under technological monitoring.[9]

In our sample, although children using CGM had lower current HbA1c values and more pronounced ΔHbA1c improvements, these glycemic indicators did not independently account for maternal anxiety or caregiver burden in multivariable models. This finding suggests that caregiver well-being is not determined solely by metabolic averages. While prior research has reported associations between parental diabetes distress and children's HbA1c, our results imply that maternal anxiety and burden may persist even when glycemic control improves.[3] Moreover, HbA1c, as a 2–3 month average, may be insufficient to capture shorter-term psychosocial fluctuations, highlighting the need for time-sensitive CGM metrics and momentary assessments.[27] Within this framework, psychosocial processes such as fear of hypoglycemia, perceived control, and coping/resilience may play a more direct role in shaping maternal outcomes than HbA1c alone.[28] Therefore, outcomes in T1D should not be limited to clinical markers alone; the psychosocial effects of CGM on families and its broader impacts on the health system should also be considered.[18]

These findings carry practical implications for diabetes care. Although CGM use was associated with lower maternal anxiety, benefits varied across families, underscoring the need for individualized counselling. Routine CGM implementation should therefore include discussion of caregiver expectations, alarm settings, and integration into daily routines. Recent studies from Türkiye report lower CGM uptake among low-income families and indicate that caregiver burden varies with parental sociodemographic and family characteristics.[21,29] Addressing these psychosocial dimensions may help maximize the benefits of CGM while minimizing stressors. In addition, family-centered empowerment interventions have been shown to reduce short-term caregiver burden and improve children's HbA1c, and may complement counselling.[30]

Our study has several strengths: maternal anxiety (STAI-S/T) and caregiver burden (ZBI) were assessed with validated instruments; analyses used adjusted models with prespecified covariates and checked assumptions; we demonstrated a duration-sensitive pattern linking longer CGM use to lower anxiety; device-related heterogeneity was minimized by the use of a single CGM system across users (FreeStyle Libre 2); and data were collected in a real-world outpatient setting with an a priori power calculation. Together, these features strengthen the robustness and clinical relevance of the findings.

Nevertheless, our study has limitations. Its cross-sectional design precludes causal inference and may be susceptible to selection effects. CGM exposure was relatively short and range-restricted (mean 3.8 months), which is likely insufficient to drive major changes in psychological states. Glycemic data were limited to two HbA1c time points, without time-sensitive CGM metrics or sleep/stress measures. Psychosocial outcomes relied on self-report (without structured psychiatric interviews). The single-center, technologically homogeneous sample may limit generalizability; despite adjustment for prespecified covariates, residual confounding and minor bias from complete-case analyses remain possible. These limitations underscore the need for multicenter studies with longer follow-up that incorporate time-sensitive CGM metrics and sleep/stress assessments.

In conclusion, in this single-center, comparative cross-sectional study, CGM use was associated with lower maternal anxiety and caregiver burden among mothers of children with type 1 diabetes; anxiety showed an inverse association with duration of CGM use, whereas HbA1c and ΔHbA1c did not independently account for these psychosocial outcomes. These findings suggest that processes beyond glycemic averages—such as uncertainty, alarm management, and day-to-day caregiving demands—may shape maternal well-being. In clinical practice, CGM counselling may be most effective when tailored to family preferences and supported by guidance on alarm settings and integration into daily routines. Nevertheless, given the cross-sectional design and relatively brief CGM exposure, the results are not causal. Multicenter studies with longer follow-up that incorporate time-sensitive CGM metrics and sleep/stress assessments are needed to clarify temporal dynamics and mechanisms.

Ethical approval

This study has been approved by the Muğla Sıtkı Koçman University Clinical Research Ethics Committee (approval date 10.01.2025, number 2025/12). Written informed consent was obtained from the participants.

Author contribution

The authors declare contribution to the paper as follows: Study conception and design: GCY, MDŞ; Data collection: GCY, MDŞ; Analysis and interpretation of results: GCY, MDŞ; Draft manuscript preparation: GCY. 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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Research Article

Research on soft neurological signs in obese children

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ABSTRACT

Objective: Soft neurological signs (SNS) are subtle indicators detected during neurological examination in the absence of an overt neurological disorder. This study aimed to investigate the presence of SNS in obese children.

Methods: A total of 61 obese children and 57 healthy controls (HCs) were evaluated using the Neurological Evaluation Scale (NES) to assess the presence of SNS.

Results: There were no significant differences between the obese and HC groups regarding age and sex ($p>0.05$). The sensory integration, motor coordination, complex sequential motor acts, other NES, and total NES scores were significantly higher in the obese group compared with HCs ($p=0.005$, $p=0.009$, $p=0.004$, $p=0.002$, and <0.001, respectively).

Conclusion: This is the first study to demonstrate a significant presence of SNS in obese children using the NES. Incorporating SNS assessment into routine obesity evaluations may help identify children at risk for early neurodevelopmental changes.

Keywords: obesity, soft neurological signs, neurological evaluation scale, children

INTRODUCTION

Obesity is defined as the abnormal or excessive accumulation of body fat.[1] Subclinical inflammatory processes and white matter demyelination, which are related to the duration and severity of obesity, are believed to contribute to cognitive dysfunction.[2]

In particular, chronic inflammation in the developing brain has been suggested to exert neurotoxic effects. In this context, proinflammatory cytokines such as TNF-α and IL-6 have been shown to impair synaptic plasticity and myelination.[3,4] These alterations may lead to deficits in motor coordination, sensory integration, and attention regulation, potentially contributing to the emergence of soft neurological signs (SNS).[5]

Soft neurological signs are defined as subtle abnormalities in motor, sensory, cognitive, and memory-related functions that cannot be attributed to an overt brain lesion. They are often undetectable during routine neurological examinations but can be revealed through careful and detailed assessment.[6] SNS are believed to reflect functional immaturity of specific brain regions, particularly the cerebellum, basal ganglia, and prefrontal cortex. Clinically, they are important because of their association with a range of cognitive and neuropsychiatric conditions, including

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attention deficits, poor academic performance, and autism spectrum disorders.[7-9]

The most comprehensive tool for assessing SNS in children is the Neurological Evaluation Scale (NES), developed by Buchanan and Heinrichs. This scale evaluates SNS across four main domains: sensory integration (SI), motor coordination (MC), complex sequential motor acts (SCMA), and other neurological findings.[10,11]

The present study aimed to investigate the presence of SNS in obese children using the NES and to compare the results with those of healthy controls. To the best of our knowledge, this is the first study to evaluate SNS in obese children using the NES.

MATERIALS and METHODS

Study patients

This prospective study was conducted between September 2021 and June 2022. A total of 61 obese children, aged 8 to 16 years, diagnosed in the general pediatrics outpatient clinic, and 57 age-and-sex matched healthy controls (HCs) were enrolled. SNS were assessed in all participants using the NES.

Children with a body mass index (BMI) at or above the 95th percentile for age and sex were classified as obese. Those with a BMI greater than 120% of the 95th percentile or ≥35 kg/m^2, whichever was lower, were classified as morbidly obese.[12]

Children with obesity secondary to genetic syndromes, monogenic or endocrine disorders, as well as those with diagnosed psychiatric conditions (in themselves or their parents), chronic diseases (e.g., cyanotic congenital heart disease, chronic lung disease, immunodeficiency, epilepsy, hypoxic-ischemic encephalopathy, intracranial lesions, neurodegenerative diseases) were excluded. Participants taking medications that could affect body weight or those who regularly engaged in sports activities were also excluded from the study.

Similarly, children with any neurological, psychiatric, or chronic diseases; those taking medications that could affect the central nervous system; or those who regularly participated in physical exercise were excluded from the HCs.

Measurements

Body weight was measured using a digital electronic scale (SECA®, Hamburg, Germany) with a sensitivity of 0.1 kg, and height was measured using a Harpenden stadiometer with a sensitivity of 0.1 cm. BMI was calculated as weight (kg) divided by height squared (m^2). Standard deviation scores (SDS) for weight, height, and BMI were calculated using the Child Metrics online calculator for pediatric endocrinologists, based on the reference data for the Turkish population published by Neyzi et al.[13,14]

Pubertal development was assessed according to the Tanner and Whitehouse staging system. Testicular volume ≥4 mL in males and breast development at stage ≥2 in females were considered indicative of pubertal onset.[15]

Blood samples were collected from obese participants after 10-12 hours of overnight fasting. Serum glucose, lipid profile, aspartate transaminase (AST), and alanine transaminase (ALT) levels were measured using a spectrophotometric method. Insulin concentrations were determined using a chemiluminescent microparticle immunoassay (Abbott Architect i2000SR). Complete blood count parameters were analyzed using an automated hematology analyzer (Mindray BC-6800, Shenzhen, China) based on hydrodynamic focusing flow cytometry.

Neurological evaluation scale (NES)

The NES was administered to all participants.[10] The scale consists of 26 items, one of which assesses hand preference and is not scored; therefore, the total score is calculated based on the remaining 25 items. Except for the sucking and snout reflexes—each scored as 0 (absent) or 2 (present)—all other items are rated on a 3-point scale: 0 (no impairment), 1 (mild but definite impairment), and 2 (marked impairment). Fourteen of the items were assessed bilaterally.

Validity and reliability

The scale used in this study did not require separate validity and reliability analyses, as it evaluates objective neurobiological parameters rather than subjective or culturally sensitive constructs. Furthermore, all items were administered and scored by the clinician according to standardized instructions, thereby minimizing inter-rater variability and eliminating participant bias.[16]

Ethics

Ethical approval for the study was obtained from the local ethics committee in accordance with the principles of the Declaration of Helsinki (Approval No: 2021/129). Written informed consent was obtained from all participants and their parents prior to enrollment.

Statistical method

The research data were analyzed using the IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA). The normality of distribution for continuous variables was assessed using both visual methods (histograms and probability plots) and analytical tests (Kolmogorov-Smirnov and Shapiro-Wilk tests). Descriptive statistics for normally distributed variables were expressed as mean ± standard deviation, whereas non-normally distributed variables were presented as median (25^{th} –75^{th} percentile). Categorical variables were summarized as frequencies and percentages. The independence of categorical variables was tested using the chi-square test. Continuous variables with parametric distribution were compared between independent groups using the Student's t-test or one-way ANOVA. For non-parametric variables, the Mann-Whitney U test or Kruskal-Wallis test was applied. A p-value <0.05 was considered statistically significant.

RESULTS

Table 1 compares the demographic characteristics and body measurements of obese children and healthy controls. A total of 118 participants were included in the study, of whom 37 (31.4%) were classified as obese, 24 (20.3%) as morbidly obese, and 57 (48.3%) as HCs. There were no statistically significant differences between the obese and HCs with respect to age or sex ($p > 0.05$). In contrast, height percentile and SDS, body weight percentile and SDS, and BMI, BMI percentile, and BMI SDS were significantly higher in obese children than in HCs ($p < 0.001$).

Table 2 compares the laboratory parameters of obese and morbidly obese children. The median neutrophil count and insulin level were significantly higher in the morbidly obese group ($p = 0.022$ and $p < 0.001$, respectively), while no significant differences were observed in the other laboratory parameters ($p > 0.05$).

Pairwise comparisons revealed that both obese and morbidly obese children had significantly higher total and subscale NES scores than HCs (all $p < 0.05$), whereas no significant differences were observed between the obese and morbidly obese groups ($p > 0.05$) (Table 3).

No significant differences in NES scores were observed based on sex, place of residence, family income level, or maternal education in either the obese or HCs ($p > 0.05$; data not shown).

Table 4 compares NES scores across age groups in obese children and HCs. No statistically significant differences in NES scores were observed among the age groups within the obese group. However, in the HC group, prepubertal children demonstrated significantly higher total NES, SCMA, and other subscale scores compared with those in the early adolescent period. Similarly, mid-adolescent children exhibited significantly higher total NES, SI, SCMA, and other subscale scores than early adolescents ($p < 0.005$).

DISCUSSION

To the best of our knowledge, this is the first study to investigate SNS in obese children through the NES. Our results revealed that obese children exhibited significantly higher total NES scores compared with HCs.

Obesity is known to promote an increase in inflammatory cells through cytokine activation.[17,18] Marginean et al. reported higher levels of leukocytes, lymphocytes, and platelets in obese children.[19] Similarly, Anık et al. found that leukocyte, neutrophil, and lymphocyte counts were significantly higher in obese children with insulin resistance compared to those without, and that insulin levels increased with the severity of obesity.[20] Consistent with these findings, our study demonstrated significantly higher neutrophil counts and insulin levels in morbidly obese children compared with both obese and HCs. These results support the presence of systemic inflammation in morbid obesity, which may contribute to the pathophysiology underlying increased SNS.

Yau et al. reported that as obesity severity increases, children exhibit poorer arithmetic and reading performance, shorter attention spans, and reduced overall cognitive functioning.[21] In addition, several studies have suggested that weight loss may improve obesity-related neurological impairments.[22,23] In our study, although higher NES scores were expected in morbidly obese children due to more severe and prolonged inflammation, no significant differences were observed between the obese and morbidly obese groups. This may be partly attributed to the limited sample size of the morbidly obese subgroup

Table 1. Comparison of demographic data and body measurements of obese children and healthy control

Parameter	Obese Children	Healthy Controls	p-value
	n=61	n=57	
Age (years), median (IQR)	13 (10-15)	13 (10-15)	0.648
Sex (n, %)			
Female	36 (59%)	30 (52.6%)	0.485
Male	25 (41%)	27 (47.4%)	
Height (cm), median (IQR)	158 (152-165)	156 (146-162)	0.104
Height p, median (IQR)	81.9 (61.8-97.6)	40 (24.2-69.2)	**<0.001**
Height SDS, median (IQR)	0.9 (0.3-2.2)	-0.2 [(-0.7)-0.5]	**<0.001**
Body Weight (kg), median (IQR)	76 (61-84)	48 (36.0-53.5)	**<0.001**
Body Weight p, median (IQR)	99.7 (98.6-100)	36.3 (20.6-64.4)	**<0.001**
Body Weight SDS, median (IQR)	2.7 (2.2-3.4)	-0.3 [(-0.7)-0.4]	**<0.001**
BMI (kg/m²), median (IQR)	29 (26.3-32)	19.5 (17.7-21.3)	**<0.001**
BMI p, median (IQR)	99.1 (97.9-99.7)	46.0 (21.8-68.1)	**<0.001**
BMI SDS, median (IQR)	2.4 (2.0-2.8)	-0.1 [(-0.7)-0.5]	**<0.001**
Birth Length (cm), median (IQR)	51 (50-52)	50 (50-52)	0.494
Birth Weight (kg), median (IQR)	3.4 (3.0-3.7)	3.2 (3.0-3.5)	0.276
Educational Status, median (IQR)			
Primary School	16 (26.2)	12 (21.1)	0.459
Middle School	18 (29.5)	23 (40.4)	
High School	27 (44.3)	22 (38.6)	
Screen Time (n, %)			
≤ 4 h	33 (54.1%)	35 (61.4%)	0.422
> 4 h	28 (45.9%)	22 (38.6%)	
Residence (n, %)			
Urban	45 (73.8%)	46 (80.7%)	0.370
Rural	16 (26.2%)	11 (19.3%)	
Income Level (n, %)			
Minimum wage or less	25 (41%)	16 (28.1%)	0.141
Above minimum wage	36 (59%)	41 (71.9%)	
Mother Educational Status (n, %)			
High School or less	58 (95.1%)	48 (84.2%)	0.051
Above High School	3 (4.9%)	9 (15.8%)	
Father Educational Status (n, %)			
High School or less	57 (93.4%)	37 (64.9%)	**<0.001**
Above High School	4 (6.6%)	20 (35.1%)	
Number of Siblings, median (IQR)	2 (1-3)	1 (1-2)	0.007
Mother's Age, median (IQR)	40 (35.0-45)	39 (36.0-42.0)	0.604
Father's Age, median (IQR)	43 (38.5-48)	43 (41.0-45.0)	0.894
Pubertal status (n, %)			
Prepubertal	11 (18%)	13 (22.8%)	0.520
Pubertal	50 (82%)	44 (77.2%)	

IQR, interquartile range; n, number; cm, centimeter; kg, kilogram; p, percentile; SDS, standard deviation score; m², square meter; BMI, body mass index. Data are presented as n (%) for categorical variables and as median (IQR) for continuous variables.

Table 2. Comparison of laboratory parameters in obese and morbidly obese patients

Parameter	Groups		p-value
	Obese children (n=37)	Morbidly Obese children (n=24)	
	Median (25-75 p)	Median (25-75 p)	
Hb (g/dL)	13.2 (12.6-13.8)	13.2 (12.4-13.7)	0.989
Leukocyte (10^3 /uL)	8050 (6950-9210)	9190 (7380-9860)	0.224
Neutrophil (mm^3)	3975 (3295-4665)	5220 (4010-5980)	0.022
Lymphocyte (mm^3)	2860 (2475-3545)	2930 (2665-3485)	0.958
PLT (10^9 /l)	361 (286-407)	327 (283-371)	0.174
Ferritin (ng/mL)	36.4 (15.2-51.1)	39.3 (21.3-52.2)	0.800
Vitamin B_{12} (pg/mL)	342 (235.5-402)	306 (231-344)	0.233
25-Hydroxy Vitamin D (ng/mL)	13.3 (10.9-21.3)	13.1 (9.7-17.9)	0.407
Glucose (mg/dL)	90 (86.0-94)	90 (85-95)	0.700
AST (U/L)	21 (16-27)	20.5 (16.5-27.5)	0.945
ALT (U/L)	19 (16-28)	21 (16-27)	0.552
Urea (mg/dL)	21.5 (17.5-24)	18 (15-22)	0.072
Creatinine (mg/dL)	0.6 (0.6-0.7)	0.6 (0.6-0.7)	0.320
Triglyceride (mg/dL)	112 (71.0-136)	99.5 (77-120.5)	0.466
Total Cholesterol (mg/dL)	159 (143.0-181)	159.5 (128-174.5)	0.338
HDL (mg/dL)	46.6 (41.9-53.3)	43.8 (37.3-53.1)	0.128
LDL (mg/dL)	82 (69.5-102)	92 (60-107)	0.853
HbA1c (%)	5.3 (5.1-5.4)	5.3 (5.2-5.8)	0.562
Insulin (µU/mL)	12.4 (8.5-16.1)	21.5 (15.2-25.5)	<0.001

IQR, interquartile range; Hb, hemoglobin; PLT, platelet; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HbA1c, Hemoglobin A1c; g, gram; mg, milligram; mm^3, cubic millimeter; dL, deciliter; ng, nanogram; uL, microliter; L, liter; pg, pictogram; mL, milliliter. All data are presented as median (IQR).

Table 3. Comparison of neurological evaluation scale scores between healthy, obese and morbidly obese controls

Parameter	Healthy Children (1) (n=57)	Obese Children (2) (n=37)	Morbidly Obese Children (3) (n=24)	p-value
SI score	0 (0–1)	1 (0–2)	1 (0–2.5)	1–2: 0.005 ‖ 1–3: 0.003 † 2–3: 0.713 †
MC score	0 (0–0)	0 (0–1)	0 (0–2)	1–2: 0.009 ‖ 1–3: 0.001 † 2–3: 0.222 †
SCMA score	0 (0–1)	1 (0–2)	0 (0–1)	1–2: 0.004 ‖ 1–3: 0.401 † 2–3: 0.131 †
Other NES score	1 (0–2)	2 (1–4)	2 (0–3.5)	1–2: 0.002 ‖ 1–3: 0.097 † 2–3: 0.485 †
Total NES score	2 (0–4)	5 (2–8)	4.5 (1.5–8.5)	1–2:<0.001 ‖ 1–3:0.008 † 2–3: 0.853 †

QR, interquartile range; n, number; SI, sensory integration; MC, motor coordination; SCMA, sequencing of complex motor acts; NES, neurological evaluation scale. Values are presented as median (IQR). Pairwise comparisons: 1 = healthy controls, 2 = obese children, 3 = morbidly obese children. Tests: Wilcoxon signed-rank (‖, 1 vs 2); Mann–Whitney U (†, 1 vs 3; 2 vs 3). p<0.05 was considered statistically significant.

Table 4. Comparison of neurological evaluation scale scores by age group in obese and healthy controls

Parameter	Obese Children			p-value	Healthy Controls			p-value
Age Groups	Prepubertal (8–10 yr)	Early Adolescence (11–14 yr)	Middle Adolescence (15–16 yr)		Prepubertal (8–10 yr)	Early Adolescence (11–14 yr)	Middle Adolescence (15–16 yr)	
SI score [2]	2 (0–3)	1 (0–3)	1 (0–1)	0.243	1 (0–1)	0 (0–1)	0 (0–0)	0.040
MC score	1 (0–1)	0 (0–0.5)	0 (0–2)	0.220	0 (0–1)	0 (0–0)	0 (0–0)	0.133
SCMA score [1, 2]	1 (0–2)	1 (0–1)	0 (0–2)	0.509	1 (0–2)	0 (0–0)	0 (0–0)	<0.001
Other NES score [1, 2]	3 (1–4)	2 (0.5–4)	2 (1–3)	0.130	2 (1–3)	1 (0–1)	0 (0–0.5)	0.001
Total NES score [1, 2]	6 (3–9)	4.5 (2–8.5)	4 (1–6)	0.206	4 (3–6)	1 (0–3)	0 (0–1.5)	<0.001

Abbreviations: IQR, interquartile range; SI; sensory integration; MC, motor coordination; SCMA,sequencing of complex motor acts;NES,neurological evaluation scale.

[1] In the healthy group, there is a statistically significant difference between the prepubertal group and the early adolescent group.

[2] In the healthy group, there is a statistically significant difference between the prepubertal group and the mid-adolescent group.

and, more importantly, to the absence of data regarding obesity duration. The chronicity of inflammation may play a critical role in the extent of neurological dysfunction. These findings indicate that obesity, even at moderate levels, is associated with higher NES scores compared to healthy peers, while further increases in BMI do not appear to result in additional neurological impairment. Future studies should incorporate obesity duration as a variable to better elucidate this relationship.

Previous studies have reported the presence of SNS in healthy individuals.[24-27] A longitudinal study of 48 healthy boys demonstrated that SNS increased over one year among those who initially exhibited such signs.[28] In our study, SNS were detected in both obese and healthy children; however, NES scores were significantly higher in the obese group. Beyond inflammation, physical inactivity and consequent immobility in obese children may also have contributed to these findings. Physical activity is known to exert neuroprotective effects by enhancing neuroplasticity, motor coordination, and cognitive performance.[29] In our study, children who regularly engaged in physical exercise were excluded to minimize potential confounding; however, objective measures of physical activity were not recorded. Therefore, the lack of quantitative assessment of physical activity represents a limitation, and future studies should incorporate comprehensive evaluations to better elucidate its role.

Several studies have suggested that SNS tend to decrease with age. For instance, Martins et al. reported a decline in SNS scores among healthy children over a five-year period. Their study found higher SNS scores in boys aged 11–14 years, with this sex difference diminishing between 15 and 17 years of age, which was interpreted as reflecting neurodevelopmental maturation.[27] Similarly, Patankar et al.[30] and Ardila et al.[31] also observed age-related reductions in SNS. A separate study involving 101 children aged 4–11 years demonstrated a comparable trend.[27] In our study, within the healthy group, children aged 8–11 years exhibited significantly higher total NES scores, as well as higher scores in the SCMA and other subscales, compared with older age groups (11-14 and 15-16 years). Conversely, no significant age-related differences in NES scores were observed among obese children. These findings support the notion that SNS decline with age in healthy children as a consequence of brain maturation[32], whereas in obese children, this developmental trajectory may be disrupted by persistent chronic inflammation affecting all age groups.

This study has several limitations. First, the relatively small number of morbidly obese children reduces statistical power for subgroup analyses. Second, the cross-sectional design precludes causal inference and evaluation of temporal changes in SNS. Third, the absence of data on obesity duration limits the understanding of cumulative inflammatory exposure. Fourth, although children who regularly engaged in physical exercise were excluded, objective quantification of physical activity was not performed. Finally, as this was a single-center study, the generalizability of the findings may be limited.

Despite these limitations, the study has several notable strengths. These include its prospective design, the

objective and standardized assessment of SNS using the NES, and the exclusion of potential confounding effects of regular physical activity. Moreover, this is among the first studies to investigate SNS in obese children using a validated neurological assessment tool.

CONCLUSION

In conclusion, childhood obesity may influence neurodevelopmental processes and be associated with SNS. The underlying mechanisms linking obesity to these findings, as well as their potential long-term implications, remain to be clarified. Future studies with larger cohorts and longitudinal designs are needed to better elucidate these relationships. Such research could facilitate earlier identification and prevention strategies aimed at supporting healthy neurodevelopment in obese children.

Author contributions

Conception and design: T.D., E.C.; Data acquisition: T.D.; Data analysis: T.D., E.C.; Data interpretation: T.D., E.C.; Drafting of the manuscript: T.D., E.C., A.A., A.T. All authors reviewed the results, approved the final version of the manuscript, and agreed to be accountable for all aspects of this study.

Ethical approval

This study was approved by the Aydın Adnan Menderes University Faculty of Medicine Ethics Committee (Decision/Protocol No: 2021/129). Informed consent was obtained from all participants involved in this study.

Conflict of interest

The authors declare that this study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Generative AI statement

The authors declare that no generative AI or AI-assisted technologies were used in the writing or preparation of this study.

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Research Article

Transcatheter closure of atrial septal defect with Occlutech Figulla Flex II in children: A single-center experience

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ABSTRACT

Objective: Advances in transcatheter closure device materials ensure safety and long-term effectiveness in most atrial septal defect (ASD) cases.

Methods: This single-center study retrospectively evaluated outcomes in 26 pediatric patients who underwent transcatheter ASD closure between 2023 and 2025. Transcatheter closure was attempted using the Occlutech® Figulla Flex II ASD Occluder (OFSO). Follow-up evaluations of device-specific outcomes, procedural success rates, and complications were recorded.

Results: The average age of the patients was 9.3 ± 4.1 years, and 61.5% were girls. Of the total patients, 11.5% had a large defect. A complication occurred in 1 patient (3.8%).

Conclusion: Transcatheter closure of ASD with the OFSO device is a safe and effective treatment strategy for children, demonstrating a high procedural success rate and an overall complication rate of 3.8%.

Keywords: atrial septal defect, child, transcatheter closure, device

INTRODUCTION

Atrial septal defect (ASD) is one of the most common congenital heart defects, comprising approximately 6–10% of all cases. The secundum type is particularly prevalent and is usually the most suitable for transcatheter closure. The clinical course of secundum ASDs varies; small defects may remain asymptomatic throughout life, while moderate-to-large defects can result in right ventricular volume overload, arrhythmias, and pulmonary overcirculation if left untreated. Closure is generally indicated when the ratio of pulmonary to systemic blood flow (Qp/Qs) exceeds 1.5.[1-5]

Over the past two decades, percutaneous ASD closure has become the preferred treatment for selected pediatric patients, largely due to its minimally invasive nature and shorter recovery times. The Amplatzer Septal Occluder (ASO) is the most widely used device for this procedure.[3] The other devices used for ASD closure are the Cera-Flex Occluder, Occlutech ASD Occluder, Amplatzer Cribriform Occluder, Gore Cardioform Septal Occluder, and Gore Cardioform ASD Occluder.[6-14] The results of the Occlutech Figulla Septal Occluder (OFSO) have not been reported as frequently. Haas et al. found that ASD closure using OFSO is feasible in a large variety of patients (in 1315 patients

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of all age groups) and is safe with only a minimal risk of severe side effects. However, the safety and efficacy of newer or less commonly utilized devices in the pediatric population are still not well established.[15] The OFSO devices have important structural differences, especially an absent left atrial hub, and the latest generations have a tiltable delivery system that seems to be advantageous regarding the feasibility of implantation in complex ASDs, device delivery, as well as device alignment to the atrial septum, and thereby echocardiographic assessment during implantation.[16] Roymanee et al. found that there were no significant differences between the major and minor complications when comparing the OFSO and ASO devices.[17]

This study aimed to present our single-center experience with the Occlutech® Figulla Flex II ASD Occluder device for the transcatheter closure of secundum ASDs in children. We focused on evaluating device-specific outcomes, procedural success rates, and complications.

MATERIAL and METHODS

This retrospective study included pediatric patients aged 2 to 18 years who underwent transcatheter closure of secundum ASDs with the Occlutech® Figulla Flex II ASD Occluder device at the İzmir City Hospital from 2023 to 2025. Several ASD devices, such as Amplatzer, CERA, and OFSO, are used in our center. The OFSO is preferred over other devices due to its ease of use for both the operator and previous ASD closure options. Because the OFSO connector allows for free rotation up to 50 degrees and angulation without requiring any force, the device is easier to insert. Therefore, it is frequently preferred by operators. This study was conducted solely to share our experiences with the OFSO. All procedures presented in this study were performed by the same two interventional cardiologists.

Inclusion criteria were secundum ASD greater than 8 mm, Qp/Qs ratio greater than 1.5, and enlargement of the right heart structures. Exclusion criteria were an echocardiographic (ECO) diameter greater than 30 mm and inadequate inferior and posterior rims.

The cohort consisted of 16 girls and 10 boys, all of whom exhibited significant left-to-right shunting as confirmed by echocardiography and demonstrated evidence of right heart volume overload. Importantly, none of the patients presented with severe pulmonary hypertension. The institutional ethics committee approved the study (Approval Number: 2025/392).

Demographic data, body surface area (BSA), ECO diameter, mean-PAP, right ventricular end-diastolic (RVED) diameter, device size, fluoroscopy time, Qp-Qs, defect diameter (with transesophageal echocardiography), balloon sizing, total septum diameter, rim adequacy, defect size/total septum diameter, defect size/weight, defect size/BSA were recorded. Pre-procedure echocardiographic evaluations were performed using either transthoracic (TTE) (Figure 1 and Figure 2) or transesophageal echocardiography (TEE), based on the patient's weight. Balloon sizing was conducted in all cases (Figure 3).

Procedure

The procedure was performed under general anesthesia in a pediatric catheterization lab. Occlutech® Figulla ASD Occluder was used in all cases (Figure 4). A large defect is defined as one with a diameter-to-weight ratio greater than 1.2 or a diameter-to-BSA ratio exceeding 20 mm/m². Post-procedural care included 24 hours of in-hospital observation, acetylsalicylic acid for six months, and prophylaxis for infective endocarditis for one year. Follow-up evaluations, including ECG, echocardiography (Figure 5), were scheduled at one week, one month, three months, and six months. The procedural complications, such as device embolization and arrhythmia, were evaluated. The presence of a residual shunt was assessed by color Doppler using TTE.

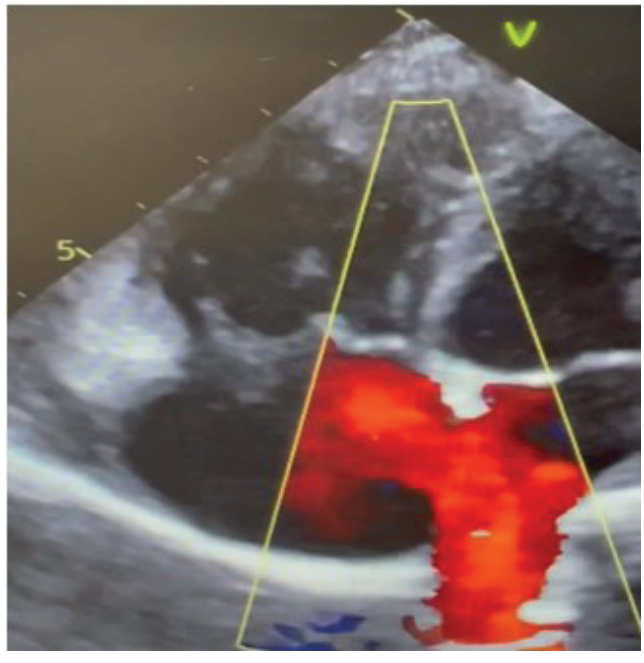


Figure 1. 16mm ASD colored left-to-right shunt

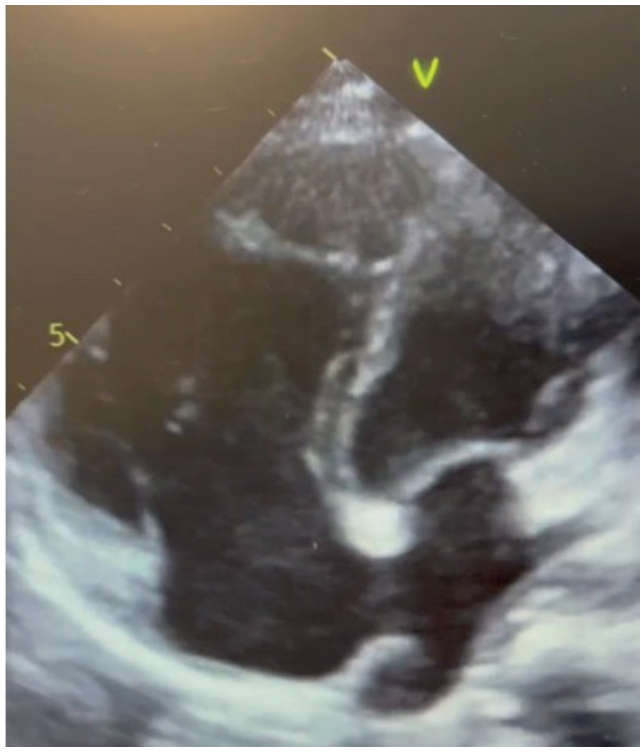


Figure 2. Enlargement of right heart structures on TTE

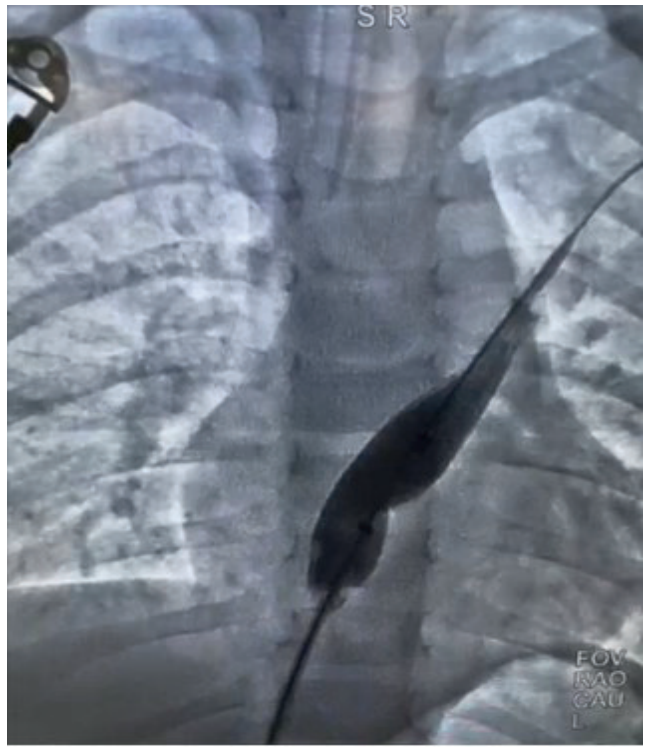


Figure 3. Measurement of defects with balloon sizing

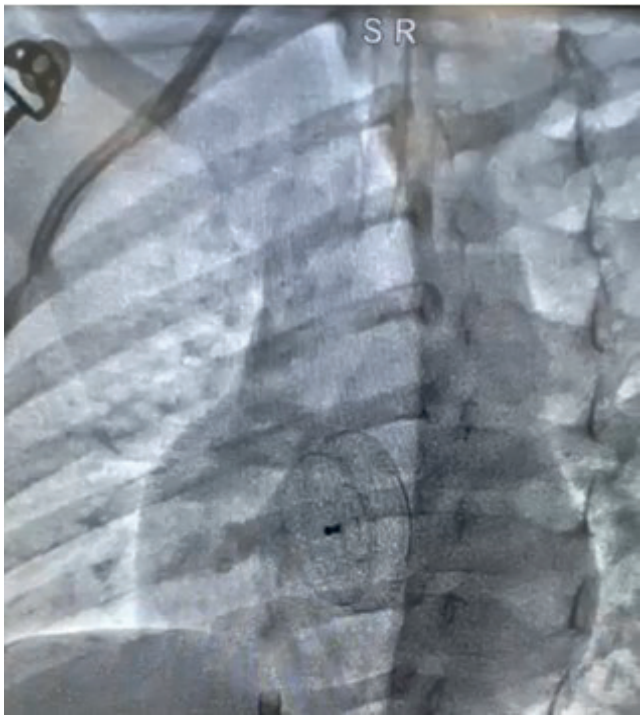


Figure 4. Fluoroscopy image after release of the OFSO device into an 18 mm ASD



Figure 5. The echocardiography image of the OFSO device shows that it does not compress the aorta

Statistical analysis

Statistical analysis was conducted using SPSS version 23.0. Categorical variables were reported as frequencies and percentages, while continuous variables were presented as means with standard deviations.

RESULTS

Demographics

A total of 26 patients were included in the study. The mean age was 9.3 ± 4.1 years, 61.5% were female, and 11.5% had congenital heart disease. The average body weight was 34.8 ± 19.1 kg (Table 1). Before the procedure, 73.1% of the patients had right bundle branch block, 3.8% had complete AV block, and 23.1% had normal ECGs.

Procedure results

The ASD diameter was assessed using TTE before the procedure, as shown in Figure 1 and Figure 2. Figure 1 shows an echocardiographic image of a patient with a 16-mm ASD. Figure 2 shows an image of a patient with enlargement of the right heart structures using TTE. ASD diameter was measured with balloon sizing in all patients. Figure 3 shows an image of a patient who underwent balloon sizing.

The mean echocardiographic ASD diameter was 12.7 ± 2.9 mm, while the mean balloon-stretched diameter measured 15.0 ± 4.8 mm. The average device size used was 16.0 ± 5.2 mm. In terms of procedural metrics, the mean fluoroscopy time was 9.0 ± 2.1 minutes. Regarding hemodynamic measurements, the average Qp/Qs ratio was 1.7 ± 0.1 (Table 2).

Out of the total patients, 3 (11.5%) were identified as having a large defect. Deficient rims were observed in 7 patients (26.9%), with the aortic rim being the most affected in 6 patients, and the inferoposterior rim was affected in 1 patient. OFSO was placed in 25 patients without complications. Figure 4 shows a fluoroscopy image after release of the OFSO device in a patient with an 18 mm ASD. Figure 5 shows an image of a patient in whom OFSO was placed without creating aortic compression.

The patient with complications (n = 1) had a small defect, while three of the patients without complications (n = 25) had large defects, and the other 22 patients had small defects. The patient with complications had an insufficient rim, while six of the patients without complications (24%) had insufficient rims. There was no residual shunt in the patient with complications, whereas one of the patients without complications (4%) had a residual shunt.

Table 1. Patient characteristics

	N	%	M±SD	Min-Max
Age (year)			9.3 ± 4.1	2.5 - 18
Weight (kg)			34.8 ± 19.1	12 - 80
Height (cm)			129.9 ±24.6	82 - 176
Gender				
Female	16	61.5		
Male	10	38.5		
Congenital Heart Disease				
No	23	88.5		
Yes*	3	11.5		

*Aortic Coarctation, Ventricular Septal Defect, Congenital AV block.

Table 2. Procedure characteristics

	M ± SD	Min- Max
ECO diameter (mm)	12.7 ± 2.9	8 - 22
Mean-PAP (mm-hg)	16.3 ± 1.3	14 - 19
Right ventricular end-diastolic (RVED) diameter (mm)	30.9 ± 4.4	22 - 40
Device size (mm)	16.0 ± 5.2	10.5 - 30
Fluoroscopy time (min)	9.0 ± 2.1	6 - 15
Qp-Qs	1.7 ± 0.1	1.5 – 2.2
Defect diameter (TEE) (mm)	14.2 ± 4.3	9 - 27
Balloon-stretched diameter (mm)	15.0 ± 4.8	9.7 - 28
Total septum diameter (mm)	44.2 ± 10.3	12 - 64
Defect size/total septum diameter	0.3 ± 0.1	0.1 – 0.9
Defect size/weight	0.4 ± 0.2	0.1 – 1.0
Defect size/body surface area	12.8 ± 4.9	6.5 – 23.6

*ECO: Echocardiography, PAP: Pulmonary artery pressure, BSA: Body surface area, RVED: Right ventricular end-diastolic.

When comparing patients with and without complications, the patient with complications (n = 1) had a small defect, while three of the patients without complications (n = 25) had large defects, and the other 22 patients had small defects. The patient with complications had an insufficient rim, while six of the patients without complications (24%) had insufficient rims. There was no residual rim in the patient with complications, whereas one of the patients without complications (4%) had a residual rim.

Complications occurred in only one patient (3.8%), resulting in device embolization. On the first day after the procedure, an echocardiogram revealed that the device had embolized into the ascending aorta. The patient underwent further angiography, and attempts were made to retrieve the device with a snare. Because the device could not be removed, the patient was referred for surgery. The device was removed from the aorta, and the ASD was surgically closed. In another patient, the device was not placed due to the insufficient and flexible inferior vena cava (IVC) rim, and the patient was referred for surgery. During the follow-up, no residual shunt was observed in any of the patients.

DISCUSSION

This single-center, retrospective study presented our OFSO device experience in the transcatheter closure of secundum ASD in a pediatric population. Our findings confirmed that percutaneous closure of ASD with the OFSO device is a safe and effective treatment strategy for children, demonstrating a high procedural success rate and a complication rate of 3.8%. A key strength of this study was the evaluation of OFSO devices in real-world pediatric use. These results aligned with prior large-scale studies, including multicenter registries and device-specific trials, which report complication rates ranging from 3% to 7% in pediatric and mixed-age populations. However, there are limitations due to the small sample size (n = 26) and single-center design.

Roymanee et al. found that OFSO devices were safe and effective for percutaneous ASD closure (success rate: 97.4%). The OFSO had the benefit of a shorter fluoroscopic time (ASO 13.7 min; OFSO 9.0 min).[17] In our study, the mean fluoroscopy time was 9.0 ± 2.1 minutes.

In our study, device embolization occurred in one patient who had a deficient rim and large defects. As previously noted by Santoro et al. and Sommer et al., deficiencies in the retro-aortic or posterior rims significantly elevate the risk of device instability and migration.[9,10] In our study, the device was not placed due to the insufficient and flexible IVC rim in one patient, and the patient was referred for surgery. In other patients, no residual shunt was observed during the follow-up. In another mixed-group study comparing the devices, 6 (3%) patients in the OFSO group had a large residual shunt, and 12 (6%) had a small residual shunt. In the ASO group, 5 (3%) patients had a large residual shunt, and 19 (10%) had a small residual shunt. The prevalence of a residual shunt did not differ between the two groups.[18]

Although rare, AV block is one of the most feared complications of ASD closure, particularly in small children and those with oversized devices relative to their body size. In our cohort, we did not observe AV block. Houeijeh et al. and Muroke et al. noted that AV block occurred in up to 1% of patients, especially those with oversized devices.[11,12] Our results highlighted the importance of carefully considering the device-to-weight and device-to-septal diameter ratios during patient selection, particularly for children weighing under 15 kg or those with large defects.

The study found that a large ASD, defined as a defect size-to-body surface area ratio greater than 20 mm/m², or a defect size-to-weight ratio greater than 1.2, was present in 11.5% of patients. While most of these patients achieved successful closure, our findings aligned with prior literature[12-14], indicating that large ASDs should be approached with increased caution and meticulous planning. In another study, successful implantation with OFSO was achieved in all pediatric patients, and neither residual shunt nor conduction abnormality was observed in any case.[19] This study emphasized the importance of long-term follow-up. Residual shunts were not identified in patients. Notably, during the 6-month follow-up, no cases of device erosion or late-onset pericardial effusion were observed. This may suggest that modern imaging and sizing protocols are effective in preventing these rare but serious complications.

Limitations

Despite its strengths, this study had several limitations. The retrospective, single-center design may restrict its generalizability. This study presented results for up to 6 months. Another limitation of this study was the short follow-up period; these patients need to be observed for a longer term to establish the safety of the device with long-term use. Additionally, the small number of patients limited our ability to draw definitive conclusions about their safety profiles. Nonetheless, these findings offer valuable real-world insights into the OFSO device, procedural planning, and complications in pediatric ASD closure.

CONCLUSION

In conclusion, our experience indicated that transcatheter ASD closure with the OFSO device is a reliable and safe procedure for children. Although major complications such as device embolization were rare (3.8%), they require prompt recognition and management. Future multicenter, randomized, prospective studies are essential to further define the optimal device choice and procedural strategies for anatomically complex defects and for younger pediatric patients.

Author contributions

Conception and design: E.G., C.K.; Data acquisition: E.G., K.Y., S.Ö., M.A.A.; Data analysis: E.G.; Data interpretation: E.G.; Drafting of the manuscript: E.G., K.Y., M.A.A., S.Ö., C.K. All authors reviewed the results, approved the final version of the manuscript, and agreed to be accountable for all aspects of this study.

Ethical approval

This study was approved by the Medical Research Ethics Committee of İzmir City Hospital (Decision/Protocol No: 2025/392). Informed consent was obtained from all participants involved in this study.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of interest

The authors declare that this study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The authors declare that this study received no funding.

Generative AI statement

The authors declare that no generative AI or AI-assisted technologies were used in the writing or preparation of this study.

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Research Article

Association of nutritional literacy and healthy lifestyle beliefs with metabolic control in adolescents with type 1 diabetes

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ABSTRACT

Objective: The study aims to evaluate the nutrition literacy and healthy lifestyle beliefs among adolescents with Type 1 Diabetes Mellitus (T1D) and identify their relationship to metabolic control.

Methods: This cross-sectional study included 153 adolescents aged 10-19 years who were being followed in the outpatient clinic of a tertiary hospital with a diagnosis of T1D for more than one year and had no comorbidities requiring dietary treatment. All participants completed the Adolescent Nutrition Literacy Scale (ANLS) and Healthy Lifestyle Belief Scale for Adolescents (HLBS) during a regularly scheduled medical visit. Hospital records yielded the last three months' HbA1c levels to assess metabolic control. Targeted metabolic control was defined as ≤7% HbA1c.

Results: The median age of the participants was 14.66 (4.42) years (45.8% were female), 58.2% had a normal BMI z-score, and 26.8% were achieving target HbA1c (≤7%). There was a positive correlation between the HLBS total score and the ANLS total score (r=0.39, p=0.001). The 'interactive' subfactor of ANLS, which evaluates the capacity to manage the process of nutrition in cooperation with nutrition and health professionals, was correlated with healthy lifestyle beliefs (r= 0.28, p= 0.001). Another ANLS subfactor, the 'critical' subfactor, which assesses the capacity to make critical judgments about nutrition-related information and to take actions to raise awareness in this area, was also correlated with healthy lifestyle beliefs (r = 0.37, p = 0.001). There was no difference between HLBS and ANLS total and subfactor scores between those who achieved (≤7%) and failed to achieve (>7%) the HbA1c target (p>0.05).

Conclusions: The findings of this study suggest that nutrition literacy is a notable determinant of the adoption of healthy lifestyle beliefs among adolescents with T1D. Further research with a larger sample is needed to investigate indirect effects on diabetes self-management and long-term metabolic outcomes.

Keywords: adolescents, type 1 diabetes mellitus, nutrition literacy, healthy lifestyle beliefs

INTRODUCTION

T1D is characterized by autoimmune destruction of pancreatic β-cells, leading to loss of endogenous insulin secretion.[1] Nutritional management is an essential component of diabetes education and care. For children and adolescents with T1D, the primary goals of nutritional management are to promote normal growth and development, healthy dietary habits that can sustain lifelong macro- and micronutrient needs, and achieve optimal glycemic control. It also aims to implement nutritional interventions to prevent or delay diabetes complications.[2]

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Adolescence is characterized by peak physical development, psychological and cognitive maturation, autonomy, and social independence. Rapid physical and sexual maturation creates a period of physiological and behavioral vulnerability. Hormonal changes that occur in adolescents are important for managing chronic diseases such as diabetes because they directly affect the physiology of glycemic control. Despite recent advances in diabetes technologies, achieving optimal glycemic control during adolescence remains a challenge. Adolescents with T1D are often more independent in their food choices and have more freedom over when and how much they eat. This can negatively impact their glycemic control and food choices.[3] Alterations in food consumption and eating disturbances—e.g., skipping meals, insufficient carbohydrates, consuming low-carbohydrate diets, or exercise performed without taking carbohydrate intake before, during, or after exercise—are risk factors for hypoglycemia, which is one of the most severe acute T1D complications. Postprandial hypoglycemia may also occur due to a mismatch between bolus insulin dose and carbohydrate intake-e.g., when insulin to carbohydrate ratio (ICR) is higher than the actual requirement, or when the ICR is accurate but carbohydrate intake is underestimated.[4] Therefore, providing continuous diabetes education to adolescents with T1D is essential in achieving glycemic targets, preventing complications, and promoting a healthy lifestyle. During this stage, healthy lifestyle habits may develop in adolescents following their exposure to nutrition information.[5-7] Physical activity levels, sociodemographic characteristics, nutritional status, and emotional and psychosocial well-being influence the attitudes and beliefs of adolescents toward healthy living. In this regard, building health-promoting behaviors might contribute to overall health. Adolescents with a higher level of nutrition literacy are more likely to possess greater food knowledge and the ability to make informed food choices, maintain adequate nutrition, and promote health preservation.[5,8-10] Nutrition literacy, defined as the capacity to obtain, process, and understand basic nutrition information for making appropriate dietary decisions, plays a crucial role in shaping adolescents' eating behaviors and overall diet quality.[9] Evidence indicates that higher nutrition literacy levels are associated with healthier food choices, better adherence to dietary guidelines, and improved heart health attitudes among adolescents.[11] In addition to cognitive skills, behavioral and motivational factors, such as healthy lifestyle beliefs and self-efficacy, also strongly influence adherence to diabetes self-care practices. Adolescents who possess greater confidence in their ability to maintain healthy routines are more likely to follow dietary recommendations and perform consistent self-management behaviors, contributing to optimal metabolic outcomes.[12] Despite these associations, few studies have simultaneously examined the interplay between nutrition literacy, healthy lifestyle beliefs, and metabolic control among adolescents with T1D. Exploring these relationships may enhance the development of a comprehensive intervention framework. For this purpose, the present study aimed to assess the nutrition literacy level in adolescents with T1D, identify their attitudes and motivations towards healthy lifestyle beliefs, and examine the relationship among these factors and metabolic control. We hypothesized that adolescents with higher nutrition literacy and stronger healthy lifestyle beliefs would exhibit more favorable metabolic outcomes.

MATERIALS and METHODS

This descriptive, cross-sectional study was conducted in the Department of Pediatrics, Division of Pediatric Endocrinology and Diabetes, Faculty of Medicine, Ege University, from November 2023 to May 2024, with 167 adolescents with T1D aged 10-19 years. All participants answered an ANLS and HLBS during regularly scheduled medical visits. The purpose of the study was explained to each participant, and written informed consent was obtained from all participants and their parents. Patients' records were reviewed for the following criteria: duration of T1D≥ 1 year, no major medical problems requiring dietary treatment (e.g., celiac disease), and no psychiatric disorders or communication difficulties. Finally, the data of 153 participants who met the eligibility criteria and responded to all items of the ANLS and HLBS were included in the analysis. The sample size was calculated using a power analysis (G*Power 3.1) based on previous literature. An expected small effect size of 0.2, a desired statistical power of 80%, and a Type I error rate of 0.05 were set. This analysis indicated a minimum required sample size of 146 participants. To account for a predicted 15% attrition rate, we aimed to enroll a total of 167 participants. The study was conducted in accordance with the Helsinki Declaration and was approved by the İzmir Tınaztepe University Non-Intervention Research Ethics Committee (Prot. no. 2023/19).

Anthropometric evaluation

Height was measured to the nearest millimeter using a Seca 264® stadiometer. Weight was measured unclothed using an electronic scale to the nearest 100 g (Desis Model

KW®). Body mass index (BMI) was calculated by the weight (kg)/ height (m^2) equation. Standard deviation scores (SDS) for weight, height, and BMI were calculated according to gender and age using reference values for Turkish children and adolescents by using Child Metrics.[13] The participants were categorized into four groups: underweight (BMI-SDS <-1), normal weight (BMI-SDS≥-1 - <+1), overweight (BMI-SDS ≥+1 to <+2), and obese (BMI-SDS ≥+2).[14]

Glycemic control

HbA1c was measured by turbidimetric inhibition immunoassay (Roche Cobas c513 analyzer using the Tina quant® HbA1c Gen. 3 assay, Germany). Participants were categorized into two groups based on their HbA1c levels, as either achieved or non-achieved HbA1c targets, according to the HbA1c target (≤7%) recommendations of the American Diabetes Association (ADA) and the International Society of Pediatric and Adolescent Diabetes (ISPAD).[15,16]

Adolescent nutrition literacy scale

The 'Adolescent Nutrition Literacy Scale (ANLS)' was utilized to measure participants' nutrition literacy. ANLS was developed by Bari in 2012[17], and the Turkish reliability and validity were established by Türkmen et al.[18] in 2017. ANLS, a five-point Likert-type scale, consists of 22 items with three subfactors: 'functional nutrition literacy', 'interactive nutrition literacy', and 'critical nutrition literacy'. 'Functional nutrition literacy' evaluates an individual's ability to read, comprehend, and write basic nutrition information, 'interactive nutrition literacy' measures the capacity to manage the process of nutrition in cooperation with nutrition and health professionals, and 'critical nutrition literacy' assesses the capacity to make critical judgments about nutrition-related information and to take action leading to awareness in this domain. The total score on the scale is 22-110, and greater scores indicate increased levels of nutrition literacy. The Turkish version of ANLS has been shown to have good internal consistency (Cronbach's alpha = 0.80).[17,18]

Healthy lifestyle belief scale for adolescents

The Healthy Lifestyle Belief Scale for Adolescents (HLBS) was developed by Kelly et al.[19], and a Turkish validity and reliability study was conducted by Kudubeş and Bektaş.[20] This scale is used to assess adolescents' beliefs towards various aspects of having a healthy lifestyle. HLBS on a five-point Likert-type scale contains 16 items with three subscales: 'health beliefs', 'physical activity', and 'nutrition'. 'Health beliefs' subfactor assesses general attitudes and beliefs related to a healthy way of life, e.g., self-efficacy in making choices on health-related issues and believing one can set up and achieve health goals, 'physical activity' subfactor identifies physical activity-related beliefs and attitudes, including perceived benefits of regular exercise, emotional and physical restoration effects of active living and 'nutrition' subfactor assesses healthy eating behaviors beliefs, where it tracks the selection of healthy snacks, consumption of nutrient-dense foods regularly, and identification of favorable health effects of eating habits. Total score ranges from 16 to 80, where higher scores indicate greater beliefs in adherence to a healthy lifestyle. The original HLBS and Turkish versions have shown good internal consistency (respectively, Cronbach's alpha=0.89, Cronbach's alpha=0.90).[19,20]

Statistical analysis

Normal distribution was tested for quantitative variables by the Shapiro-Wilk test. Quantitative variables with normal or skewed distribution were presented as mean±SD or median (IQR). Qualitative data were presented as frequencies (n) and percentages (%). Group differences were investigated using the Mann–Whitney U and Kruskal–Wallis tests. Post-hoc pairwise comparisons were tested using the Bonferroni correction. The chi-square test was used to investigate the association between categorical variables. Correlation analyses were used to explore relationships between HLBS total score, and other constructs hypothesized to covary with HLBS score such as ANLS total score, ANLS subfactor scores, diabetes duration and HbA1c, in line with Cohen, correlations of 0.10–0.29 were interpreted as small, 0.30–0.49 as a medium, and 0.50–1.0 as large.[21] All results were verified on a confidence level of 95%, and the significance level was defined as $p < 0.05$. Statistical analyses were conducted using Statistical Package for the Social Sciences version 25.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

The mean age of the participants was 14.66 ± 4.42 years (45.8% were female), 58.2% had a normal BMI z-score, and 26.8% were achieving target HbA1c (≤7%). The median HbA1c levels in MDI users and IIPT users were 8.3% (2.1) and 7.5% (1.6), respectively ($p = 0.04$). The characteristics of the participants are detailed in Table 1.

Table 1. Characteristics of participants			
Variables	**All (n=153)**	**Female (n=70)**	**Male (n=83)**
Age (years)*	14.66 (4.42)	14.43 (4.17)	14.43 (4.17)
Diabetes duration (years)*	5 (6.3)	6.35 (6)	5.50 (6)
BMI z-score*	0.15 (1.67)	0.11 (1.48)	0.50 (1.61)
HbA1c (%)*	8.05 (2.2)	8.27 (2)	8.48 (2.5)
Insulin (U/kg/day)**	0.86±0.29	0.88±0.27	0.85±0.31
Basal insulin%*	40.5 (15)	39.16 (15)	43.16 (16.3)
Bolus insulin%*	59 (15)	59.46 (16)	56.76 (16)
Treatment model* **			
IIPT	53 (34.6)	24 (34.3)	29 (34.9)
MDI	100 (65.4)	46 (65.7)	54 (65.1)
BMI* **			
Underweight	24 (15.7)	14 (20)	10 (12)
Normal weight	89 (58.2)	46 (65.7)	43 (51.8)
Overweight	26 (17)	8 (11.4)	18 (21.7)
Obese	14 (9.2)	2 (2.9)	12 (14.5)
Metabolic Control* **			
HbA1c ≤7%	41 (36.6)	20 (28.6)	21 (25.3)
HbA1c >7%	112 (63.4)	50 (71.4)	62 (74.7)
HLBS total score*	71.0 (14.0)	69.79 (9)	62.24 (15.3)
Belief subfactor	31.0 (6.0)	30.56 (4)	30.32 (7.3)
Physical Activity subfactor	23.0 (6.8)	22.07 (4.3)	20.07 (9)
Nutrition subfactor	17.0 (6.0)	16.87 (5)	15.84 (7)
ANLS total score *	68.0 (15.0)	66.13 (14)	66.96 (16.5)
Functional subfactor	15.0 (9.8)	16.34 (10)	14.43 (9.5)
Interactive subfactor	18.0 (8.0)	18.37 (6)	19.05 (8.3)
Critical subfactor	33.0 (10.0)	31.41(8)	33.47(12.3)

*Data presented as median (IQR) **Data presented mean ± SD ***Data presented n (%), IIPT: Insulin infusion pump therapy, MDI: Multiple dose injection. BMI: Body Mass Index, HLBS: Healthy Lifestyle Belief Scale, ANLS: Adolescent Nutrition Literacy Scale.

The median scores obtained with the ANLS for the total sample, females, and males were 68.0 (15.0), 68.0 (14.0), and 68.0 (17.0), respectively, and there was no difference between females and males ($p>0.05$). It was observed that females had a higher ANLS functional subfactor score, and males had a higher critical subfactor score ($p<0.05$).

The median scores obtained with HLBS for the total sample, females, and males were 71.0 (14.0), 72.0 (10.0), and 70.0 (16.0), respectively, and there was no difference between genders ($p>0.05$); however, females had a higher physical activity subfactor score than males ($p<0.05$).

There were no differences between the HLBS total score, ANLS total score, and their subfactor scores between those who achieved the HbA1c target and those who did not ($p>0.05$).

While there were no differences in median ANLS total scores and subfactor scores according to treatment models, both the HLBS median total score and the 'nutrition' subfactor median score were higher in those on multiple dose insulin therapy (MDI) ($p=0.02$, $p=0.01$, respectively).

Obese participants had lower total and subfactor scores on the HLBS ($p<0.05$) (Table 2).

There was a small-sized correlation between age and both ANLS ($r=-0.24$, $p<0.01$) and HLBS ($r=-0.21$, $p<0.01$) total scores, while diabetes duration was small-sized correlated only with ANLS total score ($r=-0.21$, $p<0.01$).

Table 2. Comparison of ANLS and HLBS scores and subfactors by group characteristics

	ANLS	p	Functional	p	Interactive	p	Critical	p	HLBS	p	Health beliefs	p	Physical Activity	p	Nutrition	p
Gender																
Female	68 (14)	0.74	16 (10)	0.01*	18 (6)	0.59	31 (8)	0.02*	72 (10)	0.18	31 (5)	0.86	24 (4)	0,03*	18 (5)	0.23
Male	68 (17)		13 (10)		19 (8)		36 (11)		70 (16)		32 (8)		22 (9)		17 (7)	
BMI																
Underweight	68 (15)	0.24	13 (10)	0.82	18 (11)	0.62	31 (5)	0.70	72 (13)	0.02 **	31 (5)	0.03**	22 (6)	0.001**	18 (5)	0.001**
Normal	68 (16)		15 (9)		19 (8)		36 (9)		72 (12)		32 (5)		24 (4)		18 (5)	
Overweight	67 (12)		16 (11)		18 (4)		31 (10)		69 (15)		30 (5)		22 (7)		16 (7)	
Obese	66 (27)		13 (8)		15 (8)		31 (15)		50 (24)		26 (8)		13 (10)		12 (7)	
HbA1c (%)																
≤7	65 (15)	0.71	13 (10)	0.46	20 (7)	0.75	32 (9)	0.46	67 (13)	0.27	30 (6)	0.14	21 (6)	0.45	17 (5)	0.19
> 7	68 (14)		15 (10)		18 (8)		33 (10)		72 (14)		32 (6)		23 (6)		18 (6)	
Treatment model																
IIPT	67 (15)	0.30	14 (8)	0.38	18 (7)	0.65	33 (9)	0.56	68 (16)	0.02*	30 (9)	0.09	21 (6)	0.17	16 (7)	0.01*
MDI	69 (15)		14 (10)		18 (7)		34 (10)		72 (12)		32 (5)		23 (6)		18 (5)	

Data presented median (IQR) BMI: Body Mass Index, HLBS: Healthy Lifestyle Belief Scale, ANLS: Adolescent Nutrition Literacy Scale, IIPT: Insulin infusion pump therapy, MDI: Multiple dose injection
*Mann-Whitney U test, **Kruskal-Wallis test.

Table 3. Correlations between HLBS, ANLS, and subfactors

	1	2	3	4	5	6	7	8
1- HLBS	1							
2- Health beliefs	0.82*	1						
3- Physical Activity	0.80*	0.49*	1					
4- Nutrition	0.82*	0.61*	0.53*	1				
5- ANLS	0.39*	0.33*	0.30*	0.42*	1			
6- Functional	-	-	-	-	-	1		
7- Interactive	0.28*	0.18**	0.23**	0.33**	0.65*	-	1	
8- Critical	0.37*	0.37*	0.33*	0.32*	0.75*	-	0.50*	1

Spearman correlation, *p <0.05, **p <0.01, HLBS: Healthy Lifestyle Belief Scale, ANLS: Adolescent Nutrition Literacy Scale.

Medium-sized correlation existed between the HLBS and the ANLS (r=0.39, p=0.001). HLBS and ANLS scores have different degrees of relationship for all the subfactors except for the functional subfactor of the ANLS (Table 3).

DISCUSSION

To our knowledge, this is the first study to evaluate nutrition literacy, healthy lifestyle beliefs, and their relationship with metabolic control in adolescents with T1D. In adolescents with T1D, interactive and critical nutrition literacy, in particular, is associated with healthier lifestyle beliefs. However, these beliefs or literacy levels were not directly associated with HbA1c. This suggests that literacy is linked to an individual's ability to access, evaluate, and use information in daily decisions, rather than metabolic control. The current study's median ANLS total score was consistent with previous studies conducted with healthy populations.[11,22-24]

Although previous research has reported higher ANLS scores in adolescent girls, in our sample of adolescents with T1D, unlike previous studies, the median ANLS score did not differ by gender. The authors speculated that this may be related to children and adolescents with T1D receiving structured nutrition education appropriate for their age, and that non-T1D adolescents are less interested in nutrition-related issues than girls. The study demonstrated that higher levels of nutrition literacy among adolescents with T1D were associated with stronger healthy lifestyle beliefs. Notably, the 'interactive' and 'critical' subfactors of nutrition literacy—which encompass communication with healthcare professionals, nutritional self-management skills, critical evaluation of nutrition-related information, and awareness—were observed to result in increased healthy lifestyle beliefs. This suggests that these competencies may contribute to more effective diabetes management. Although the research indicates a lack of consensus regarding the factors influencing adolescents' healthy lifestyle behaviors, evidence from a randomized controlled trial has shown that improving health literacy in this population enhances nutritional behaviors.[25-27] A study conducted with 810 adolescents in Turkey demonstrated a moderate association between healthy eating and exercise behaviors and health literacy.[28] Another study investigating the nutrition literacy levels of young adults with T1D and its relationship with disease-related emotional burden found that, although nutritional knowledge was generally adequate, the emotional burden associated with the disease may negatively impact nutritional behaviors and social interactions.[29] Lindbloom et al.[30] reported that nutrition literacy was associated with motivation for healthy eating, which was reflected in actual eating behaviors in the general population. This study found no significant relationship between metabolic control in adolescents with T1D and nutrition literacy and healthy lifestyle beliefs. This finding suggests that metabolic control cannot be explained solely by an individual's level of nutrition literacy and beliefs about a healthy lifestyle, and suggests that more complex psychosocial processes underlie behaviors. The literature defines this phenomenon as the "intention-behavior gap". It is associated with environmental and psychosocial factors that prevent individuals' positive intentions for healthy living from being translated into behavior.[30]

Especially during adolescence, peer influence, the need for social acceptance, and group affiliation may play a stronger role than cognitive beliefs in guiding individuals' self-care behaviors.[31,32] Adolescents with T1D may neglect self-care behaviors necessary for diabetes management (e.g., insulin administration, glucose monitoring, or adherence to a nutritional management plan) due to reasons such as fear of social exclusion, a desire to fit in with their peer group, or an effort to "not look different"[33,34] These

findings suggest that interventions by health professionals to support metabolic control should focus on information transfer, peer relationships, social support systems, and psychosocial empowerment approaches. In this context, peer support groups, cognitive-behavioral-based education programs, and self-efficacy-enhancing psychosocial interventions for adolescents with T1D are thought to be effective in strengthening metabolic control and self-care behaviors[35] Sociodemographic factors, such as age and gender, are known to affect the dietary habits of adolescents.[11] In our study, age was inversely associated with nutrition literacy and healthy lifestyle beliefs. Contrary to our findings, studies show that age has a positive or no effect at all. It has been discussed that age and other influencing factors (gender, physical activity, BMI) should be evaluated together. [10,26,32,33] The literature indicates that female adolescents tend to score higher than males in terms of nutrition literacy.[9,17] Unlike the previous studies, in this study, females had a higher median score on the 'functional' subfactor of the ANLS, which provides information about the ability to process basic nutrition information, while males had a higher median score on the 'critical' subfactor, which provides information about the ability to evaluate nutrition-related content critically and take action to increase awareness in this area ($p<0.05$). In our study, MDI users had higher ANLS 'nutrition' subfactor scores than insulin infusion pump therapy (IIPT) users. This subfactor includes items assessing healthy dietary choices, regular consumption of nutrient-dense foods, and the positive health effects of dietary habits. Despite receiving the same structured nutrition education, the difference between these two treatment groups was interpreted as follows: Individuals with T1D who use both MDI and insulin infusion pumps achieve better metabolic control through the practice of accurate carbohydrate counting.[36] Insulin infusion pumps, bolus types (such as extended bolus, square bolus), and/or algorithms (such as low glucose suspend, automatic bolus, and safe meal bolus) have the potential to compensate for errors in carbohydrate counting or to cover the postprandial glycemic response caused by high-fat and protein foods. However, MDI users should pay more attention to healthy food choices and carbohydrate counting to maintain an optimal postprandial glycemic response. This attention may have led to an increase in interest in these subjects and an increase in nutrition literacy.

Obesity during childhood and adolescence is a multifactorial condition arising from the interplay of genetic predisposition, unhealthy dietary habits, insufficient physical activity, and psychosocial factors. Therefore, education programs focusing on physical activity, nutrition, and lifestyle modification in adolescents are crucial for promoting comprehensive health improvements.[37,38] For young people with T1D, other possible causes of obesity include over-insulinization, excess energy intake to avoid or treat hypoglycemia, and additional carbohydrate consumed for exercise. In addition to these, consumption of low-carbohydrate, high-fat diets to reduce postprandial glucose excursions and chronic exposure of peripheral tissue to non-physiologic hyperinsulinemia via subcutaneous insulin injections or insulin infusion pump therapy may lead to increased adipose tissue in the periphery.[39,40]

Consistent with our findings, several studies conducted with adolescents have reported no relationship between nutrition literacy and BMI.[41,42] Although there was no relationship between nutrition literacy and BMI, in our study, it is noteworthy that obese adolescents with T1D had the lowest HLBS scores compared to those with underweight, normal, or overweight ones. It may be a sign that beliefs and habits related to healthy living, physical activity, and nutrition tend to be lower among individuals with obesity. However, in our sample, overweight/obese participants the low ratio may have contributed to this result and should be interpreted with caution. Furthermore, the association between physical activity levels and dietary habits reported in a study involving healthy adolescents from 89 countries supports the relationships observed between the HLBS subfactors in our study.[43] Therefore, comparisons can be drawn with research investigating the relationship between health literacy and metabolic parameters in adolescents with T1D. Existing literature suggests a positive association between health literacy and metabolic control, and an indirect relationship with insulin dose optimization, although a direct link has not been established.[44,45]

The limitation of this study is that it was conducted as a single-center study in a tertiary hospital outpatient clinic. This limits the generalizability of the findings, as the sample came from a specific geography and had similar follow-up standards. Furthermore, data on participants' socioeconomic status were not collected, which is another factor that may affect sample homogeneity. Additionally, food and physical activity diaries were not assessed in this study, limiting the practical interpretation of healthy lifestyle beliefs and nutrition literacy. It is recommended that future studies address these limitations to increase generalizability. Another limitation of this study is that metabolic control was assessed using only HbA1c. The inclusion of additional metabolic parameters, such

as hypoglycemia frequency and continuous glucose monitoring metrics (time in range, time above range, time below range, glycemic variability, etc.) in future research may provide more comprehensive information on the association of nutrition literacy and healthy lifestyle beliefs with metabolic control in adolescents with T1D.

In conclusion, further studies are needed to evaluate nutrition literacy and/or healthy lifestyle beliefs among adolescents with T1D. Research in this area will help address existing gaps in the literature and provide valuable insights to guide the education of self-care strategies and nutritional management.

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Author contributions

Conception and design: M.Y., Y.A.A., S.D., D.G.; Data acquisition: S.D., Y.A.A.; Data analysis: M.Y.; Data interpretation: M.Y.; Drafting of the manuscript: M.Y., Y.A.A., D.G. All authors reviewed the results, approved the final version of the manuscript, and agreed to be accountable for all aspects of this study.

Ethical approval

This study was approved by the Izmir Tınaztepe University Non-Intervention Research Ethics Committee (Decision/ Protocol No: 2023/19). Informed consent was obtained from all participants involved in this study.

Conflict of interest

The authors declare that this study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Generative AI statement

The authors declare that no generative AI or AI-assisted technologies were used in the writing or preparation of this study.

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Research Article

Mediterranean diet adherence, sleep disturbances, and quality of life in children with asthma: A cross-sectional study

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This study was previously presented as an oral presentation at the 4th International Healthy Nutrition Congress & 1st İstanbul Medeniyet University International Nutrition and Dietetics Congress, April 19-21, 2024, İstanbul, Türkiye. This study was derived from the Master's thesis of Münevver Aybey (currently Taşar), titled "The relation between adherence to the Mediterranean diet on quality of life and sleep disorder in children aged between 7–12 with asthma", conducted under the supervision of Assoc. Prof. Dr. Hülya Yılmaz Önal at İstanbul Atlas University, Institute of Graduate Education, in 2023.

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ABSTRACT

Objective: This study aimed to examine the association between adherence to the Mediterranean diet (MD), sleep disturbances, and quality of life (QoL) in children with asthma.

Methods: A cross-sectional study was conducted with 77 children aged 7–12 years diagnosed with physician-diagnosed, well-controlled asthma receiving low-dose controller therapy. Dietary intake was evaluated using three-day food records and the KIDMED index. Sleep quality and QoL were analyzed using the Sleep Disturbance Scale for Children (SDSC) and the Pediatric Asthma Quality of Life Questionnaire (PAQLQ), respectively. Correlation and regression analyses were performed.

Results: Moderate adherence to the MD was observed in 49.4% of participants. Greater adherence to MD was associated with fewer arousal-related sleep disturbances ($r = –0.283$, $p < 0.05$) and and lower total sleep disturbance scores ($r = −0.241$, $p < 0.05$).. A one-point increase in KIDMED score was associated with a 0.758-point decrease in SDSC score. Higher SDSC scores were significantly associated with lower PAQLQ scores ($r = −0.356$, $p < 0.01$).

Conclusions: Greater adherence to the Mediterranean diet may reduce sleep disturbances and enhance quality of life in asthmatic children, supporting its potential role in asthma management.

Keywords: asthma, mediterranean diet, sleep disorders, child, quality of life, nutritional status

INTRODUCTION

Asthma is the most common chronic respiratory disease in childhood and is characterized by persistent airway inflammation, recurrent wheezing, and coughing episodes.[1] The pathophysiology involves infiltration and activation of immune cells, including dendritic cells, eosinophils, neutrophils, lymphocytes, innate lymphoid cells, and mast cells, which contribute to airway narrowing and bronchial hyperresponsiveness.[2,3] In 2021, the Centers for Disease

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Control and Prevention reported a prevalence of asthma among children aged 5 to 14 years at 7.7%.[4] In addition to its respiratory symptoms, asthma has significant psychosocial implications, including alterations in personality traits, increased psychological distress, and reduced quality of life (QoL).[5]

Children with asthma tend to have lower QoL and health status compared to their healthy peers, participate less in physical activities, and experience higher rates of emotional and behavioral difficulties.[6,7] Assessing QoL in this population is essential to understanding the disease's impact on functional and psychosocial domains during daily life.

Nocturnal worsening of asthma symptoms is a common and clinically significant feature, often triggered by circadian variations in airway inflammation, hormonal levels, and airway reactivity. These physiological alterations lead to sleep disturbances characterized by coughing, wheezing, and dyspnea during the night, which degrade sleep quality. A reciprocal relationship has been proposed between asthma severity and sleep disorders, in which each may aggravate the other.[8,9]

The Mediterranean diet (MD) is a dietary pattern traditionally consumed in Mediterranean countries, emphasizing a high intake of fruits, vegetables, legumes, nuts, and whole grains, as well as olive oil; moderate intake of fish and poultry; and limited consumption of red meat, dairy products, and sweets. This dietary model constitutes a balanced composition of monounsaturated and polyunsaturated fatty acids, dietary fibre, antioxidants, and bioactive compounds associated with anti-inflammatory and antioxidant effects.[10]

Adherence to the MD may reduce airway inflammation and bronchial hyperresponsiveness by modulating oxidative stress and inflammatory pathways.[11,12] Additionally, components of the MD, such as omega-3 fatty acids, polyphenols, and tryptophan-rich foods, may support sleep regulation through their effects on melatonin and serotonin synthesis, gut microbiota modulation, and neuroendocrine function.[13]

This study was designed to investigate the association between adherence to the MD and both sleep quality and QoL in children aged 7 to 12 years diagnosed with asthma. This cross-sectional study assessed dietary intake, sleep disturbances, and QoL using validated measurement tools. We hypothesized that higher adherence to the Mediterranean Diet would be associated with better sleep quality and improved quality of life in children with asthma.

MATERIALS and METHODS

Study design and participants

This cross-sectional study was conducted between January 1 and March 31, 2023, at Prof. Dr. Cemil Taşcıoğlu City Hospital, İstanbul, Türkiye. The study population consisted of children aged 7–12 years with physician-diagnosed asthma, evaluated according to the Global Initiative for Asthma (GINA) guidelines.[14] Asthma status was evaluated at enrollment by the treating physician as part of routine clinical follow-up. Only children with well-controlled asthma receiving low-dose controller therapy were included, whereas those with partly controlled or uncontrolled asthma or requiring higher treatment steps were not included. Eligibility was based on clinical assessment consistent with GINA symptom control, including the absence of asthma-related nocturnal awakenings at enrollment. This approach is consistent with asthma managed at low treatment steps according to the GINA framework. Participants continued their prescribed asthma treatments in accordance with routine clinical practice, and no intervention or modification of medication use was undertaken as part of the study. Children with other chronic diseases or previously diagnosed psychiatric disorders were excluded. Eligible participants were recruited consecutively from children attending the Pediatric Allergy and Immunology outpatient clinic during the study period. A total of 96 children were assessed for eligibility. Nineteen children were excluded (did not meet the inclusion criteria, n=14; did not complete the study procedures, n=5), and the remaining 77 children were included in the final analysis.

Ethics approval was obtained from the Non-Interventional Scientific Research Ethics Committee of İstanbul Atlas University, and written informed consent was obtained from the legal guardians of all participants.

Data collection

Data were collected using a structured 26-item questionnaire covering sociodemographic characteristics, dietary habits, and physical activity. Anthropometric measurements (weight, height) were obtained by trained personnel using standardized procedures. Body Mass Index (BMI) was calculated using the WHO 2007 growth references for children aged 5–19 years.[15]

Measurement tools

Mediterranean diet quality index (KIDMED)

Adherence to the Mediterranean diet was assessed using the KIDMED index, a 16-item questionnaire developed by Serra-Majem et al.[16] The Turkish version was adapted and validated by Akar Şahingöz et al.[17] Scores range from 0 to 12, with ≥8 indicating high adherence, 4–7 moderate adherence, and ≤3 low adherence.

Sleep disturbance scale for children (SDSC)

Sleep quality was assessed using the SDSC, developed by Bruni et al.[18], which consists of 26 items across six subscales. The Turkish validation was performed by Ağca et al.[19] Each item is scored on a 5-point Likert scale; higher scores indicate greater sleep disturbances.

Pediatric asthma quality of life questionnaire (PAQLQ)

Quality of life was assessed using the PAQLQ, developed by Juniper et al.[20] and validated in Turkish by Bozkurt and Yıldız.[21] The scale consists of 23 items across three domains: Activity Limitations, Symptoms, and Emotional Function. Each item is scored on a 7-point scale, with higher scores indicating better quality of life.

Dietary intake assessment

Three-day dietary intake records (including one weekend and two weekdays) were obtained from each participant and analyzed using the Nutrition Information System (BeBiS) software.[22] Participants and their parents received standardized and structured training on how to complete the three-day dietary records, and written instructional materials were provided. To support accurate portion size estimation, the Food and Meal Photograph Catalogue: Measures and Portions developed by Rakıcıoğlu et al. was used as a visual reference during the completion and verification of the dietary records.[23] After completion of the dietary records, telephone interviews were conducted to assess and verify the accuracy of the recorded information. Daily energy and nutrient intake were evaluated and compared with reference values from the Turkish Nutrition Guideline (TÜBER) and the Dietary Reference Intakes (DRI).[24,25]

Statistical analysis

Descriptive statistics were expressed as mean±standard deviation (SD) for continuous variables and as frequency (%) for categorical variables. The Shapiro–Wilk test was used to assess normality. Independent samples t-test and chi-square test were used for group comparisons. Pearson correlation coefficients were calculated to examine relationships among KIDMED, SDSC, and PAQLQ scores. Indirect and total effects were estimated using bias-corrected bootstrap procedures to assess the association between dietary quality, sleep disturbances, and quality of life. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY). A two-sided p value <0.05 was considered statistically significant.

RESULTS

A total of 96 children were assessed for eligibility, and 77 children were included in the final analysis. Of the participants, 20 (26.0%) were girls and 57 (74.0%) were boys, with ages ranging from 7 to 12 years. According to body mass index classification, approximately half of the children were of normal weight, while a smaller proportion were classified as overweight or obese. The baseline demographic and clinical characteristics of the study population are presented in Table 1.

Dietary habits according to sex are summarized in Table 2. As shown in Table 2, meal skipping was common among both boys and girls, with breakfast being the most frequently skipped meal. Snack consumption was predominantly based on fruits and fruit juices in both sexes, whereas dairy-based snacks were less commonly consumed. When eating outside the home, fast food consumption was more frequent than homemade food consumption among both boys and girls.

The distribution of Mediterranean Diet adherence categories by sex is presented in Table 3. Overall, most participants demonstrated moderate adherence to the Mediterranean diet, and no statistically significant differences were observed between boys and girls in the distribution of KIDMED categories ($p > 0.05$).

Comparisons of the mean KIDMED, SDSC, and PAQLQ scores between genders are shown in Table 4. The mean KIDMED score was 5.49±2.84 for boys and 5.70±2.39 for girls. The mean SDSC total score was 40.49±9.13 for boys and 39.75±6.73 for girls. There were no statistically significant differences between genders in the mean total or subdimension scores of the KIDMED, SDSC, and PAQLQ scales ($p>0.05$).

Table 1. Baseline characteristics of the study population

	Boys (n=57)		Girls (n=20)		Total (n=77)	
	n	%	n	%	n	%
Age (years)						
7	24	42.10	9	45.00	33	42.90
8	11	19.30	2	10.00	13	16.90
9	5	8.80	2	10.00	7	9.10
10	7	12.30	1	5.00	8	10.40
BMI classification						
Underweight	10	17.50	4	20.00	14	18.20
Normal weight	28	49.10	13	65.00	41	53.20
Overweight	9	15.80	2	10.00	11	14.30
Obese	10	17.50	1	5.00	11	14.30
Gestational age						
≤37 weeks	10	17.50	3	15.00	13	16.90
≥38 weeks	47	82.50	17	85.00	64	83.10
Mode of delivery						
Vaginal	29	50.90	8	40.00	37	48.10
Cesarean section	28	49.10	12	60.00	40	51.90
Breastfeeding duration						
≤6 months	12	21.10	4	20.00	16	20.80
7–12 months	8	14.00	2	10.00	10	13.00
13–24 months	31	54.40	9	45.00	40	51.90
>24 months	6	10.50	5	25.00	11	14.30
Formula feeding in first year						
Yes	26	45.60	7	35.00	33	42.90
No	31	54.40	13	65.00	44	57.10
Food allergy						
Yes	4	7.00	1	5.00	5	6.50
No	53	93.00	19	95.00	72	93.50

BMI: Body Mass Index.

Correlations between the KIDMED, SDSC, and PAQLQ scores are presented in Table 5. Weak negative correlations were found between the total KIDMED score and both DOA (r=-0.283, p<0.05) and the total SDSC score (r=-0.241, p<0.05). SRBD scores were negatively correlated with total PAQLQ scores (r=-0.395, p<0.01), as well as the PAQLQ subscales of Symptoms (r=-0.255, p<0.05) and Emotional Function (r=-0.434, p<0.01). A weak negative correlation was observed between DOES scores from the SDSC and the Activity scores from the PAQLQ (r=-0.250, p<0.05). HSD scores from the SDSC showed negative correlations with both PAQLQ

Table 2. Distribution of dietary habits by gender

	Boys (n=57)		Girls (n=20)		Total (n=77)	
Dietary habits	n	%	n	%	n	%
Number of meals consumed daily						
2	4	7.00	0	0.00	4	5.20
3	9	15.80	9	45.00	18	23.40
4	28	49.10	7	35.00	35	45.50
≥5	16	28.10	4	20.00	20	26.00
Skipping daily meals						
Yes	19	33.30	7	35.00	26	33.80
No	38	66.70	13	65.00	51	66.20
Most frequently skipped meal						
Breakfast	9	47.40	3	42.90	12	15.60
Lunch	9	47.40	3	42.90	12	15.60
Dinner	1	5.30	1	14.30	2	2.60
Reason for skipping meals						
Waking up late in the morning	2	10.50	1	14.30	3	3.90
Coming home late from school	0	0.00	0	0.00	0	0.00
Insufficient time	1	5.30	2	28.60	3	3.90
Reluctance to eat	16	84.20	4	57.10	20	26.00
Nausea	1	5.30	0	0.00	1	1.30
Choices of snacks						
No snacks consumption	3	5.30	0	0.00	3	3.90
Grain-based foods	18	31.60	10	50.00	28	36.40
Packaged snacks	23	40.40	6	30.00	29	37.70
Dairy products	16	28.10	3	15.00	19	24.70
Fruits and fruit juices	35	61.40	16	80.00	51	66.20
Choices of meals outside home						
Fast food	38	66.70	12	60.00	50	64.90
Homemade food	19	33.30	8	40.00	27	35.10

Multiple responses were allowed for snack choices.

Table 3. KIDMED adherence categories by gender

	Boys, n (%)	Girls, n (%)	Chi-square	p
Low	14 (24.6)	5 (25)	0.013	0.993
Moderate	28 (49.1)	10 (50)		
High	15 (26.3)	5 (25)		

Chi-square test; KIDMED: Mediterranean Diet Quality Index; *significance at p<0.05.

Table 4. Mean KIDMED, SDSC, and PAQLQ scores by gender

	Boys (n=57)	Girls (n=20)	t	p
Scales	**Mean±SD**	**Mean±SD**		
KIDMED				
Total KIDMED	5.49±2.84	5.7±2.39	-0.294	0.770
SDSC				
DIMS	11.07±4.39	12.35±4.13	-1.139	0.258
SRBD	5.4±1.91	4.65±1.87	1.527	0.131
DOA	3.47±1.66	3.2±0.52	0.722	0.472
SWTD	8.95±3	8.95±2.72	-0.003	0.997
DOES	7.49±3.27	7.2±2.61	0.360	0.720
HSD	4.11±2.6	3.4±2.41	1.061	0.292
Total SDSC	40.49±9.13	39.75±6.73	0.332	0.741
PAQLQ				
Activity	31.05±5.04	31.5±4.32	-0.353	0.725
Symptoms	60.98±8.25	61.7±7.43	-0.343	0.732
Emotional Function	52.77±4.77	53.6±2.91	-0.729	0.468
Total PAQLQ	144.81±15.08	146.8±11.09	-0.541	0.590

Independent two-sample t-test; SD: standard deviation; KIDMED: Mediterranean Diet Quality Index; SDSC: Sleep Disturbance Scale for Children; DIMS: Disorders of Initiating and Maintaining Sleep; SRBD: Sleep-Related Breathing Disorders; DOA: Disorders of Arousal; SWTD: Sleep-Wake Transition Disorders; DOES: Disorders of Excessive Somnolence; HSD: Hyperhidrosis in Sleep Disorders; PAQLQ: Pediatric Asthma Quality of Life Questionnaire; *significance at p<0.05.

Symptoms (r=-0.276, p<0.05) and total PAQLQ scores (r=-0.232, p<0.05). Additionally, total SDSC scores correlated negatively with all PAQLQ subscales—Activity (r=-0.240, p<0.05), Symptoms (r=-0.296, p<0.01), and Emotional Function (r=-0.344, p<0.01)—as well as with total PAQLQ scores (r=-0.356, p<0.01).

Correlations between BMI and KIDMED, SDSC, and PAQLQ scores are presented in Table S. No statistically significant correlations were observed between BMI and any of these variables (all p > 0.05). Nutrient correlations with the KIDMED and SDSC scores are summarized in Table 6. The total KIDMED score was positively correlated with fat (g), fat (%), carotene, and calcium intake, and negatively correlated with carbohydrate intake (all p<0.05). The total SDSC score showed a negative correlation with calcium intake (p<0.05). No statistically significant correlations were found between total PAQLQ scores and nutrient intake (p>0.05).

The indirect and total effects are summarized in Table 7. As shown in Table 7, a one-unit increase in the KIDMED score was significantly associated with a decrease of 0.758 units in the SDSC score (β = −0.758, 95% CI: −1.406 to −0.017). In addition, higher SDSC scores were significantly associated with lower PAQLQ scores (β = −0.660, 95% CI: −0.991 to −0.258).

DISCUSSION

The present cross-sectional study, conducted among children aged 7–12 years with physician-diagnosed, well-controlled asthma receiving low-dose controller therapy, examined the associations between adherence to the Mediterranean diet (MD), sleep disturbances, and quality of life (QoL). Our findings showed that higher adherence to the MD was associated with fewer sleep disorder symptoms, while sleep disturbances were inversely related to QoL. No direct relationship was observed between MD adherence and overall QoL, suggesting that additional factors may influence this association in pediatric asthma.

In Türkiye, the prevalence of pediatric asthma among children aged 5–18 years is estimated at 7.4%, affecting nearly one in ten children.[26,27] Boys are more likely to develop asthma in preadolescence[28], and our study was consistent with this pattern. Similar trends have been reported in Finland, where asthma incidence rises from age 10 and is more common among boys.[29] The PIAMA study also demonstrated higher rates in boys compared with girls.[30] These differences may be linked to hormonal, genetic, and socioeconomic factors.

Table 5. Correlations between KIDMED, SDSC, and PAQLQ scores

	KIDMED-Total	SDSC-DIMS	SDSC-SRBD	SDSC-DOA	SDSC-SWTD	SDSC-DOES	SDSC-HSD	SDSC-Total	PAQLQ-Activity	PAQLQ-Symptoms	PAQLQ-Emotional Function	PAQLQ-Total
KIDMED-Total	1.000	-0.201	0.011	-0.283*	-0.128	-0.131	-0.009	-0.241*	0.056	-0.157	-0.042	-0.083
SDSC-DIMS	-0.201	1.000	0.012	-0.003	0.104	0.348**	0.004	0.673**	-0.117	-0.006	-0.211	-0.109
SDSC-SRBD	0.011	0.012	1.000	0.097	0.113	0.023	0.288*	0.380**	-0.202	-0.434**	-0.255*	-0.395**
SDSC-DOA	-0.283*	-0.003	0.097	1.000	0.151	0.179	0.051	0.322**	0.046	0.001	-0.018	0.011
SDSC-SWTD	-0.128	0.104	0.113	0.151	1.000	0.120	0.079	0.512**	-0.135	-0.210	-0.124	-0.204
SDSC-DOES	-0.131	0.348**	0.023	0.179	0.120	1.000	-0.001	0.616**	-0.250*	-0.113	-0.189	-0.208
SDSC-HSD	-0.009	0.004	0.288*	0.051	0.079	-0.001	1.000	0.402**	-0.022	-0.276*	-0.220	-0.232*
SDSC-Total	-0.241*	0.673**	0.380**	0.322**	0.512**	0.616**	0.402**	1.000	-0.240*	-0.296**	-0.344**	-0.356**
PAQLQ-Activity	0.056	-0.117	-0.202	0.046	-0.135	-0.250*	-0.022	-0.240*	1.000	0.484**	0.409**	0.744**
PAQLQ-Symptoms	-0.157	-0.006	-0.434**	0.001	-0.210	-0.113	-0.276*	-0.296**	0.484**	1.000	0.542**	0.901**
PAQLQ-Emotional Function	-0.042	-0.211	-0.255*	-0.018	-0.124	-0.189	-0.220	-0.344**	0.409**	0.542**	1.000	0.757**
PAQLQ-Total	-0.083	-0.109	-0.395**	0.011	-0.204	-0.208	-0.232*	-0.356**	0.744**	0.901**	0.757**	1.000

Pearson correlation analysis; KIDMED: Mediterranean Diet Quality Index; SDSC: Sleep Disturbance Scale for Children; DIMS: Disorders of Initiating and Maintaining Sleep; SRBD: Sleep-Related Breathing Disorders; DOA: Disorders of Arousal; SWTD: Sleep-Wake Transition Disorders; DOES: Disorders of Excessive Somnolence; HSD: Hyperhidrosis in Sleep Disorders; PAQLQ: Pediatric Asthma Quality of Life Questionnaire; * significance at: $p<0.05$; **: $p<0.01$.

Table 6. Correlations between dietary intake and questionnaire scores

	KIDMED-Total	SDSC-Total	PAQLQ-Total
Energy (kcal)	0.029	-0.132	0.066
Protein (g)	-0.088	-0.112	0.118
Protein (%)	-0.156	0.051	0.085
Fat (g)	0.298**	-0.125	-0.016
Fat (%)	0.423**	-0.030	-0.167
Carbohydrates (g)	-0.125	-0.107	0.092
Carbohydrates (%)	-0.333**	-0.008	0.115
Fiber (g)	0.087	-0.059	0.011
Polyunsaturated fat (g)	0.170	0.028	-0.011
Cholesterol (mg)	0.059	-0.011	0.021
Vitamin A (µg)	0.089	0.103	-0.060
Carotene (mg)	0.288*	-0.111	-0.101
Vitamin E (eq.) (mg)	0.141	-0.006	-0.072
Vitamin B1 (mg)	0.129	0.022	0.023
Vitamin B2 (mg)	0.214	-0.073	-0.018
Vitamin B6 (mg)	0.109	0.079	-0.047
Folate, total (µg)	0.159	0.050	-0.064
Vitamin C (mg)	0.156	0.055	-0.050
Sodium (mg)	0.046	0.008	0.031
Potassium (mg)	0.118	-0.070	0.003
Calcium (mg)	0.244*	-0.288*	-0.002
Magnesium (mg)	0.115	-0.076	0.051
Phosphorus (mg)	0.108	-0.184	0.089
Iron (mg)	0.096	0.026	0.010
Zinc (mg)	0.092	-0.170	0.120

Pearson correlation analysis; KIDMED: Mediterranean Diet Quality Index; SDSC: Sleep Disturbance Scale for Children; PAQLQ: Pediatric Asthma Quality of Life Questionnaire; * significance at: p<0.05; **: p<0.01.

Table 7. Indirect and total effects based on bootstrap estimates

				95% C.I.				
Type	**Effect**	**Estimate**	**SE**	**Lower**	**Upper**	**β**	**z**	**p**
Indirect	KIDMED ⇒ SDSC ⇒ PAQLQ	0.501	0.266	0.055	1.261	0.096	1.881	0.060
Component	KIDMED ⇒ SDSC	-0.758	0.348	-1.406	-0.017	-0.241	-2.182	0.029
	SDSC ⇒ PAQLQ	-0.660	0.178	-0.991	-0.258	-0.400	-3.707	<.001
Direct	KIDMED ⇒ PAQLQ	-0.930	0.560	-1.993	0.418	-0.179	-1.661	0.097
Total	KIDMED ⇒ PAQLQ	-0.429	0.594	-1.436	0.988	-0.083	-0.722	0.470

Bias-corrected bootstrap analysis; KIDMED: Mediterranean Diet Quality Index for children and adolescents; SDSC: Sleep Disturbance Scale for Children; PAQLQ: Pediatric Asthma Quality of Life Questionnaire; CI: confidence interval.

The MD is characterized by a high intake of vegetables, legumes, fruits, cereals, nuts, and olive oil, with moderate

consumption of fish and dairy, and limited intake of red meat.[31] Although MD adherence is generally associated with better health outcomes, several studies indicate that children in Mediterranean countries increasingly adopt Western dietary habits, resulting in suboptimal adherence.[32-34] A previous study found that each one-point increase in the KIDMED score was associated with reduced asthma symptoms.[35] In contrast, our results did not demonstrate a significant relationship between MD adherence and QoL, which may be explained by the sample size, disease severity, or other unmeasured environmental factors.

Asthma is well known to negatively impact QoL.[36-38] Case-control studies have reported significantly lower QoL in children with asthma compared with healthy peers.[39] While some studies and meta-analyses have shown a positive association between MD adherence and QoL[40], we did not observe such a correlation in our study population. This discrepancy may be due to the inclusion of only mild-to-moderate asthma cases and the potential influence of social and environmental factors.

In addition to the established links between dietary patterns and quality of life, evidence in the literature indicates an association between dietary habits and sleep quality.[41-43] Notably, a large population-based study reported that higher adherence to the Mediterranean diet was associated with better sleep duration and fewer sleep-related problems, supporting a potential role of diet quality in sleep regulation.[44] Consistent with these observations, our study found that children with higher scores on the SDSC awakening disorders subscale had lower adherence to the Mediterranean diet, indicating a potential relationship between overall diet quality and sleep disturbances. When other factors commonly discussed in relation to sleep disturbances are considered, obesity and body mass index (BMI) have been reported to be associated with obstructive sleep apnea and sleep fragmentation in children.[45] However, in the present study, no statistically significant association was observed between BMI and sleep disturbance scores. This finding may be related to the characteristics of the study sample and the limited number of obese participants; the use of a general approach to the assessment of sleep disturbances may also have influenced the observed results.

Beyond overall dietary patterns, specific nutrients may also be related to sleep-related outcomes. In our study, calcium intake was positively associated with better sleep outcomes, consistent with existing literature. Observational evidence indicates that higher dietary calcium intake is associated with fewer sleep-related difficulties, including shorter sleep latency and improved sleep maintenance, while lower serum calcium levels have been linked to disrupted sleep–wake regulation and altered rest–activity rhythms, even within the normal reference range.[46,47] Calcium may influence sleep through its role in sleep–wake regulatory and neuroendocrine pathways implicated in sleep quality.

In addition, the positive association observed between fat intake and adherence to the Mediterranean diet in our study suggests that fat quality, rather than quantity alone, may be relevant to sleep-related outcomes. Omega-3 long-chain polyunsaturated fatty acids, which constitute a key component of the Mediterranean diet, have been reported to be associated with sleep quality and sleep efficiency. Given the anti-inflammatory properties of omega-3 fatty acids and the bidirectional relationship between inflammation and sleep regulation, these mechanisms may contribute to sleep-related outcomes.[48,49] In this context, the observed associations between fat intake and Mediterranean diet adherence in our study may reflect a potential link between dietary fat quality and sleep regulation; however, further studies are warranted to clarify these relationships.

Children with asthma often experience sleep-related anxiety[50], which has been linked to lower QoL.[51] In a study of 160 children with asthma, poor asthma control was associated with daytime sleepiness and impaired asthma-related QoL.[52] Our study found a weak but significant negative correlation between DOES scores and PAQLQ activity scores, suggesting that the absence of sleep disturbances may support better daily functioning. Previous studies have also shown that fewer sleep disturbances are associated with higher QoL and improved school performance.[53-55] Conversely, higher MD adherence has been linked to better sleep quality.[56] Our findings similarly suggest that MD adherence may play a role in reducing sleep disturbances, which in turn may positively influence QoL in children with asthma. To improve the clinical interpretability of our findings, the magnitude of the associations derived from the bootstrap-based analyses was summarized in the text. Accordingly, a one-unit increase in the KIDMED score was significantly associated with an average decrease of 0.758 units in the SDSC score. In addition, a one-unit increase in the SDSC score was associated with an average decrease of 0.660 units in the PAQLQ score. These estimates quantify the strength of the observed associations, suggesting that even modest improvements in adherence to the Mediterranean diet may be associated with measurable reductions in sleep disturbance burden, which in turn may

be related to improvements in asthma-related quality-of-life scores.

In conclusion, this cross-sectional study indicates that children with asthma generally exhibit moderate adherence to the Mediterranean diet and that greater adherence is associated with fewer sleep disturbance symptoms. Although no direct association was observed between Mediterranean diet adherence and overall quality of life, the findings suggest that dietary patterns may influence quality of life indirectly through their effects on sleep. These results underscore the potential role of the Mediterranean diet as part of a holistic approach to managing sleep-related problems in pediatric asthma. Further longitudinal and interventional studies are needed to confirm these relationships and to better define their clinical implications.

Study limitations

This study has several limitations that should be considered when interpreting the findings. The cross-sectional design does not allow causal conclusions regarding the associations between Mediterranean diet adherence, sleep disturbances, and quality of life. Although the study population consisted of children with well-controlled asthma, asthma control was not analyzed as a separate variable, which limits the assessment of potential differences across varying control levels. In addition, the potential effects of asthma medications on sleep outcomes were not examined, and other factors that may influence both dietary habits and sleep quality in children, including passive smoking exposure and socioeconomic status, were beyond the scope of this study. Moreover, unmeasured comorbidities—such as allergic rhinitis, suspected obstructive sleep apnea/adenoid hypertrophy, and obesity-related influences—may also have affected sleep outcomes. Despite the measures taken to improve data accuracy, dietary intake assessment may still be subject to recall-related limitations. Finally, as the study was conducted at a single center, the generalizability of the findings may be limited.

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Author contributions

Conception and design: M.G.T., H.Y.Ö.; Data acquisition: M.G.T., F.D., D.Ö.; Data analysis: M.G.T., H.Y.Ö.; Data interpretation: M.G.T., H.Y.Ö.; Drafting of the manuscript: M.G.T., H.Y.Ö.; Critical revision of the manuscript: H.Y.Ö., F.D., D.Ö. All authors reviewed the results, approved the final version of the manuscript, and agreed to be accountable for all aspects of this study.

Ethical approval

This study was approved by the Non-Interventional Scientific Research Ethics Committee of Istanbul Atlas University (Date: 15.06.2022, Decision/Protocol No: E-22686390-050.99-10853). Informed consent was obtained from all participants involved in this study.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of interest

The authors declare that this study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Generative AI statement

The authors declare that during the preparation of this study, the following AI-assisted technology was used: Generative AI. Extent of Use: Generative AI was used only for grammar editing. The authors confirm that they have critically reviewed and edited any AI-generated content and take full responsibility for the integrity, accuracy, and originality of the publication. The authors certify that the original human contribution is maintained and that AI-assisted tools are not listed or cited as authors.

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Research Article

Familial aggregation rate of psoriasis in pediatric rheumatic diseases: A tertiary center cross-sectional study and insights into shared autoimmune pathways

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ABSTRACT

Objective: The coexistence of psoriasis and juvenile-onset systemic lupus erythematosus (jSLE) is rare, and data on familial aggregation of psoriasis across pediatric rheumatic diseases are limited. This study evaluated the co-existence of psoriasis in jSLE, its familial clustering, and its association with the jSLE phenotype.

Methods: In this single-center cross-sectional study, patients with jSLE, familial Mediterranean fever (FMF), and juvenile systemic sclerosis (jSSc) were systematically screened for personal and family histories of psoriasis. Recurrence risk ratios for psoriasis were calculated separately for patients and their relatives within each disease group. Among patients with jSLE, clinical manifestations, laboratory parameters, and disease activity (SLEDAI-2K) were compared between those with and without personal and/or familial psoriasis.

Results: Of 189 patients with pediatric rheumatic diseases included, 94 (49.7%) had jSLE, 73 (38.6%) had FMF, and 22 (11.7%) had jSSc; 69.3% were female, with a higher frequency in jSLE patients (85.1%). Overall, 7,034 individuals (patients and relatives) were systematically screened for psoriasis. Psoriasis was identified in 4 patients (2.1%), all with jSLE (4.3%), and in 25 relatives (0.36%), yielding an overall prevalence of 0.41%. The combined prevalence of psoriasis in jSLE patients and their relatives (0.54%) was significantly higher than in FMF (0.35%) and jSSc (0%) families ($p = 0.034$). Recurrence risk ratios (λ) for psoriasis in jSLE families were 10.13 for patients and 3.07, 1.16, and 0.67 for first-, second-, and third-degree relatives, respectively; corresponding λ values in FMF families were 0, 1.88, 1.11, and 0.45. Among 94 patients with jSLE, 20 had a personal or family history of psoriasis. However, their clinical signs, laboratory results, and SLEDAI-2K scores showed no significant differences compared with those without a history of psoriasis ($p > 0.05$).

Conclusion: A positive family history of psoriasis is more common in jSLE than in FMF or jSSc, supporting the hypothesis of a shared genetic background between psoriasis and jSLE, but it was not associated with more severe jSLE in this cohort. These findings underscore the importance of routinely assessing familial psoriasis in jSLE and related disorders and warrant confirmation in larger, prospective, population-based studies.

Keywords: autoimmunity, FMF, jSLE, jSSc, prevalence, psoriasis, recurrence rate

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INTRODUCTION

Autoimmune diseases are chronic, often systemic inflammatory disorders characterized by a persistent and inappropriate immune response by B and T lymphocytes against self-antigens in genetically susceptible individuals, influenced by environmental triggers. Viewed separately, most autoimmune diseases are considered orphan diseases; however, approximately 5% of the general population is affected by one or more autoimmune conditions.[1]

Two inflammatory diseases with an autoimmune background are psoriasis and systemic lupus erythematosus (SLE). Despite their distinct cutaneous manifestations, both disorders are associated with an increased risk of co-occurrence with other autoimmune diseases compared with the general population.[2] Psoriasis affects approximately 3% of people worldwide, usually appearing in the second decade of life and primarily driven by T-lymphocyte-mediated immune dysfunction. However, a prevalence study in Türkiye reported a lower rate of 0.42%.[2,3]

Systemic lupus erythematosus (SLE) is an autoimmune disease caused by a combination of genetic, environmental, and hormonal factors leading to immunologic abnormalities. SLE affects mainly women during childbearing age, but in approximately 20% of all cases, the diagnosis is first established during childhood and is called juvenile-onset SLE (jSLE).[4,5]

Familial aggregation of autoimmune diseases suggests shared genetic predisposition and common environmental exposures. Indeed, concurrent cases of SLE and other autoimmune diseases within the same families have been repeatedly reported.[6-8] These observations raise the possibility that certain autoimmune conditions may cluster together in families due to overlapping pathogenic mechanisms.

This study is, to our knowledge, the first to evaluate the familial recurrence rates of psoriasis among patients with jSLE, familial Mediterranean fever (FMF), and juvenile systemic sclerosis (jSSc) followed in a pediatric rheumatology outpatient clinic. We selected these diseases because of their distinct pathogenetic pathways, which facilitate the investigation of whether familial aggregation of psoriasis occurs across different pediatric rheumatic and autoimmune disorders.

MATERIALS and METHODS

Study design

This retrospective cross-sectional study included patients attending the pediatric rheumatology outpatient clinic at Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, between 2023 and 2025, whose clinical and familial data were collected from medical records and subsequently confirmed during follow-up visits.

Patient selection

Patients with jSLE, FMF, and jSSc who were regularly followed at our outpatient clinic were included. FMF patients who met the Eurofever classification criteria and had genetic confirmation were included. Genetic confirmation was defined as the presence of homozygous or compound-heterozygous pathogenic variants in exon 10 of the Mediterranean FeVer (MEFV) gene.[9] All patients with jSLE and jSSc met the American College of Rheumatology (ACR)/ European Alliance of Associations for Rheumatology (EULAR) 2019 criteria for SLE[10] before 18 years of age and the Pediatric Rheumatology European Society (PReS)/ACR/EULAR provisional criteria for jSSc.[11] Patients with overlap syndrome or mixed connective tissue disease, early-onset SLE with monogenic inheritance, and those with irregular follow-up were excluded from the study. Based on these exclusion criteria, the jSLE cohort comprised 94 patients from the initial 142.

Familial psoriasis history was systematically assessed during outpatient visits, supplemented by follow-up contact with relatives when necessary, and confirmed at the patient's final outpatient visit. The diagnosis of psoriasis in both patients and their affected family members was clinically established and confirmed by dermatologists. Relatives were classified as first-, second-, or third-degree relatives according to standard definitions. First-degree relatives (FDR) included parents, children, and siblings. Second-degree relatives (SDR) encompassed grandparents, grandchildren, aunts, uncles, nephews, nieces, and half-siblings. Third-degree relatives (TDR) included first cousins, great-aunts, great-uncles, grandnephews, grandnieces, great-grandparents, and great-grandchildren.

To avoid family-level clustering, only one individual per family was included in the study. We excluded patients with a known monogenic/genetic diagnosis of SLE and ensured that no first-, second-, or third-degree relatives (including siblings and cousins) of enrolled patients were included in

the cohort. Thus, the final sample of 189 jSLE, FMF, and jSSc patients represented unrelated individuals.

jSLE patients with a personal or familial history of psoriasis were compared with those without psoriasis. Clinical, laboratory, immunological characteristics, and disease activity as assessed by the SLE Disease Activity Index 2000 (SLEDAI-2K) were analyzed between the two groups.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Mac, Version 31.0 (IBM Corp., Armonk, NY, USA). Categorical variables were summarized as frequencies and percentages (%), whereas continuous variables were presented as mean ± standard deviation (SD) for normally distributed data or as median with interquartile range (IQR, Q1–Q3) for non-normally distributed data. Normality of continuous variables was assessed using histograms and the Kolmogorov-Smirnov test.

For comparisons between two independent groups, the Mann–Whitney U test was used for non-normally distributed continuous variables, whereas the independent-samples t-test was used for normally distributed continuous variables. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Where prevalence rates across more than two groups were compared and expected cell counts were low, the Fisher–Freeman–Halton exact test with Monte Carlo simulation (10,000 sampled tables) was used instead of Fisher's exact test.

The recurrence rate (λ) was calculated as the ratio of relatives affected by psoriasis (number of relatives affected by psoriasis divided by the total number of relatives in that category), normalized by the prevalence of psoriasis in the general Turkish population (0.42% according to the Havsa study). The relative recurrence rate of psoriasis was calculated for each degree of relationship among patients with jSLE and FMF, because jSSc had no measurable psoriasis frequency (λ = 0 in both relatives). To assess statistical significance, Fisher's exact test or the chi-square test was used to compare the proportion of affected relatives in each degree-of-relation group with a hypothetical general population proportion, assuming the same number of relatives. All statistical tests were two-sided, and a p-value < 0.05 was considered statistically significant.

Ethics approval

The study received approval from the Istanbul University-Cerrahpasa Institutional Review Board on December 28, 2022 (Protocol number: 576635). Written informed consent was obtained from the patients' legal representatives in accordance with the Declaration of Helsinki.

RESULTS

Study population

A total of 189 patients followed in the pediatric rheumatology outpatient clinic were included in the study. Of these, 94 (49.7%) had jSLE, 73 (38.6%) had FMF, and 22 (11.7%) had jSSc. Overall, 131 patients (69.3%) were female, and the proportion of females was significantly higher among jSLE patients (85.1%). The mean age at the last visit was 17.7 ± 4.8 years and was significantly lower in the FMF group (14.9 ± 3.6 years). Parental consanguinity was present in 44 patients (23.2%) and was more frequent among FMF patients (30.1%), although this difference did not reach statistical significance. In total, 7,034 individuals, including the patient cohort and their relatives, were

Table 1. Demographic features in the study population

	Total N=189 (%) Mean (±SD)	jSLE N=94 (%) Mean (±SD)	FMF N=73 (%) Mean (±SD)	jSSc N=22 (%) Mean (±SD)	P-value
Gender (female)	131 (69.3%)	80 (85.1%)	34 (46.5%)	17 (77.2%)	<0.01
Age at last visit (year)	17.7 (±4.8)	19.6 (±4.8)	14.9 (±3.6)	18.5 (±4.5)	<0.001
Consanguinity	44 (23.2%)	18 (19.1%)	22 (30.1%)	4 (18.1%)	0.2
FDR	738	387	253	98	
SDR	2380	1229	856	295	
TDR	3727	2131	1051	545	
Total	7034	3841	2233	960	

FDR: First-degree relatives; FMF: Familial Mediterranean fever; jSLE: juvenile-onset systemic lupus erythematosus; jSSc: juvenile systemic sclerosis; SDR: Second-degree relatives; TDR: Third-degree relatives.

screened for psoriasis. Among them, 738 were first-degree relatives (FDR), 2,380 were second-degree relatives (SDR), and 3,727 were third-degree relatives (TDR) (Table 1).

Prevalence and recurrence rate of psoriasis in study groups and their relatives

Psoriasis was detected in 4 of 189 patients (2.1%). Although the frequency was higher in the jSLE group (4.3%), no statistically significant difference was observed among the three disease groups (p = 0.23). The prevalence of psoriasis among first-, second-, and third-degree relatives was 7 (0.94%), 10 (0.42%), and 8 (0.21%), respectively, with no significant differences between these relative categories (p > 0.05). Overall, the prevalence of psoriasis in the entire study population, including patients and relatives, was 0.41%. The combined prevalence of psoriasis in jSLE patients and their relatives was 0.54%, which was significantly higher than in FMF (0.35%) and jSSc (0%) families (p = 0.034) (Table 2).

Since neither jSSc patients nor their relatives exhibited psoriasis, recurrence rates (λ) were calculated only for jSLE and FMF families. In jSLE, recurrence rates (λ) for the patient and their first-, second-, and third-degree relatives were 10.13, 3.07, 1.16, and 0.67, respectively. Although λ was highest in patients and FDR, comparison with an expected number of psoriasis cases based on general population prevalence did not show a statistically significant increase (p > 0.05) (Figure 1, Table 3). In FMF patients and their FDR, SDR, and TDR, recurrence rates (λ) were 0, 1.88, 1.11, and 0.45, respectively (Table 3).

Comparison of clinical, laboratory, and activity features in jSLE patients, with and without psoriasis

Among the 94 jSLE patients, four had psoriasis, all of whom were female. Twenty patients with a personal or family history of psoriasis (21 psoriasis cases in total) were compared with 74 patients without a history of psoriasis to assess the impact on clinical and laboratory features. In the overall jSLE cohort, 80 patients (85.1%) were female. The mean ages at symptom onset and diagnosis were 11.5 ± 3.7 and 12.5 ± 3.3 years, respectively. The most common clinical manifestations were malar rash (74.4%), arthritis (50.0%), oral/nasal ulcers (43.6%), and photosensitivity (36.1%). Median SLEDAI-2K scores at diagnosis and at the last visit were 8 (5–12) and 2 (0–4), respectively. There were no statistically significant differences in clinical manifestations, laboratory parameters, or disease activity indices between patients with and without psoriasis (p > 0.05) (Table 4).

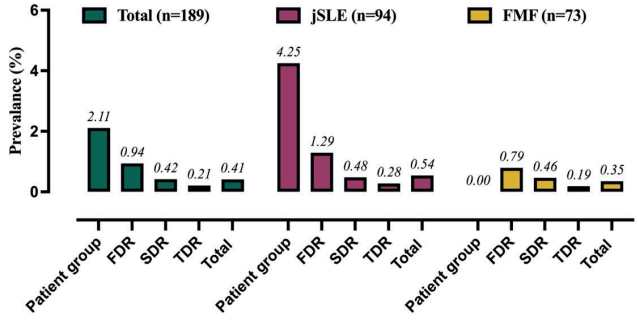


Figure 1. Prevalence of psoriasis among jSLE, FMF patients, and their relatives in the study group

FDR: First-degree relatives; FMF: Familial Mediterranean fever; jSLE: juvenile-onset systemic lupus erythematosus; SDR: Second-degree relatives; TDR: Third-degree relatives

Table 2. Comparison of psoriasis prevalence among study patients and their relatives

	Total N=189 (%)	jSLE N=94 (%)	FMF N=73 (%)	jSSc N=22 (%)	P-value*
Patients	4/189 (2.11%)	4/94 (4.25%)	0/73 (0%)	0/22 (0%)	0.23
FDR	7/738 (0.94%)	5/387 (1.29%)	2/253 (0.79%)	0/98 (0%)	0.65
SDR	10/2380 (0.42%)	6/1229 (0.48%)	4/856 (0.46%)	0/295 (0%)	0.74
TDR	8/3727 (0.21%)	6/2131 (0.28%)	2/1051 (0.19%)	0/545 (0%)	0.70
Total	29/7034 (0.41%)	21/3841 (0.54%)	8/2233 (0.35%)	0/960 (0%)	0.034

* Exact test (Fisher–Freeman–Halton) with Monte Carlo simulation

FDR: First-degree relatives; FMF: Familial Mediterranean fever; jSLE: juvenile-onset systemic lupus erythematosus; jSSc: juvenile systemic sclerosis; SDR: Second-degree relatives; TDR: Third-degree relatives.

Table 3. Recurrence rate of psoriasis in patients with jSLE, FMF, and their relatives

	Patient	FDR	SDR	TDR
jSLE				
Affected relatives, no	4	5	6	6
Recurrence rate (λ)	10.13	3.07	1.16	0.67
p#	0.36	0.45	0.76	0.59
FMF				
Affected relatives, no	0	2	4	2
Recurrence rate (λ)	0	1.88	1.11	0.45
p#	1	1	1	0.68

Fisher's exact test assesses the difference in psoriasis rates between relatives and the general population using the same sample size.
FDR: First-degree relatives; FMF: Familial Mediterranean fever; jSLE: juvenile-onset systemic lupus erythematosus; SDR: Second-degree relatives; TDR: Third-degree relatives.

Table 4. Comparison of clinical, laboratory, and activity features in jSLE patients and their relatives with and without psoriasis

	Total n=94 (%) Mean (±SD) Median (Q1-Q3)	History of psoriasis^ N=20 (%) Mean (±SD) Median (Q1-Q3)	No history of psoriasis N=74 (%) Mean (±SD) Median (Q1-Q3)	p- value
Gender (female)	80 (85.1%)	18 (90.0%)	62 (83.7%)	0.73
Symptom onset age (year)	11.5 (±3.7)	11.9 (±3.0)	11.4 (±3.8)	0.59
Diagnosis age (year)	12.5 (±3.3)	12.7 (±3.1)	12.5 (±3.4)	0.84
Acute or subacute cutaneous lupus	59 (62.7%)	12 (60.0%)	47 (63.5%)	0.77
Chronic cutaneous lupus	25 (26.6%)	6 (30.0%)	19 (25.6%)	0.69
Malar rash	70 (74.4%)	16 (80.0%)	54 (72.9%)	0.52
Discoid rash	17 (18.0%)	3 (15.0%)	14 (18.9%)	0.93
Photosensitivity	34 (36.1%)	7 (35.0%)	27 (36.4%)	0.90
Alopecia	24 (25.5%)	6 (30.0%)	18 (24.3%)	0.60
Oral/nasal ulcers	41 (43.6%)	10 (50.0%)	31 (41.9%)	0.51
Arthritis	47 (50%)	12 (60.0%)	35 (47.2%)	0.31
Neuropsychiatric involvement	11 (11.7%)	1 (5.0%)	10 (13.5%)	0.51
Hematological involvement	60 (63.8%)	13 (65.0%)	47 (63.5%)	0.90
Proteinuria	26 (27.6%)	6 (30.0%)	20 (27.0%)	0.79
Anti-dsDNA positivity	78 (82.9%)	16 (80.0%)	62 (83.7%)	0.94
Anti-Sm positivity	44 (46.8%)	8 (40.0%)	36 (48.6%)	0.49
SLEDAI-2K (at diagnosis)	8 (5-12)	6.5 (4.5-10)	8 (5-12)	0.38
SLEDAI-2K (at last visit)	2 (0-4)	3 (0-5)	2 (0-4)	0.64

^Psoriasis cases among jSLE patients and their relatives
Anti-Sm: anti-Smith antibody; Anti-dsDNA: anti-double-stranded DNA antibody; jSLE: juvenile-onset systemic lupus erythematosus; SLEDAI-2K: SLE Disease Activity Index 2000

DISCUSSION

This study is the first to investigate the risk of psoriasis among patients with jSLE and their relatives and to estimate the familial transmission of psoriasis across pediatric rheumatic diseases using a population-based prevalence reference. We observed that the recurrence rate of psoriasis in jSLE patients (10.1) and their first-degree relatives (3.0) was higher than in individuals with FMF or jSSc and their relatives. Although the difference between patients and their relatives with psoriasis was not statistically significant, we demonstrated that the combined group of jSLE patients and their relatives had a significantly higher prevalence

of psoriasis compared with the combined FMF and jSSc groups and their relatives. In this study, a positive family history of psoriasis was not associated with more severe jSLE. Clinical, laboratory, and disease activity characteristics in our jSLE cohort were comparable to those reported in previous published cohorts.[12-15]

The coexistence of psoriasis and jSLE is very rare, and only a limited number of such cases have been reported in the literature.[16] In the study by Walters et al., including 62 patients with jSLE, psoriasis was reported in the families of four (6%) patients, and in three of them, the affected relative was FDR.[17] Tselios et al. identified psoriasis in 3.46% of 832 adult-onset SLE (aSLE) patients; the prevalence of psoriasis in this lupus cohort was approximately twice that of the general Canadian population.[18] Similar to our findings, Walhelm et al. evaluated 351 aSLE patients and found psoriasis in 12 (3.4%), with no significant differences in clinical, laboratory, or SLEDAI-2K scores between those with and without psoriasis. Overall, clinical and immunological features were similar in both groups.[19]

In a large population-based study, Huang et al. demonstrated clear familial aggregation of psoriasis, reporting a 5.5-fold and 2.5-fold increased risk of psoriasis among individuals with affected FDR and SDR, respectively, compared with the general population, indicating a relationship between genetic proximity and psoriasis risk. Notably, individuals with a family history of psoriasis also had higher risks of rheumatoid arthritis, primary Sjögren's syndrome, SLE, and SSc, supporting shared autoimmune susceptibility.[20] Similarly, Barut et al. reported a markedly higher frequency of psoriasis family history in children with FMF compared with healthy controls and patients with juvenile idiopathic arthritis.[21] In another study specifically addressing familial aggregation of SLE, the risks of SLE and other autoimmune diseases (mainly primary Sjögren's syndrome, SSc, and myasthenia gravis) were elevated among relatives of SLE patients, and the heritability of SLE was estimated at 43.9%, underscoring the importance of considering familial aggregation and heritability when counseling affected families.[22] Consistent with this, Sinicato et al. further documented familial aggregation by demonstrating differences in recurrence risk ratios by degree of relatedness between juvenile-onset and adult-onset SLE within the same population, suggesting a higher genetic load and a more polygenic and epistatic pattern of inheritance in jSLE. Together, these findings support the notion that the genetic architecture of SLE may differ according to age at disease onset.[23]

Genome-wide association studies (GWASs) have identified numerous genetic risk loci for many autoimmune diseases. Among these loci, several are shared by psoriasis and SLE, including PTPN22, STAT4, TNIP1, NFKBIA, and IL28RA.[24] NFKBIA encodes the inhibitory protein IκBα, which restrains NF-κB dimers in the cytoplasm and thereby suppresses their activation. Chronic activation of the NF-κB pathway enhances pro-inflammatory gene expression in the pathogenesis of both SLE and psoriasis, whereas dysfunction of NFKBIA/IκBα may fail to adequately constrain this pathway, thereby increasing disease susceptibility and amplifying inflammatory responses.[25] In a previous study, serum NF-κB levels in patients with jSLE showed a trend toward higher levels than in healthy controls.[26]

This study has several limitations. First, the cross-sectional design precludes any inference of causality between family history of psoriasis and the occurrence or clinical features of jSLE, jSSc, or FMF. Second, the study was conducted in a single tertiary referral center, and the control group was hospital-based, potentially limiting the generalizability of the results to the broader pediatric population. The relatively low number of psoriasis cases in our cohort, including the absence of psoriasis in the jSSc group, may have reduced the statistical power of some between-group comparisons; therefore, these findings should be interpreted with caution. Finally, we were not able to evaluate the impact of psoriasis subtype, severity, or treatment on the observed relationships, which may have provided further insight into potential shared genetic or immunologic mechanisms.

In conclusion, our findings indicate that a positive family history of psoriasis is more common in jSLE than in FMF or jSSc, supporting the hypothesis of a shared genetic background between psoriasis and jSLE. Although our results should be interpreted in light of the study limitations, they highlight the importance of systematically asking about familial psoriasis when evaluating children with SLE and related conditions. Larger, prospective, population-based studies are needed to confirm these associations and to clarify the underlying genetic and immunological mechanisms.

Author contributions

Conception and design: E.K.K., S.Ş., Ö.K.; Data acquisition: G.E.Ş., K.U., E.K.K., Z.T., E.A., N.A., Ü.G., A.G.; Data analysis: F.H., M.Y., E.K.K.; Data interpretation: F.H., M.Y., E.K.K.; Drafting of the manuscript: E.K.K., E.A., S.Ş., A.A., K.B., Ö.K.; Critical revision of the manuscript: E.K.K., E.A., S.Ş.,

A.A., K.B., Ö.K. All authors reviewed the results, approved the final version of the manuscript, and agreed to be accountable for all aspects of this study.

Ethical approval

This study was approved by the Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine Institutional Review Board (Date: 28.12.2022, Decision/Protocol No: 576635). Informed consent was obtained from all participants involved in this study.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of interest

The authors declare that this study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Generative AI statement

The authors declare that no generative AI or AI-assisted technologies were used in the writing or preparation of this study.

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Research Article

Clinical spectrum of ebstein's anomaly: From fetal life to adolescence

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ABSTRACT

Objective: Ebstein's anomaly is a rare congenital heart defect featuring a varied spectrum of clinical presentation. Anatomical variability in the malformation, together with a frequent association with other cardiac defects and arrhythmias, can complicate diagnosis and long-term management.

Methods: Data from a total of 26 patients with Ebstein's anomaly followed up at two university clinics between 2009 and 2025 were analyzed retrospectively. Cases diagnosed from the prenatal period through adolescent period were included.

Results: The cohort consisted of 26 patients; 69.2% (18/26) were males with a median diagnostic age of 8 days. Diagnoses were established prenatally 15.4% (4/26), neonatally 50.0% (13/26), or during later childhood and adolescence 34.6% (9/26). Diagnosis was made during the index NICU admission in 34.6% (9/26) of patients and based on referral for murmur 26.9% (7/26) or cyanosis 7.7% (2/26). Common associated anomalies included atrial-level shunts 61.5% (16/26), mitral regurgitation 23.1% (6/26), and ventricular septal defects 15.4% (4/26). Arrhythmias were documented in 23.1% (6/21) of the cohort; 42.3% (11/26) underwent catheter-based procedures, and 30.8% (8/26) required surgery (median age at first surgery, 8.4 months), with 15.4%(4/26) undergoing reoperation. Over a median 5-year follow-up, mortality was 15.4% (4/26), with no perioperative deaths. Among prenatally diagnosed cases (n=4), three deaths occurred (3/4, 75%).

Conclusions: The clinical spectrum of Ebstein's anomaly is exceptionally broad. Our findings show frequent left heart involvement and a substantial need for catheter-based and surgical interventions, supporting the importance of individualized assessment and follow-up across the disease course.

Keywords: Ebstein's anomaly, prenatal diagnosis, congenital heart defect

INTRODUCTION

A rarely seen congenital cardiac malformation, Ebstein's anomaly is often attributed to abnormal delamination of the tricuspid valve leaflets during embryogenesis, and it is defined by apical displacement of the septal and posterior leaflets.[1] Incidence is relatively low; according to the most recent counts, the estimated rate stood at 0.2–0.7 per 10,000 live births, so the condition accounts for 0.3–0.6% of all congenital heart defects.[2,3]

Aberrant displacement and adherence of the leaflets is thought to split the right ventricle into functionally different atrialized and ventricular components.[4] In doing so, the malformation affects the tricuspid valve, the right ventricle, and the electrical conduction system alike.[5]

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Clinical presentation therefore varies widely. At one end, intrauterine demise and profound neonatal cyanosis; at the other, incidental diagnosis in adults who remain asymptomatic for decades. For the most part, such variation traces back to the severity of the anatomical derangement itself; the degree of leaflet displacement besides right ventricular impairment largely sets the clinical course.[1]

In neonates, cyanosis and congestive heart failure, as well as pronounced cardiomegaly are the usual findings. Older children tend to show right ventricular failure instead, whereas adolescents and adults more often come to clinical attention because of arrhythmias.[6] Of note, the anomaly frequently coexists with an atrial septal defect (ASD) or patent foramen ovale (PFO); they have been reported in more than 80% of patients and may predispose them to paradoxical embolism.[7]

Since the condition can be highly variable in its clinical presentation and accompanying anomalies can be frequent, Ebstein's anomaly should be managed on an individualized patient-by-patient basis. We therefore aimed to describe the clinical, electrocardiographic, and echocardiographic findings, the burden of catheter-based and surgical interventions, and the outcomes of 26 patients followed up from fetal life through adolescent period at two university clinics.

MATERIAL and METHOD

Our study followed a retrospective cohort design. Patients diagnosed with Ebstein's anomaly were included. All had been managed at the Pediatric Cardiology Clinics of the Faculties of Medicine of Necmettin Erbakan University and Selçuk University between 2009 and 2025. Patients were identified by searching the institutional electronic health record database for relevant diagnostic codes and reviewing clinic records. The study protocol received approval from the Necmettin Erbakan University Faculty of Medicine Ethics Committee (Ethics approval number: 2025/5792), which waived the need for individual patient consent due to the study's retrospective nature. All data were handled in a de-identified/anonymized manner in accordance with institutional policies. De-identified data underlying the findings of this study are available from the corresponding author upon reasonable request.

The primary inclusion criterion was a definitive diagnosis of Ebstein's anomaly confirmed by transthoracic echocardiography with availability of sufficient clinical and imaging data for phenotypic characterization and outcome assessment. Patients with secondary tricuspid regurgitation without morphological features of Ebstein's anomaly or with records insufficient to confirm the diagnosis were excluded. Patients with incomplete clinical or follow-up data precluding outcome assessment were excluded from the analysis.

Diagnostic confirmation was based on the Mayo Clinic criteria, which specify a septal tricuspid valve leaflet displacement toward the apex of ≥0.8 cm/m^2 body surface area from the mitral valve anterior leaflet insertion point during systole.[8] All echocardiograms were reviewed retrospectively, and anatomical severity was categorized according to the Carpentier classification (types A-D) based on echocardiographic morphology, including the functional right ventricular volume, the extent of atrialized right ventricle, and the mobility/tethering of the anterior tricuspid leaflet. All echocardiograms were independently reviewed by two pediatric cardiologists; disagreements were resolved by consensus. Associated cardiac lesions (e.g., ASD/PFO, Ventricular Septal Defect (VSD), left-sided lesions) were recorded from echocardiography and relevant operative/interventional reports. Valvular insufficiency severity was classified as mild, moderate, or severe according to established Doppler and color flow imaging guidelines. Tricuspid regurgitation severity was graded using an integrative Doppler approach (color Doppler jet characteristics and supportive qualitative/quantitative parameters when available) in accordance with standard echocardiography recommendations.[9]

We evaluated demographic and clinical data, including age at diagnosis, gender, date of last follow-up, presenting signs and symptoms (e.g., murmur, cyanosis, heart failure), and clinical outcomes, including mortality; electrocardiographic findings, echocardiographic data, details of any cardiac catheterization, electrophysiological study with ablation, or surgical intervention, including the type of procedure, age at intervention, and any complications and long-term follow-up outcomes. Given the retrospective design, some variables were incompletely documented in a small subset of patients; missing data were reported explicitly in table footnotes. Analyses were performed using a complete-case approach without imputation. Unless otherwise

specified, proportions were calculated using n=26 as the denominator; subgroup proportions (e.g., surgically treated patients) used the corresponding subgroup denominator.

Statistical analysis

Statistical analysis was performed with IBM SPSS Statistics for Windows v.22.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics are presented as median (minimum–maximum), frequency distributions, and percentages. Continuous variables were summarized as median (min–max) given the small sample size and non-normal distributions. Given the small sample size, analyses were primarily descriptive and inferential subgroup comparisons were not performed.

RESULTS

The study cohort comprised 26 patients with Ebstein's anomaly. The timing of diagnosis varied: 15.4% (4/26) of cases were identified prenatally through fetal echocardiography, 50% (13/26) during the neonatal period, 19.2% (5/26) during childhood, and 15.4% (4/26) during adolescence. The median age at diagnosis was 8 days (range: 1 day–18 years), with a male predominance 69.2% (18/26). Among surviving patients, the median follow-up duration was 5 years (range: 1–16 years). As for the pathway to diagnosis, 34.6% (9/26) were diagnosed during the index NICU hospitalization, whereas 26.9% (7/26) were referred for evaluation of a murmur and 7.7% (2/26) for cyanosis. Other reasons included recurrent pneumonia, referral based on an outside medical report, and missing/unknown presentation. All patients had tricuspid regurgitation, which was classified as mild in 23.1% (6/26) of patients, moderate in 57.7% (15/26), and severe in 19.2% (5/26).

Anatomical subtyping according to the Carpentier classification for Ebstein's anomaly distributed the cohort as follows: Type A in 38.5% (10/26), Type B in 26.9% (7/26), Type C in 19.2% (5/26), and Type D in 15.4% (4/26). Detailed findings are presented in Table 1, with representative echocardiographic images shown in Figure 1. The most common associated anomalies were an ASD/PFO 61.5% (16/26), mild-to-moderate mitral regurgitation 23.1% (6/26), and a ventricular septal defect (VSD) 15.4% (4/26). Further findings included pulmonary hypoplasia/atresia 11.5% (3/26) and corrected transposition of the great arteries 11.5% (3/26). Left heart involvement, encompassing VSD, bicuspid aortic valve, and mitral regurgitation, was present in 50% (13/26) of patients. One patient also had left ventricular noncompaction cardiomyopathy.

Table 1. Clinical features of the patients

Features	Number of patients n(%)
Gender	
Female	8 (30.8)
Male	18 (69.2)
Age at diagnosis (median) (min-max)	8 days (range, 1 day- 18 years)
Diagnosis period	
Fetal	4 (15.4)
Neonatal	13 (50)
Child	5 (19.2)
Adolescent	4 (15.4)
Presenting status / reason for referral	
Murmur	7 (26.9)
Cyanosis	2 (7.7)
Admission to the neonatal intensive care unit	9 (34.6)
Others/Unknown*	4 (15.4)
Prenatal diagnosis on fetal echocardiography	4 (15.4)
Tricuspid regurgitation degree	
Mild	6 (23.1)
Moderate	15 (57.7)
Severe	5 (19.2)
Carpentier classification	
Type A	10 (38.5)
Type B	7 (26.9)
Type C	5 (19.2)
Type D	4 (15.4)
Follow-up duration	5 years (range, 1-16 years)

*Includes recurrent pneumonia (n=1), outside medical report (n=1), and missing/unknown presentation (n=2)

Arrhythmic disorders were documented in 23.1% (6/26) of patients. Three patients with Wolff–Parkinson–White (WPW) syndrome underwent successful catheter ablation. Among the remaining cases, one patient had supraventricular ectopy and one had ventricular ectopy. One patient with congenitally corrected transposition of the great arteries (ccTGA) developed complete atrioventricular

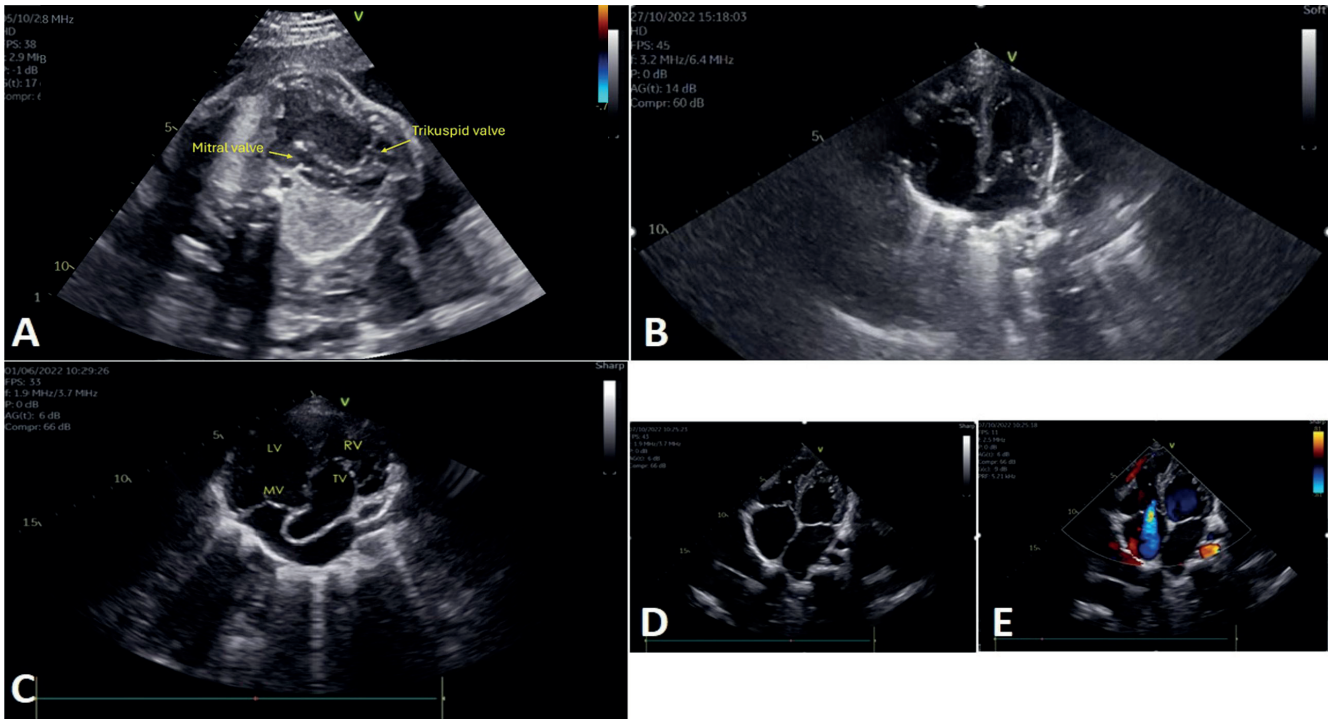


Figure 1. Apical displacement of the tricuspid valve leaflets resembling Ebstein's anomaly and massive cardiomegaly observed on fetal echocardiography (A). Postnatal echocardiographic appearance of Ebstein's anomaly in another patient (B). Tricuspid valve showing features of Ebstein's anomaly in a patient who underwent double switch surgery (C). Two-dimensional and color Doppler images illustrating Ebstein's anomaly with left ventricular noncompaction in a complex case (D, E).

block postoperatively and required permanent pacemaker implantation. Cardiac catheterization and interventional procedures were performed in 42.3% (11/26) of patients. The main interventions included diagnostic angiography 11.5% (3/26) and electrophysiological study with ablation 11.5% (3/26), with other procedures performed as clinically indicated. Another procedure was transcatheter ASD device closure (n=1).

Cardiac surgery was required in 30.8% (8/26) of patients, with a median age at the first intervention of 8.4 months (range: 4 days–25 years). Secondary surgical procedures were necessary in 15.4% (4/26) of cases. As for surgical timing, 11.5% (3/26) underwent surgical intervention during the neonatal period, and 23.1% (6/26) underwent surgery within the first year of life. The principal surgical techniques included tricuspid annuloplasty, cone reconstruction, Blalock–Taussig shunt placement, and double-switch procedures. Other surgical procedures were VSD closure (n=2), patent ductus arteriosus (PDA) ligation (n=2), and pulmonary artery banding (n=1) (Table 2). During a median follow-up of 5 years (range, 1–16 years), four patients died (15.4%, 4/26). Two of the four had been diagnosed prenatally with massive cardiomegaly and died in utero. A third patient died in the neonatal intensive care unit from sepsis and multiple organ failure. The last patient was a neonate who had been born to a mother with a known history of substance use after unmonitored pregnancy. The infant had severe tricuspid regurgitation and pulmonary hypoplasia and died within 24 hours of birth.

In adolescent patients, on the other hand, diagnoses were made at ages 13, 14, 16, and 18 years. Three of these patients had mild tricuspid regurgitation and were clinically stable during the follow-up period. At 16 years of age, the fourth patient had been diagnosed with corrected transposition of the great arteries; tricuspid valve annuloplasty and pulmonary artery banding were carried out at 25 years. No perioperative deaths were recorded.

Table 2. Associated anomalies, interventional and surgical procedures performed

Cardiac anomaly (n=26)	**Number of patients n (%)**
ASD/PFO	16 (61.5)
Congenitally Corrected Transposition of the great arteries	3 (11.5)
VSD	4 (15.4)
Pulmonary Hypoplasia/Atresia	3 (11.5)
Aortic regurgitation	2 (7.7)
Mild-to-moderate mitral regurgitation	6 (23.1)
Right aortic arch	1 (3.8)
Coarctation of the aorta	1 (3.8)
Patent Ductus Arteriosus	2 (7.7)
Bicuspid Aortic Valve	3 (11.5)
Left Ventricular Noncompaction	1 (3.8)
Catheter-based and electrophysiologic procedures (n=26)	
Diagnostic Angiography	3 (11.5)
Ablation	3 (11.5)
Pulmonary Balloon Valvuloplasty	1 (3.8)
Aortic Balloon Angioplasty	1 (3.8)
Transcatheter ASD closure	1 (3.8)
Right pulmonary artery (RPA) stenting	1 (3.8)
Balloon Atrial Septostomy	1 (3.8)
Surgery protocols	
Patients with Surgery	8 (30.8)
Age at first surgery(month)	8.4 (range: 4 days–25 years)
Patients with second surgery	4 (15.4)
Surgery Type (procedures)*	
Tricuspid Valvuloplasty	2 (7.7)
Pulmonary Artery Banding	2 (7.7)
Double Switch	2 (7.7)
Cone Reconstruction	1 (3.8)
Coarctation repair (patch aortoplasty)	1 (3.8)
PDA ligation	2 (7.7)

*Some patients underwent more than one procedure.

DISCUSSION

In our experience at two university clinics, Ebstein's anomaly can be said to show considerable variability from fetal life through adolescent period. Research providing longitudinal data covering the full developmental range is still rather limited. Our series of 26 patients, including cases detected prenatally, has therefore documented the frequency of left-heart involvement, burden of catheter-based and surgical interventions, and outcomes at each developmental stage. Most of the findings appear to be in concordance with earlier cohorts, but our fetal-to-adolescent coverage within one dataset can add to what has been reported so far in the current literature. In their study, Adıgüzel et al. reported that the mean age at diagnosis was 1.5 years (range: 1 day–24 years), with 51.9% males and 7.6% prenatal diagnoses.[10] In the multicenter study by Kapusta et al., the median age at diagnosis was under 30 days, median follow-up was 86 months, and 81% of patients survived.[11] Perinatal diagnoses were more frequent in our series, which could be attributed to the fact that our tertiary-level centers made use of fetal echocardiographic screening on a regular basis.

According to current evidence, patients who are diagnosed at early stage often tend to present with cyanosis and heart failure, but those diagnosed later generally have tachyarrhythmias or remain entirely asymptomatic.[12] Oxenius et al. found that murmur was the most frequent finding at 33%, which was followed by cyanosis at 29%, with arrhythmia in 5%.[13] Likewise, in the Adıgüzel series, cyanosis stood at 29.1% and murmur at 34.2%; 44.3% of their patients were asymptomatic.[10] Our findings were similar; murmur was the most common reason for referral, and most diagnoses were made during the neonatal period.

Ebstein's anomaly is known to be accompanied by a range of other structural defects in the human heart. For example, ASD or PFO have been reported in 80–94% of such cases.[14] Oxenius et al. found that ASD/PFO were present in 79% of their patients, along with pulmonary outflow tract obstructions observed in 17% and less frequent anomalies like left ventricular noncompaction and VSD.[13] Comparable figures were noted in the Adıgüzel series, where ASD/PFO were detected in 57% of patients, mitral regurgitation in 25.3%, pulmonary stenosis or atresia in 17.7%, as well as VSD in 16.5%.[10] Tricuspid regurgitation in that cohort was found in more than three-quarters of cases (75.9%) and it varied in severity: mild in 11.7%, moderate in 38.3%, and severe in 50%. Our own findings appear to corroborate with literature reports.

In light of recent observations in relevant works, Ebstein's anomaly may well extend beyond isolated right heart pathologies due to the fact that myocardial or valvular abnormalities of the left heart have been observed in as many as 39% of patients. These left heart lesions include left ventricular myocardial changes 17.9% resembling noncompaction, left ventricular dysfunction 43%, VSD 8%,

bicuspid aortic valve 8%, mitral valve prolapse 15%, and mitral valve dysplasia 4%.[5] Adıgüzel et al. documented left heart lesions in 58% of their cases, including VSD 16.5%, mitral regurgitation 25.3%, mitral prolapse 8.9%, aortic coarctation 3.8%, bicuspid aortic valve 2.5%, and one case of left ventricular noncompaction.[10] Our patient cohort showed similarly high rates of left heart involvement, including VSD 15.4% (4/26), mitral regurgitation 23.1% (6/26), coarctation of the aorta 3.8%(1/26), bicuspid aortic valve 11.5% (3/26), and noncompaction 3.8% (1/26). The findings point to the need for thorough left ventricular assessment during echocardiographic evaluation.

Around one-third of patients with Ebstein's anomaly exhibit atrioventricular conduction system abnormalities, with WPW syndrome reported in 5–25% of cases.[14] Delhaas et al. documented a 17% arrhythmia prevalence in children with this condition, predominantly supraventricular tachycardia, with 15% showing pre-excitation patterns.[15] Karagöz et al. identified arrhythmias in 30.3% of their patients, with ablation performed in 31%; the majority of these arrhythmias 82% were associated with accessory pathways.[6] Our study detected WPW syndrome in 11.5% of patients, which seems to be in corroboration with the ranges published in previous research. Another consideration is that Ebstein's anomaly also tends to require a high rate of invasive procedures; in our series, for example 42.3% of patients were found to show the need to undergo interventional catheterization. Relatively higher but comparable intervention rates have been reported by Geerdink et al. (60%) and Adıgüzel et al. (75%)[4], which were diagnostic angiography (52.5%), electrophysiological ablation (35.6%), and palliative surgery (11.9%). All of them can be considered to showcase the heavy disease burden over the course of a patient's lifetime.

Surgical intervention becomes necessary in cases with right heart enlargement, progressive ventricular dysfunction, or substantial valve insufficiency.[16] Contemporary surgical techniques allow for palliation of patients with early neonatal findings through tricuspid valvuloplasty, with optional atrial septal fenestration and surgical shunts. Subsequently, selected cases with pulmonary atresia or stenosis may undergo staged procedures, including one-and-a-half ventricle repair or Fontan-type operations.[17] The study by Oxenius et al.[13] found that 79% of patients required invasive treatment, with 50% undergoing at least one surgical intervention at a median age of 9.1 years (range 0.1–16.5 years). Adıgüzel et al. reported cardiac surgery in 31.6% of patients, with an average age at first surgery of 6.5 years (range: 4 days–29 years).[10] In their study, second surgical interventions were performed in 28% (n = 7) of patients, whereas this rate was 15% in our study.

The long-term prognosis for fetuses diagnosed with Ebstein's anomaly remains poor, with fetal mortality reaching 20%; the overall perinatal mortality rate approximates 45%.[18] In the study by Adıgüzel et al.[10], with an average follow-up of 5.3 years, mortality occurred in 10.1% of patients at a median age of 25 days. Causes of death included heart failure, sudden cardiac death, necrotizing enterocolitis, and renal failure. Our study's perinatal mortality was 75% (3/4) among prenatally diagnosed cases, which may reflect the small cohort size and the presence of massive cardiomegaly in these patients.

Our study included a single case with documented maternal heroin use during pregnancy. This single observation is worth noting, as the literature reports associations between Ebstein's anomaly and certain maternal exposures (e.g., lithium and benzodiazepines), although evidence remains limited and inconsistent.[19,20] However, it does not establish a teratogenic link and should be interpreted with caution. The infant in our cohort presented with a severe form of the anomaly and died on the first postnatal day, which we report as a hypothesis-generating observation rather than evidence of causality; potential confounding (including polysubstance exposure and incomplete prenatal care) cannot be excluded. Further systematically designed studies are needed to evaluate whether any association exists between maternal substance exposures and Ebstein's anomaly.

CONCLUSION

The clinical picture of Ebstein's anomaly was varied in our cohort where diagnoses spanned from fetal life to adolescent period. A high frequency of neonatal diagnosis, often in an intensive care setting for the most severe presentations, suggests earlier recognition of severe cases compared with historical reports. This rare defect is rather complex and can affect more than the tricuspid valve, with left heart involvement as defined in this study observed in half our patients and a frequent need for catheter-based or surgical interventions during follow-up. Over the long term, treatment outcomes may depend on how well disease management is individualized on a patient-by-patient basis, and the plan could involve early anatomical diagnosis, close monitoring for arrhythmias, and a plan for the timing and type of intervention.

Limitations

Our cohort size was naturally small since Ebstein's anomaly is a rare condition, which left little room for meaningful subgroup comparisons. Analyses were thus kept descriptive; comparisons by diagnostic period, Carpentier type, or left-heart involvement were not attempted, because they would have been underpowered and potentially misleading. Some variables like diagnostic pathway and maternal exposure history were incompletely documented in the medical record, and a complete-case approach without imputation was employed. Management strategies also evolved over the long study period, and our findings reflect the experience of two tertiary centers, which can limit how far the results can be generalized.

Author contributions

Conception: U.S., M.B.O.; Design: U.S., M.B.O.; Data acquisition: U.S., A.B.P., İ.D., M.T.D., A.S.; Data analysis: U.S., M.T.D., A.S.; Data interpretation: U.S., M.B.O.; Drafting of the manuscript: U.S., F.S., T.B.; Critical revision of the manuscript: U.S., M.B.O. All authors reviewed the results, approved the final version of the manuscript, and agreed to be accountable for all aspects of this study.

Ethical approval

This study was approved by the Necmettin Erbakan University Faculty of Medicine Ethics Committee (Decision/Protocol No: 2025/5792). Ethics committee approval and informed consent were not required for this study.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of interest

The authors declare that this study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The authors declare that no generative AI or AI-assisted technologies were used in the writing or preparation of this study.

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Research Article

Vascular and inflammatory biomarker profiles in pediatric Behçet's Disease

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ABSTRACT

Objective: Behçet's disease (BD) is a variable-vessel vasculitis with multisystemic involvement. Although cytokine dysregulation has been extensively investigated, data on angiogenic and vascular marker profiles remain limited in pediatric BD. This exploratory study aimed to characterize circulating vascular and inflammatory mediator profiles in pediatric BD, compare them with deficiency of adenosine deaminase 2 (DADA2) and polyarteritis nodosa (PAN). It further aimed to assess whether these markers were associated with vascular or central nervous system (CNS) involvement in BD.

Methods: Serum samples from BD (n=34), DADA2 (n=20), PAN (n=10), and healthy controls (n=8) were analyzed for thirteen vascular and inflammatory markers (TIE1, TIE2, FLT1, sT2, RAGE, CD40L, LIGHT, PlGF, TNF-α, IL-6, IL-10, IL-18, MCP-1) using a multiplex bead-based immunoassay. Statistical analyses included Kruskal–Wallis and Mann–Whitney U tests for group comparisons, logistic and linear regression for associations with clinical features, and Spearman correlation to explore interrelations among markers.

Results: TIE2 levels were significantly reduced in BD compared with healthy controls (p=0.010). DADA2 patients exhibited a distinct angiogenic–inflammatory profile, with significantly elevated levels of TIE1, TIE2, FLT1, TNF-α, IL-10, IL-18, and MCP-1 (all p<0.010) compared with both BD and PAN. None of the circulating markers independently predicted vascular or CNS involvement in BD. Strong positive correlations among angiogenic mediators (FLT1, PlGF, LIGHT) suggested a coordinated vascular signaling pattern, particularly in DADA2.

Conclusion: Although individual circulating mediators showed limited discriminatory performance across vasculitis subtypes, DADA2 displayed a more distinct vascular-inflammatory profile characterized by TNF-α- and TIE2-related pathways. In pediatric BD, reduced TIE2 may reflect altered endothelial homeostasis, although this finding should be interpreted cautiously. These results support the need for integrated multi-marker approaches and longitudinal sampling to better define vascular-immune phenotypes in pediatric vasculitis.

Keywords: Behçet's disease, adenosine deaminase deficiency, polyarteritis nodosa, vasculitis

INTRODUCTION

Behçet's disease (BD) is a variable-vessel, multisystemic vasculitis characterized by recurrent mucocutaneous ulcers, ocular inflammation, vascular thrombosis, and neurological involvement. Although the underlying mechanisms remain incompletely understood, BD is increasingly recognized as a disorder of immune-mediated vascular inflammation, in which dysregulated cytokine networks and endothelial injury play central roles. Numerous studies have demonstrated varying results with elevations of Th1 and Th17-related cytokines, including IL-6, IL-8, TNF-α, IL-17, and IFN-γ, during disease flares.[1,2]

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Beyond these classical cytokines, emerging evidence points to the importance of endothelial dysfunction and aberrant angiogenic signaling in BD pathogenesis. Biomolecules such as angiopoietin–TIE receptor pathway components (TIE1, TIE2), soluble fms-like tyrosine kinase-1 (FLT1), placental growth factor (PlGF), and receptor for advanced glycation end-products (RAGE) have been implicated in vascular homeostasis and inflammation. However, their role in BD, particularly in pediatric populations, remains largely unexplored. Most studies to date have focused on adult cohorts and have primarily addressed proinflammatory cytokines, leaving the vascular and endothelial dimensions of pediatric BD insufficiently characterized.[3-5]

Comparative analysis with other vasculitides that share overlapping vascular features may help identify shared and distinct vascular-inflammatory patterns. Deficiency of adenosine deaminase 2 (DADA2) represents a monogenic vasculitis characterized by systemic inflammation, endothelial injury, and TNF-driven vascular pathology, often mimicking polyarteritis nodosa (PAN).[6,7] Idiopathic PAN involves necrotizing arteritis of medium-sized vessels but lacks the prominent mucocutaneous and thrombotic features of BD. Studying these entities in parallel may provide insight into both overlapping and divergent angiogenic-inflammatory pathways across pediatric vasculitis.

The present study was designed as an exploratory analysis to characterize circulating vascular and inflammatory mediator profiles (including TIE1, TIE2, FLT1, soluble ST2 [sT2], receptor for advanced glycation end-products [RAGE], CD40 ligand [CD40L], lymphotoxin-like inducible protein [LIGHT], placental growth factor [PlGF], TNF-α, IL-6, IL-10, IL-18, and monocyte chemoattractant protein-1 [MCP-1]) in pediatric BD and to compare them with those observed in DADA2, PAN, and healthy controls. It further aimed to evaluate whether these markers were associated with vascular or central nervous system (CNS) involvement in BD.

MATERIALS and METHODS

Study population

This cross-sectional study included pediatric patients followed at the Pediatric Rheumatology Department of Hacettepe University, Ankara. Serum samples were collected from four groups: patients with BD (n = 34), DADA2 (n = 20), PAN (n = 10), and age-matched healthy controls (HC, n = 8). All participants were of Turkish origin. BD was diagnosed according to the Pediatric Behçet's Disease (PEDBD) classification criteria. DADA2 was confirmed by biallelic pathogenic variants in ADA2 and/or decreased ADA2 enzyme activity (<5% of normal). PAN patients fulfilled the Ankara 2008 criteria. Genetic screening for ADA2 variants was not routinely performed in PAN patients because no clinical features suggestive of DADA2 were present.

Blood samples were obtained during clinically stable visits, at least four weeks after the last disease flare. Treatment exposure at the time of sampling was also recorded for all participants. All participants were free of acute infection, metabolic, or neoplastic disease at the time of sampling. This study was approved by the Hacettepe University Ethics Commission (Approval No: GO 19/275). Written informed consent was obtained from all participants or their legal guardians prior to inclusion.

Sample collection and mediator profile analysis

Peripheral venous blood samples were collected during routine follow-up visits using serum separator tubes and centrifuged at 4000 rpm for 10 minutes. The sera were aliquoted and stored at –80°C until analysis. Serum levels of angiogenic and inflammatory analytes (TIE2, TIE1, FLT1, sT2, RAGE, CD40L, LIGHT, PlGF, TNF-α, IL-6, IL-10, IL-18, and MCP-1) were measured using a multiplex bead-based immunoassay (LEGENDplex™ HU Vascular Inflammation Panel 2 (13-plex); Cat#740966, BioLegend, San Diego, CA, USA). Assays were performed according to the manufacturer's instructions, and data acquisition was conducted using a Luminex® platform. All samples were tested in duplicate within the same assay run to minimize inter-assay variability.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics version 26.0 (Armonk, NY, USA) and GraphPad Prism 10.0. Continuous variables were summarized as mean ± standard deviation (SD) or median (interquartile range, IQR), depending on the data distribution, as assessed by the Shapiro–Wilk test. Categorical variables were expressed as frequencies and percentages. Group comparisons were conducted using the Kruskal–Wallis test followed by Dunn–Bonferroni post-hoc correction for non-normally distributed data and one-way ANOVA with Tukey correction for normally distributed data. Correlations among markers were evaluated using Spearman's rank correlation coefficient (ρ).

Multiple linear regression analyses were applied to explore associations between marker levels and disease duration, while binary logistic regression was used to identify potential predictors of vascular or CNS involvement in BD. Variables with $p < 0.100$ in univariate analysis or with biological relevance were entered into multivariable models. Model adequacy was assessed by the Hosmer–Lemeshow goodness-of-fit test, R^2, and adjusted R^2. All tests were two-tailed, and $p < 0.05$ was considered statistically significant.

RESULTS

Study population

A total of 72 serum samples were collected and analyzed from 72 consecutive individuals, including patients diagnosed with BD (n=34, 47.2%), DADA2 (n=20, 27.8%), PAN (n=10, 13.9%), and HC (n=8, 11.1%). The mean age of participants was 10.66 ± 4.42 years, and 44.4% (n=32) were male. Among BD patients, the mean age at diagnosis was 11.7 ± 3.2 years, and the mean disease duration at the time of sampling was 82.6 ± 48.2 days. Clinical characteristics of BD patients are summarized in Table 1. Vascular involvement was present in 7 (20.6%) BD patients, and CNS involvement in 5 (14.7%). All DADA2 patients had documented vascular disease. At the time of sampling, treatment exposure differed across groups. In the BD group, 10/34 patients were untreated, while the remaining patients were receiving colchicine (21/34), corticosteroids (5/34), azathioprine (4/34), adalimumab (2/34), infliximab (1/34), or cyclophosphamide (1/34), alone or in combination. All patients with DADA2 were receiving anti-TNF therapy, whereas all PAN patients and healthy controls were untreated.

Mediator profiles across disease groups

Comparative analysis revealed distinct patterns of vascular and inflammatory mediators across the four study groups (Figure 1). In BD, TIE2 levels were significantly lower than in healthy controls ($p = 0.010$). In contrast, patients with DADA2 exhibited elevated levels of angiogenic and inflammatory markers, including TIE1, TIE2, FLT1, TNF-α, IL-18, IL-10, and MCP-1, compared with both PAN and BD (all $p < 0.001$). FLT1 levels in DADA2 were also higher than in healthy controls ($p = 0.042$). PAN patients showed intermediate values, with IL-18 significantly higher than in BD ($p = 0.003$) but lower than in DADA2.

Table 1. Clinical and laboratory characteristics of patients with Behçet's disease (n = 34)

Category	Variable	Value
Demographic	Female, n (%)	17 (50.0%)
	Age at diagnosis, mean ± SD (years)	11.71 ± 3.19
	Disease duration, mean ± SD (days)	82.6 ± 48.2
Clinical	Oral ulcers, n (%)	32 (94.1%)
	Genital ulcers, n (%)	25 (73.5%)
	Cutaneous involvement, n (%)	25 (73.5%)
	Neurological involvement, n (%)	5 (14.7%)
	Ocular involvement, n (%)	9 (26.5%)
	Vascular involvement, n (%)	7 (20.6%)
	Arthritis, n (%)	16 (47.1%)
	Pathergy positivity, n (%)	8 (23.5%)
Laboratory	WBC (×10³/μL), median (IQR)	6.2 (5.4–7.7)
	Hemoglobin (g/dL), median (IQR)	13.4 (12.5–14.9)
	Platelets (×10³/μL), median (IQR)	248 (218–281)
	ESR (mm/h), median (IQR)	9 (4–16)
	CRP (mg/dL), median (IQR)	0.47 (0.2–0.9)
	HLA-B51 positivity, n (%)	19 (55.9%)

SD, standard deviation; IQR, interquartile range; WBC, white blood cell count; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; HLA, human leukocyte antigen.

Despite group-level differences, receiver operating characteristic (ROC) analyses indicated limited diagnostic performance of individual circulating markers; all area under the curve (AUC) values were < 0.7.

Multiple linear regression analysis including all markers as predictors of disease duration in BD yielded no significant associations (R^2 = 0.23, adjusted R^2 = –0.44). Similarly, in logistic regression models, none of the evaluated markers independently predicted vascular (χ^2 = 12.6, p = 0.082) or CNS involvement (all p > 0.050).

Spearman correlation analyses demonstrated strong positive relationships among several angiogenic and inflammatory markers: sT2 strongly correlated with LIGHT (ρ = 0.776, p < 0.001), PlGF (ρ = 0.681, p < 0.001), and FLT1 (ρ = 0.576, p < 0.001). FLT1 correlated with PlGF (ρ = 0.843), LIGHT (ρ = 0.797), and IL-6 (ρ = 0.617). TIE2 moderately correlated with FLT1 (ρ = 0.568) and PlGF (ρ = 0.523). These relationships were mostly pronounced in DADA2. These findings are illustrated in Figure 1.

DISCUSSION

In this study, we examined a panel of vascular and inflammatory markers in pediatric patients with BD and compared their profiles with those of patients with DADA2 and PAN, as well as healthy controls. This exploratory analysis showed that although several intergroup differences were present, individual circulating markers had limited discriminatory utility across pediatric vasculitis subtypes. Nevertheless, the observed patterns provide insight into the vascular-inflammatory milieu of these conditions, particularly in DADA2.

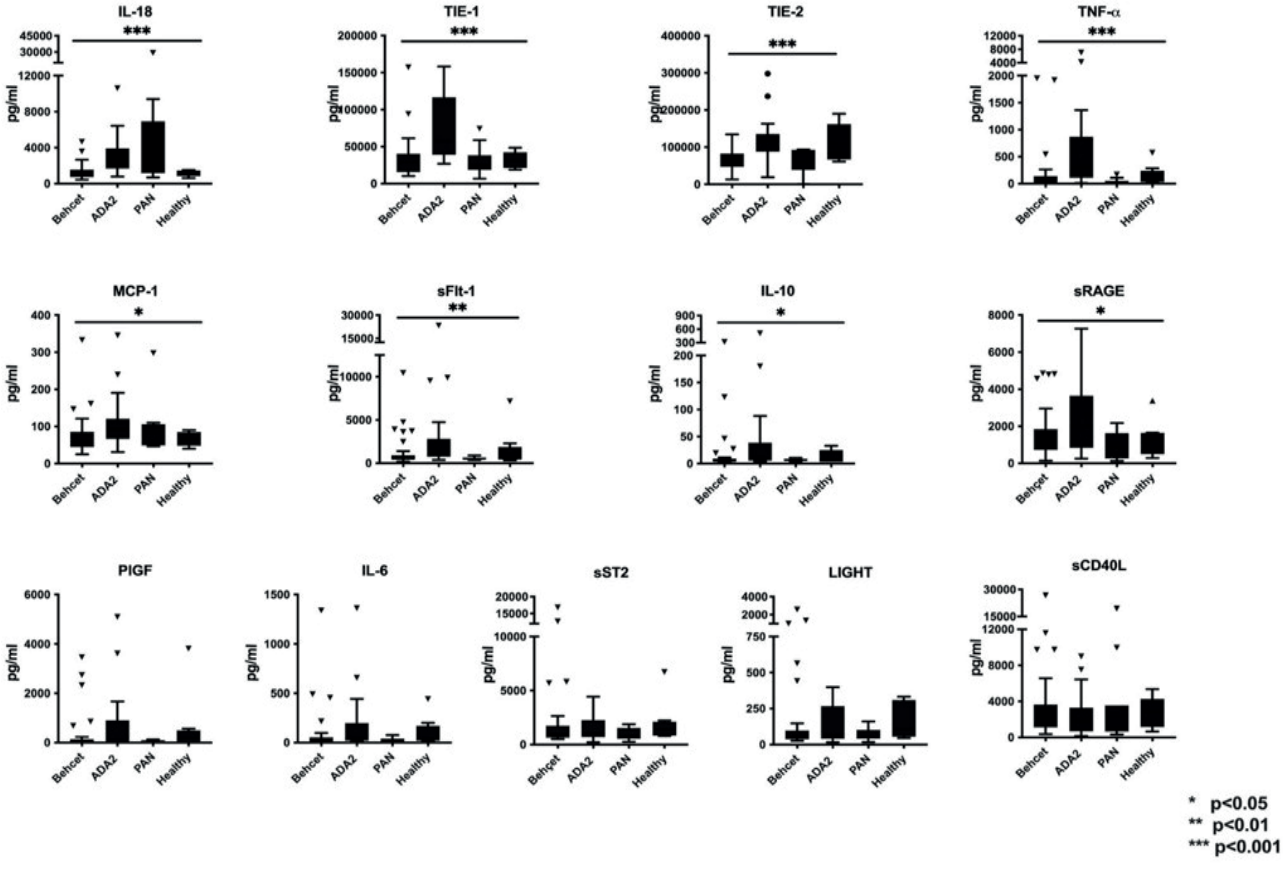


Figure 1. Circulating angiogenic and vascular markers (TIE2, TIE1, FLT1, sT2, RAGE, CD40L, LIGHT, TNF-α, PlGF, IL-6, IL-18, IL-10, MCP1) in Behçet's disease, DADA2, PAN, and healthy controls. Key patterns include reduced TIE2 levels in BD relative to healthy controls and a more prominent angiogenic-inflammatory profile in DADA2, characterized by elevations in TIE1, TIE2, FLT1, TNF-α, IL-10, IL-18, and MCP-1

Patients with DADA2 exhibited the most pronounced angiogenic-inflammatory alterations in our cohort, with significantly elevated TIE1, TIE2, FLT1, TNF-α, IL-18, IL-10, and MCP-1 compared with both BD and PAN.

These findings are consistent with previous reports highlighting endothelial dysregulation and TNF-driven vascular inflammation in DADA2.[6]

TIE2, a receptor tyrosine kinase activated by angiopoietin-1 and -2, plays a critical role in endothelial homeostasis, vascular remodeling, and inflammatory signaling.[1] Consistent with this, Kaya Akca et al. reported increased levels of TIE1, TIE2, and TNF-α in pediatric DADA2 patients compared to PAN, proposing that these markers reflect key differences in immune-mediated vascular injury despite overlapping clinical features.[6] The consistently high TNF-α levels in DADA2 align with its known therapeutic relevance and further highlight the role of TNF-driven endothelial inflammation. Taken together, our results support the notion that the angiogenic and cytokine milieu—particularly involving TIE2 and TNF-α—may serve as potential mechanistic indicators or biomarkers in DADA2, distinct from other forms of systemic vasculitis. Notably, all DADA2 patients were receiving anti-TNF therapy at the time of sampling. Therefore, the observed profile should not be interpreted as entirely treatment-independent, although the persistence of this pattern despite anti-TNF exposure may still reflect ongoing disease-related vascular immune activation.

In contrast, patients with BD showed a more heterogeneous cytokine profile, with overall lower levels of TNF-α and IL-18, and no significant elevation of angiogenic markers compared to controls, except for decreased TIE2 levels. This contrasts with previous reports suggesting elevated IL-18[2] and TNF-α levels in active BD.[4] Several factors may explain the relatively modest inflammatory signal observed in BD. First, samples were collected during clinically stable follow-up visits rather than active inflammatory attacks, which may have attenuated cytokine elevations. Second, treatment exposure was common in the BD group: only 10 of 34 patients were untreated, while the remaining patients were receiving colchicine, corticosteroids, azathioprine, or biologic agents. These factors may partly explain the comparatively low levels of TNF-α and IL-18 in BD and the overlap observed with other disease groups.

An important finding of our study is that individual circulating markers showed limited discriminatory performance across pediatric vasculitis subtypes. All ROC AUC values remained below 0.7, indicating that no single marker provided clinically useful discrimination among BD, DADA2, and PAN in this cohort. Although negative, this finding is clinically relevant because it argues against overinterpretation of isolated serum measurements and suggests that single-marker approaches are insufficient for disease classification in pediatric vasculitis.[5]

We also did not identify significant associations between circulating markers and vascular or CNS involvement in BD. This contrasts with some adult studies reporting elevated cytokine levels in active or organ-specific disease; however, our findings should be interpreted in the context of important methodological constraints.[3,8] In particular, the number of BD patients with vascular (n = 7) and CNS involvement (n = 5) was small, limiting statistical power and increasing the risk of unstable estimates in regression analyses. Accordingly, these subgroup analyses should be regarded as exploratory.

This study has several important limitations. First, the sample size was modest, particularly in the BD subgroups with vascular and CNS involvement. Second, the cross-sectional design precluded assessment of longitudinal changes in marker levels over time. Third, samples were collected during clinically stable visits rather than active flares, which may have limited the detection of disease activity-related signals. Fourth, treatment exposure differed substantially across groups, with heterogeneous ongoing therapy in BD, universal anti-TNF use in DADA2, and no treatment in PAN, potentially confounding intergroup comparisons. Finally, reliance on peripheral blood measurements may not fully capture tissue-level or organ-specific vascular inflammation.

CONCLUSION

In conclusion, our findings suggest that single circulating markers are of limited value for distinguishing pediatric BD from other vasculitides or for predicting vascular and CNS involvement in BD. In contrast, DADA2 demonstrated a more distinct vascular-inflammatory pattern characterized by coordinated angiogenic and TNF-related signals. These observations support the need for larger, longitudinal, treatment-stratified studies and integrated multi-marker approaches to better define clinically meaningful vascular-immune phenotypes in pediatric vasculitis.

Author contributions

Conception and design: S.Ö., E.S.; Data acquisition: D.U., E.S., S.D.; Data analysis: D.U., E.S., S.D.; Data interpretation: D.U., E.S., S.D.; Drafting of the manuscript: D.U., E.S. All authors reviewed the results, approved the final version of the manuscript, and agreed to be accountable for all aspects of this study.

Ethical approval

This study was approved by the Hacettepe University Ethics Committee (approval date 25.09.2019, number: GO 19/275). Informed consent was obtained from all participants involved in this study.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of interest

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Generative AI statement

The authors declare that no generative AI or AI-assisted technologies were used in the writing or preparation of this study.

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Case Report

An adolescent case presenting with urinary retention to the pediatric emergency department

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ABSTRACT

Acute urinary retention is an uncommon clinical condition in childhood and adolescence and is typically linked to neurological, infectious, or structural causes. Hematometrocolpos secondary to imperforate hymen is a well-recognized gynecologic condition that may be overlooked and may present with urinary retention, particularly in adolescents.

We report the case of a 12-year-old girl with no significant past medical history who presented to the pediatric emergency department with suprapubic pain and an inability to void. Despite clear pubertal development (Tanner stage IV), she had primary amenorrhea. Pelvic imaging demonstrated a large fluid-filled mass consistent with hematometrocolpos due to an imperforate hymen. Hymenotomy was performed with drainage of approximately 500 mL of retained menstrual blood. The postoperative course was uneventful, and spontaneous menstruation began three weeks later.

This case highlights the educational value of recognizing gynecologic causes of urinary retention, particularly in emergency settings where the diagnosis may be missed due to the predominance of urologic and neurologic considerations. A careful physical examination in pubertal girls presenting with acute urinary retention, especially in the presence of primary amenorrhea and cyclic abdominal pain, is essential to ensure early diagnosis and to avoid unnecessary investigations and delays in management.

Keywords: urinary retention, hematometrocolpos, imperforate hymen, primary amenorrhea, adolescent

INTRODUCTION

Acute urinary retention is an uncommon clinical condition in adolescents and is most commonly associated with neurological disorders, urinary tract infections, urolithiasis, or structural anomalies.[1-3] Gynecologic causes, although less frequent, should be considered in selected patients, particularly in those with pubertal development and primary amenorrhea accompanied by cyclic pelvic pain and voiding difficulty.[2,3] Imperforate hymen, the most common congenital obstructive anomaly of the female genital tract, has an estimated incidence of 0.014%–0.1% (approximately 1 in 1,000 to 1 in 10,000 females), and represents a well-recognized clinical entity that may nevertheless be overlooked in acute care settings.[1,2]

Hematometrocolpos is a congenital obstructive anomaly usually caused by an imperforate hymen and typically presents with primary amenorrhea, abdominal pain, pelvic distension, and occasionally low back pain.[1-4] Although cyclic pelvic pain and abdominal mass are common features, acute urinary retention as the initial manifestation is an infrequent but clinically important presentation.[5-7] Providing this epidemiologic context is essential for

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understanding why atypical presentations, such as urinary retention, warrant careful diagnostic consideration.

Ultrasonography is the first-line imaging modality because it reliably identifies pelvic fluid collections and reproductive tract distension.[7] Magnetic resonance imaging (MRI), however, provides superior delineation of the level and extent of obstruction, as well as its relationship with adjacent pelvic structures.[8] Delayed diagnosis may result in serious sequelae, including endometriosis, hydronephrosis, and even infertility.[8,9]

Here, we describe an adolescent girl with hematometrocolpos who presented with acute urinary retention, highlighting the educational value of this presentation and the importance of considering gynecologic causes in the differential diagnosis, particularly in emergency settings where early recognition can prevent unnecessary investigations and delays in management.

CASE PRESENTATION

A 12-year-old previously healthy girl presented to the pediatric emergency department with suprapubic pain and inability to void urine. She had no history of medication use or systemic illness. Despite pubertal development consistent with Tanner stage IV, she had primary amenorrhea. She reported intermittent lower abdominal pain over the past three months, which had progressively worsened over the preceding two days, culminating in acute urinary retention. One month earlier, she had been evaluated at another hospital for similar symptoms but was discharged without a definitive diagnosis.

On examination, the patient was hemodynamically stable. Physical assessment was unremarkable except for a palpable suprapubic mass consistent with bladder distension. Laboratory tests, including complete blood count, biochemical profile, and urinalysis, were within normal limits, and serum β-hCG was negative.

A Foley catheter was inserted, draining approximately 700 mL of urine, which relieved her symptoms. Pelvic ultrasonography revealed a large, homogeneous, echogenic collection measuring 17 × 7.5 cm, extending from the endometrial cavity and cervix into the vaginal canal to the hymenal level, consistent with hematometrocolpos (Figure 1). The Foley catheter was left in place for approximately 12 hours preoperatively to ensure decompression and symptomatic relief. A single

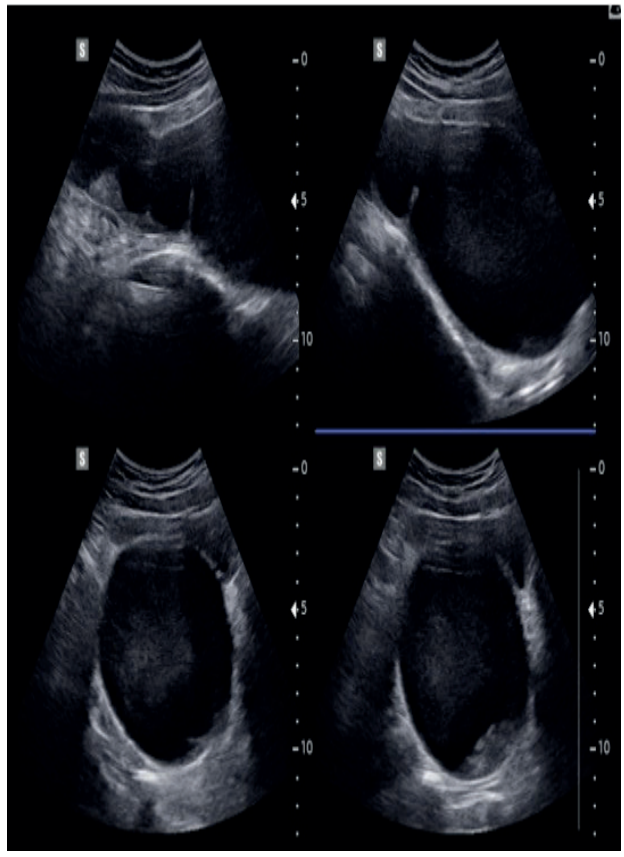


Figure 1. Sonographic image showing hematometrocolpos

preoperative prophylactic dose of intravenous cefazolin was administered, and analgesia was achieved with weight-based intravenous paracetamol, which adequately controlled her pain.

A detailed external genital examination performed by a gynecologist revealed a tense, bulging, bluish imperforate hymen, and the diagnosis was subsequently confirmed during gynecologic evaluation. Pelvic contrast-enhanced MRI demonstrated a markedly distended uterus reaching the level of the umbilicus (22 × 9 cm), with a thinned myometrium and markedly distended endometrial and vaginal cavities filled with hematic content. The bladder was displaced anteriorly with reduced capacity (Figure 2).

The patient underwent hymenotomy under general anesthesia via cruciate incision, resulting in drainage of approximately 500 mL of retained menstrual blood. Hemostasis was secured, mucosal eversion was achieved, and a vaginal Foley catheter was placed to prevent restenosis. The postoperative course was uneventful. She



Figure 2. Pelvic MRI demonstrating hematometrocolpos with anterior displacement of the bladder

was discharged on postoperative day 3, and at follow-up, she reported complete resolution of symptoms. Menstruation commenced spontaneously three weeks after the procedure.

DISCUSSION

Acute urinary retention in adolescence is an uncommon clinical presentation and is typically related to neurological, infectious, lithiasis-related, or structural causes.[1-3] Gynecologic etiologies, though less frequently considered, should be included in adolescent girls with pubertal development, primary amenorrhea, cyclic pelvic pain, and voiding difficulties. In this context, the differential diagnosis should be approached systematically and should include neurologic disorders such as spinal cord lesions, tethered cord syndrome, transverse myelitis, or Guillain–Barré syndrome; infectious etiologies including severe cystitis, vulvovaginitis, or pelvic inflammatory disease; and mechanical or obstructive causes such as urolithiasis or urethral anomalies. Psychological or functional conditions—such as dysfunctional voiding, psychogenic urinary retention, or acute anxiety—may also mimic obstructive symptoms.[1-3] In addition, medication-related urinary retention, particularly associated with anticholinergic drugs, antihistamines, or psychotropic agents, should be considered when relevant. Recognizing this broad range of potential causes is essential to avoid misdiagnosis and ensure timely identification of structural gynecologic conditions that may otherwise be overlooked, especially when clinical features such as primary amenorrhea and cyclic pelvic pain are present.

Hematometrocolpos, most often secondary to imperforate hymen, is a well-recognized congenital anomaly. The classical presentation includes primary amenorrhea and abdominal or pelvic pain; however, urinary retention as the predominant symptom represents an infrequent but clinically important manifestation.[4-7] This case emphasizes the educational value of recognizing this presentation, particularly for clinicians working in emergency and primary care settings, where urologic and neurologic causes are often considered first.

Previous reports have highlighted similar presentations: Ercan et al.[5] and Asikhia et al.[6] described adolescents with hematometrocolpos complicated by acute urinary retention, while Santos et al.[7] emphasized the role of imaging in diagnosis. Niang et al.[8] demonstrated that delayed recognition may lead to hydronephrosis and endometriosis, and Liang et al.[9] confirmed favorable long-term outcomes following surgical correction. More recently, Al-Bulushi et al.[10] described a comparable case successfully managed with hymenotomy. Collectively, these reports indicate that early recognition is the key determinant of positive clinical outcomes.

In emergency department settings, acute urinary retention in adolescent girls is often evaluated from a urologic or neurologic perspective, which may delay recognition of underlying gynecologic causes. Early identification of conditions such as hematometrocolpos can markedly change clinical management by preventing unnecessary investigations and expediting definitive treatment. A careful physical examination—particularly in pubertal girls presenting with urinary retention accompanied by primary amenorrhea or cyclic pelvic pain—is therefore essential to avoid diagnostic delay and optimize patient outcomes.[5-9]

Ultrasound remains the first-line diagnostic modality due to its accessibility and sensitivity in identifying pelvic masses. MRI, however, is indispensable in delineating the extent of obstruction and its impact on adjacent pelvic structures, as in our case, where anterior displacement of the bladder explained the retention.[7,8] In emergency department settings, a diagnostic approach that begins with a careful physical examination and is supported by timely imaging is essential to prevent unnecessary investigations and delays in appropriate management.

Failure to diagnose promptly may result in retrograde menstruation, endometriosis, urinary tract obstruction, and infertility.[8,9] Notably, our patient had previously been evaluated elsewhere without a correct diagnosis, illustrating the potential for misdiagnosis. Early recognition is particularly crucial in both primary care and emergency departments, as an imperforate hymen is a fully correctable cause of acute urinary retention when identified promptly. Delayed diagnosis, however, may lead not only to avoidable investigations and repeated healthcare visits but also to preventable complications such as hematosalpinx, endometriosis, hydronephrosis, and infertility.[8,9] These observations highlight the importance of sustaining heightened clinical vigilance and conducting a comprehensive physical examination in pubertal female patients who present with urinary retention.

Surgical hymenotomy is the gold-standard treatment, with cruciate or annular incisions most commonly employed.[4-6,10] In this case, cruciate hymenotomy successfully relieved symptoms, with no recurrence or postoperative complications.

Hematometrocolpos should therefore be considered in the differential diagnosis of acute urinary retention in adolescent girls presenting with primary amenorrhea and pubertal development. This report emphasizes the educational value of this clinical presentation and highlights the importance of maintaining a high level of clinical awareness for early recognition. Clinicians evaluating adolescents with urinary retention should remain attentive to gynecologic etiologies, particularly when symptoms are accompanied by cyclic pain or menstrual abnormalities, to facilitate timely intervention and prevent potentially serious long-term complications.

Author contributions

Conception and design: M.A., Ş.D., A.Ç.; Data acquisition: M.A., Ş.D.; Data analysis: M.A., A.Ç.; Data interpretation: M.A., A.Ç.; Drafting of the manuscript: M.A., Ş.D., A.Ç. All authors reviewed the results, approved the final version of the manuscript, and agreed to be accountable for all aspects of this study.

Ethical approval

Written informed consent was obtained from the patient(s) or their legal guardians for the publication of this study and any accompanying images.

Conflict of interest

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Letter to the Editor

A diagnostic challenge: Chronic ITP and acute rheumatic fever mask underlying APS

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Dear Editor,

Pediatric antiphospholipid syndrome (APS) remains a challenging diagnosis due to its rarity, heterogeneous presentation, and frequent overlap with other autoimmune or inflammatory disorders. Unlike adults, children often present with non-thrombotic manifestations, and features such as chronic thrombocytopenia or valvular involvement may easily be misinterpreted as more common pediatric conditions.[1,2] Early recognition is critical to preventing long-term complications, yet delays frequently occur because APS is not initially suspected.

With this letter, we aim to highlight a diagnostically challenging case in which a child initially labeled as having immune thrombocytopenic purpura (ITP) and later acute rheumatic fever (ARF) was ultimately diagnosed with APS. This case underscores the importance of maintaining a broad differential diagnosis in children with persistent cytopenias and unexplained cardiac findings, and it demonstrates how early recognition of APS-related features can change the entire trajectory of care.

CASE REPORT

A 13-year-old male first presented at the age of seven with petechial purpura on his trunk. Laboratory investigations revealed thrombocytopenia, leading to an initial diagnosis of ITP. He was treated with intravenous immunoglobulin (IVIG) and steroids; however, no sustained response was achieved. Eltrombopag was also ineffective, and repeated bone marrow evaluations ruled out myelodysplasia or malignancy.

At the age of nine, the patient developed fever, chest pain, and arthralgia. The chest pain was non-positional and unaffected by movement. Laboratory findings showed elevated troponin (40 ng/L) and brain natriuretic peptide (BNP) (>400 pg/mL), raising suspicion of multisystem inflammatory syndrome in children (MIS-C)-related myocarditis, and treatment with IVIG and steroids was initiated.

During follow-up, echocardiography revealed an eccentric jet flow, mitral valve thickening, and mitral regurgitation, but no thrombus was detected. Given the patient's previous history of arthralgia, the condition was initially considered acute rheumatic fever (ARF), and secondary penicillin prophylaxis was initiated. However, upon referral to our hospital, the patient's history of thrombocytopenia raised suspicion of APS, prompting further evaluation.

Laboratory findings revealed positive antiphospholipid antibodies, including anti-cardiolipin IgG (81.3 GPL/mL),

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beta-2 glycoprotein IgG (52.6 RU/mL), and a highly positive lupus anticoagulant test (LA ratio: 2.24, dRVVT: 86 sec), while anti-cardiolipin IgM and beta-2 glycoprotein IgM were negative. His autoantibody profile, including ANA, anti-dsDNA, and anti-Sm were negative.

Based on the presence of antiphospholipid antibody positivity, thrombocytopenia, and mitral valve thickening, the patient was classified as having APS according to the 2023 ACR/EULAR APS classification criteria. In this context, the prior history of arthralgia—without additional supportive features or laboratory evidence suggestive of acute rheumatic fever—was not considered sufficient to support a diagnosis of ARF, and APS was therefore favored. Treatment with intravenous immunoglobulin and corticosteroids was subsequently initiated in a stepwise manner. However, as the steroid dose was tapered, he developed severe thrombocytopenia (<10,000/mm³) and mucosal bleeding, necessitating rituximab therapy (2 doses of 500 mg/m² at 2-week intervals).

By the first month of follow-up, the platelet count improved to 223,000/mm³. By the third month, persistent antiphospholipid antibody positivity led to the initiation of low-dose acetylsalicylic acid (ASA). In the sixth month, the platelet count increased to 308,000/mm³ without any new symptoms. As a result, rituximab was not repeated.

At the one-year follow-up, the patient remained clinically stable, with no recurrence of symptoms. He continued low-dose ASA during follow-up.

In the present case, APS was considered primary, as there was no clinical, serological, or immunological evidence of an underlying systemic autoimmune connective tissue disease. In particular, features suggestive of juvenile systemic lupus erythematosus, such as hypocomplementemia, anti-dsDNA or anti-Sm antibody positivity, renal or neuropsychiatric involvement, or persistent inflammatory markers, were absent during follow-up.[3]

Mitral valve abnormalities are a well-recognized but often underestimated feature of APS. On echocardiography, APS-related valvular involvement is typically characterized by non-inflammatory leaflet thickening and small, sterile vegetations, whereas ARF is associated with inflammatory carditis, showing leaflet edema, commissural fusion, and chordal involvement. Notably, the “Sapporo” classification criteria for APS primarily focus on thrombotic events, which might not fully capture the spectrum of APS in pediatric patients.[4] However, the 2023 ACR/EULAR classification criteria provide a more comprehensive framework for identifying APS, particularly in cases with non-thrombotic presentations.[5] In our case, the valvular involvement was initially misdiagnosed as ARF. However, APS-related valvular disease often presents with thrombotic vegetations and valvular dysfunction, resembling other valvular disorders such as ARF. This diagnostic challenge was overcome through antiphospholipid antibody testing, leading to the correct diagnosis.

Although chronic ITP is the most common cause of persistent thrombocytopenia, APS should be considered in patients who are unresponsive to standard immunomodulatory therapies.[6] In cases where IVIG, steroids, and thrombopoietin receptor agonists (e.g., eltrombopag) fail, recurrent episodes of thrombocytopenia may indicate an underlying systemic autoimmune disorder such as APS. Therefore, routine screening for antiphospholipid antibodies should be considered in patients with chronic, treatment-resistant thrombocytopenia. Moreover, transient aPL positivity can also be observed in healthy individuals, necessitating cautious interpretation of results. For instance, low-to-moderate lupus anticoagulant positivity or isolated positivity of a single antiphospholipid antibody is not uncommon and may not always indicate APS.[7] The ACR/EULAR-recommended scoring system places greater emphasis on persistent lupus anticoagulant positivity in repeated tests, reflecting its stronger association with APS-related complications. [5] Furthermore, strongly positive lupus anticoagulant results or simultaneous positivity for three different antiphospholipid antibodies are linked to a higher risk of APS-related complications, reinforcing the need for a holistic risk assessment in clinical practice.[7]

The management of APS is a dynamic process that requires continuous reassessment of thrombotic and bleeding risks. In cases of active bleeding or severe thrombocytopenia, temporary discontinuation of antithrombotic therapy may be warranted to mitigate hemorrhagic risk.[6] However, as platelet levels recover or in cases of mild thrombocytopenia, the balance shifts toward an increased thromboembolic risk, necessitating careful consideration of prophylactic anticoagulation. Individualized risk assessment, considering both bleeding and thrombotic tendencies, is essential to optimize management in APS patients with fluctuating platelet counts.

Rituximab is a monoclonal antibody targeting CD20, a surface protein expressed on B lymphocytes.[8] By depleting B cells, it reduces autoantibody production and modulates immune responses, making it an effective treatment for various autoimmune and hematologic conditions.[9] In

APS, where B-cell dysregulation plays a role in persistent autoantibody production and immune-mediated thrombocytopenia, rituximab offers a targeted therapeutic approach, especially in refractory cases.[10]

Rituximab has been utilized in cases of life-threatening organ involvement, refractory thrombocytopenia, and, according to some case series, for the treatment of APS-related cutaneous ulcers and cognitive dysfunction.[11-13]

This case highlights the diverse clinical manifestations of pediatric APS, which can extend beyond thrombotic events to include hematologic abnormalities, such as thrombocytopenia, or cardiac involvement, such as mitral valve vegetations. Given the rarity and complexity of pediatric APS, early recognition and a comprehensive, multidisciplinary approach are crucial to minimizing morbidity and improving outcomes.

The 2023 ACR/EULAR classification criteria offer a more structured framework for APS diagnosis, yet the variability in pediatric presentations highlights the need for greater clinical awareness and a refined diagnostic approach. Moving forward, international collaborative efforts are crucial to establishing pediatric-specific classification criteria and standardized treatment protocols, ultimately improving disease management and long-term outcomes.

Author contributions

Conception and design: V.Ç., S.D.; Data acquisition: V.Ç., E.S., H.E.E.; Data analysis: V.Ç., H.E.E., E.S., S.D.; Data interpretation: V.Ç., H.E.E., E.S., S.D. All authors reviewed the results, approved the final version of the manuscript, and agreed to be accountable for all aspects of this study.

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