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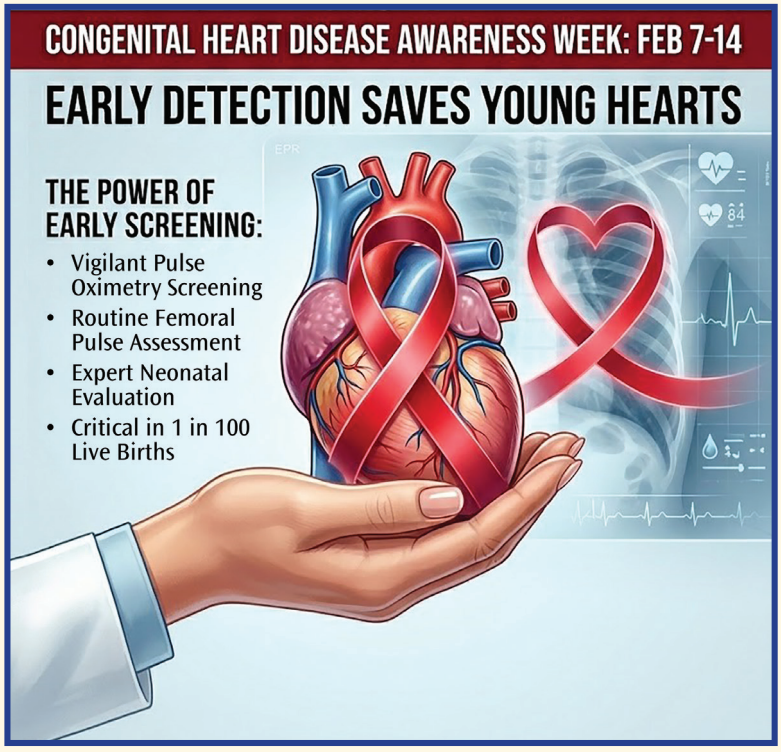

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CONTENTS

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EDITORIAL

Dear Readers,

It is with immense pleasure and a profound sense of responsibility that I welcome you to the first issue of 2026 of The Journal of Pediatric Research (JPR). I am privileged to present a collection of articles that collectively underscore the dynamic and ever-evolving landscape of pediatric science. Our commitment at JPR remains steadfast: to disseminate high-impact research that not only advances our understanding of child health and disease but also directly informs clinical practice and public health initiatives.

This issue encompasses one comprehensive review and twelve original articles spanning a broad clinical spectrum. We would like to highlight our featured review: "Lipid Profile in Children and Adolescents with Type 1 Diabetes Mellitus: A Systematic Review and Meta-analysis." This piece provides a critical, evidence-based perspective on metabolic management, offering vital insights for clinicians striving to mitigate long-term cardiovascular risks in pediatric diabetic populations.

As a pediatric cardiologist, I wish to take this opportunity to draw your attention to Congenital Heart Disease (CHD) Awareness Week, observed from February 7th to 14th.

Congenital heart defects remain the most prevalent of all birth anomalies, affecting approximately 1 in every 100 live births. These statistics underscore a fundamental duty for all pediatricians: every newborn must be systematically evaluated for potential cardiac defects.

To ensure the early detection of life-threatening conditions, particularly ductal-dependent critical CHD, we must remain vigilant in our clinical protocols:

• Pulse Oximetry Screening: A non-invasive yet indispensable tool for identifying silent hypoxemia.

• Physical Examination: The meticulous assessment of femoral pulses is vital for diagnosing obstructive left heart lesions.

• Differential Diagnosis: CHD must be definitively ruled out in any neonate presenting with central cyanosis or impaired systemic perfusion.

By refining our screening practices and maintaining a high index of clinical suspicion, we can significantly improve the prognosis and quality of life for our youngest patients.

I hope you find the articles in this issue both intellectually stimulating and practically applicable to your clinical practice. I extend my sincere gratitude to the dedicated authors, diligent peer reviewers, and the entire editorial team whose unwavering commitment to scientific excellence has made this issue possible. Their collective efforts ensure that JPR continues to uphold its reputation as a leading voice in pediatric research. To our esteemed readership, I invite you to engage deeply with the impactful research presented herein. It is through your continued engagement and intellectual curiosity that we collectively drive forward the mission of improving child health worldwide.

With warmest regards,

Prof. Dr. Zülal Ülger Tutar

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Review

Lipid Profile in Children and Adolescents with Type 1 Diabetes Mellitus: A Systematic Review and Meta-analysis

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ABSTRACT

This study aimed to compare fasting lipid profiles in children and adolescents with type 1 diabetes mellitus and healthy controls. This systematic review and meta-analysis followed Preferred Reporting Items for Systematic reviews and Meta-Analyses 2020 guidelines and was registered in PROSPERO (CRD42024600840). A systematic search was conducted in PubMed, Scopus, SpringerLink, EBSCOhost, and Google Scholar. Eligible studies were observational and included children and adolescents aged 5-19 years with type 1 diabetes mellitus. Search terms combined "Lipid profile", "Dyslipidemia", "Cholesterol", "HDL", "LDL", "Triglycerides", "Child", "Adolescent", "Pediatric", "Young people", "Type 1 Diabetes", and "Insulin Dependent Diabetes". Study quality was assessed with the Newcastle-Ottawa Scale, and data were synthesized using RevMan 5.4. Eleven studies were included with a total of 1,529 participants. Compared with the controls, children and adolescents with type 1 diabetes mellitus showed higher total cholesterol [mean difference (MD)=14.3 mg/dL; 95% confidence interval (CI): 8.4-20.4], low-density lipoprotein-cholesterol (MD=11.0 mg/dL; 95% CI: 7.0-14.8), and high-density lipoprotein cholesterol (MD=2.66 mg/dL; 95% CI: 0.1-5.2). Triglycerides were slightly increased but not significantly (MD=8.6 mg/dL; 95% CI: -0.4-21.3). This meta-analysis reveals lipid alterations in pediatric type 1 diabetes mellitus. Routine lipid screening and timely interventions are warranted in order to guide preventive care for cardiovascular disease risk.

Keywords: Type 1 diabetes mellitus, pediatric, lipid profile, dyslipidemia, meta-analysis

Introduction

Type 1 diabetes mellitus (T1DM) is one of the most common chronic endocrine disorders in children and adolescents. Its global incidence has been increasing steadily over the last three decades, with an estimated annual rise of approximately 3% worldwide (1). The International Diabetes Federation reported that, in 2021, there were approximately 1.5 million individuals under the age of 20 living with T1DM worldwide, with the highest incidence peaks occurring between the ages of 5-9 and 10-14 years (2,3). Although the disease is characterized primarily by autoimmune-mediated β-cell destruction and insulin deficiency, its long-term morbidity is driven largely by chronic complications, particularly cardiovascular disease (CVD) (4).

Dyslipidemia is a well-recognized and modifiable risk factor for CVD in T1DM, contributing to accelerated atherosclerosis and increased cardiovascular morbidity later in life (5). The American Diabetes Association (ADA) defines dyslipidemia in children as elevated total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), triglycerides

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(TG), or decreased high-density lipoprotein-cholesterol (HDL-C). For children with T1DM, ADA recommends obtaining an initial fasting lipid profile soon after diagnosis in children aged ≥2 years, with repeat screening at ages 9-11 years when initial results are normal. The recommended LDL-C target for children with T1DM is <100 mg/dL (6). Multiple factors contribute to lipid abnormalities in T1DM, including chronic hyperglycemia, insulin deficiency, increased free fatty acid flux, altered apolipoprotein metabolism, and the presence of obesity or insulin resistance in a subset of patients (7).

The prevalence of dyslipidemia in pediatric T1DM varies widely among studies—ranging from approximately 29% to over 70%, highlighting variability related to glycemic control, disease duration, pubertal status, and geographic or ethnic differences (8-10). While clinical guidelines recommend routine lipid screening in all children with T1DM starting at age 10 years or soon after diagnosis if there is a family history of dyslipidemia or premature CVD, real-world adherence to screening protocols remains suboptimal (11). Moreover, there has been limited synthesis of the contemporary evidence in describing lipid profile abnormalities in this population.

Given the critical role of dyslipidemia in the pathogenesis of CVD and its potential reversibility with timely intervention, understanding the characteristics of lipid profiles in children and adolescents with T1DM is essential for optimizing early detection and management strategies. Therefore, this systematic review and meta-analysis aimed to compare fasting lipid profiles, namely TC, TG, HDL-C, and LDL-C, in children and adolescents with T1DM and healthy controls.

Methods

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 guidelines. The review protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD42024600840.

Eligibility Criteria

Types of Studies

All published observational studies which evaluated lipid profiles in pediatric T1DM were included. Only original studies published in full-text and written in either English or Indonesian were considered. This study excluded interventional trials, reviews, conference abstracts, editorials, letters, case reports, and/or animal studies.

Participants

The eligible studies included children and adolescents aged 5-19 years diagnosed with T1DM based on their medical records or laboratory findings. The lower age limit of 5 years was selected to align with the first epidemiological peak of T1DM incidence. This study excluded studies involving adults without clearly separated pediatric data, those participants with type 2 diabetes or other endocrine/metabolic disorders, individuals on lipid-lowering therapy, congenital anomalies and those with significant comorbidities such as CVD, renal failure, or genetic dyslipidemia. Only those studies reporting at least 8-hour fasting lipid profiles were included in order to ensure standardization and the comparability of lipid measurements.

Variables of Interest

The variables of interest included demographic characteristics and fasting lipid profile parameters, namely TC, TG, HDL-C, and LDL-C.

Outcomes of Interest

The outcomes were the fasting levels of TC, TG, HDL-C, and LDL-C. All outcomes were treated as continuous variables, measured in mg/dL, and extracted as means ± standard deviations.

Search Strategy and Study Selection

A systematic literature search was conducted using five electronic databases: PubMed, Scopus, SpringerLink, EBSCOhost, and Google Scholar, covering studies published within the last 10 years in order to ensure inclusion of the most recent and clinically relevant evidence. Keywords and Medical Subject Headings of ("Lipid profile" or "Dyslipidemia" or "Cholesterol" or "HDL" or "LDL" or "Triglycerides") and ("Child" or "Adolescent" or "Pediatric" or "Young people") and ("type 1 diabetes" or "insulin dependent diabetes") were applied, guided by a structured participant, intervention, comparator, outcomes, framework (Table I). Three independent reviewers performed the screening, removed duplications, and assessed full-text eligibility. Any discrepancies were resolved through discussion and consensus.

Data Collection Process

Data were independently extracted by three reviewers using a standardized data extraction form. The demographic characteristics and lipid profiles from all included studies were summarized in a table. Disagreements among the reviewers were resolved through discussion and consensus was reached.

Table I. PICO framework of the included studies evaluating lipid profiles in children and adolescents with type 1 diabetes mellitus	
Participants	Children and adolescents aged 5 to 19 years diagnosed with T1DM based on medical records or laboratory findings
Interventions	Fasting lipid profile parameters—total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) in children and adolescents with T1DM
Comparator	Fasting lipid profiles in healthy children and adolescents
Outcomes	The differences in fasting lipid profiles, including serum TC, TG, HDL-C, and LDL-C
PICO: Participant, intervention, comparator, outcomes, T1DM: Type 1 diabetes mellitus	

Summary Measures

The primary summary measures were analyzed as continuous variables and reported in mg/dL. When outcomes were measured consistently, the results are presented as mean differences (MDs). In cases involving different correction methods, standardized MDs are given. Statistical significance was assessed using p values and 95% confidence intervals.

Risk of Bias in Evaluation

The risk of bias and methodological quality of the included studies were assessed using the Newcastle-Ottawa Scale. Cross-sectional studies were evaluated based on sample representativeness, sample size, consideration of non-respondent, exposure and outcome assessment, comparability, and statistical methods. Each domain was scored 1 or 2 points depending on the level of rigor, with a maximum total score of 10. Based on the final score, studies were categorized as very good (9-10 points), good (7-8 points), satisfactory (5-6 points), or unsatisfactory (0-4 points).

For cohort studies, criteria included cohort representativeness, the selection of non-exposed cohorts, exposure ascertainment, the absence of baseline outcomes, comparability, outcome assessment, and follow-up adequacy. For case-control studies, assessments involved case definition, case and control selection, comparability, exposure ascertainment, and non-response rates. Both study types were rated on a star scale from 0 to 9, with higher scores indicating better quality. Studies were categorized as follows: good quality: 3-4 stars in the selection domain, 1-2 in comparability, and 2-3 in the outcome/exposure domain, fair quality: 2 stars in selection, 1-2 in comparability, and 2-3 in outcome/exposure, and poor quality: did not meet the above thresholds.

Statistical Analysis

Meta-analyses were performed using RevMan 5.4 software. Pooled effect estimates were calculated using a random-effects model (DerSimonian-Laird method) if heterogeneity was substantial (I^2>50%), or a fixed-effects model if heterogeneity was low. Statistical heterogeneity was assessed using the I^2 statistic and chi-squared test, with an I^2 value above 50% indicating moderate-to-high heterogeneity. Publication bias was evaluated qualitatively using funnel plots when at least 10 studies were available for a given outcome.

Results

PRISMA

A total of 2,361 studies were identified through the initial search across five electronic databases. Of these, 807 studies were excluded due to duplicate records, and 1,031 were excluded for other reasons. Abstract screenings were carried out and they resulted in the exclusion of 177 studies. Subsequently, some studies were excluded due to ineligibility according to certain criteria, including studies unrelated to the topic, the absence of a control group as a comparator, and that they did not involve pediatric populations. Finally, this current study included 11 studies for qualitative synthesis and 9 studies for quantitative synthesis. The study selection processes are illustrated in Figure 1.

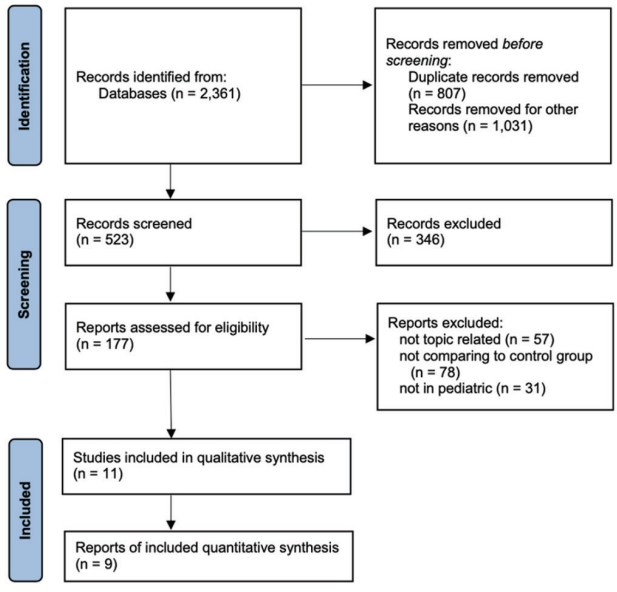

Figure 1. PRISMA 2020 flow diagram of included studies
PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses

Quality Assessment

For the cross-sectional studies, scores varied between 6 and 10 (out of 10). Two studies [Parthasarathy et al. (12) 2015 and Wu et al. (13) 2021] reached the maximum score and were rated as "Very good," while one [Prado et al. (14) 2017] was rated as "Good." The remaining three studies [Angelopoulou et al. (15) 2024; Zabeen et al. (16) 2018; and Trigona et al. (17) 2019] were considered "Satisfactory," mostly due to their less detailed reporting in certain domains. The cohort studies demonstrated consistently good quality, with scores ranging from 7-9 (out of 9). Two studies [Heier et al. (18) 2017 and Mona et al. (19) 2015] scored 7 and were rated as "Good," while one study [Pena et al. (20) 2016] achieved the highest score of 9. The case-control studies were both rated as "Good," each scoring 7 out of 9 [Alakkad et al. (21) 2020, and Alwasity et al. (22) 2022]. These studies showed solid design and comparability, although information on non-response rates was not consistently available. Taken together, the overall quality of the included studies was satisfactory to very good, with most falling into the good to very good range. Despite some variability in reporting, particularly in the cross-sectional designs, the available evidence was methodologically sound and provided a reliable foundation for the conclusions of this meta-analysis. The quality assessment of this study can be seen in Table II.

Characteristics of the Included Studies

This review included 11 observational studies published between 2015 and 2024, conducted across various geographic regions including Egypt, Iran, Greece, Norway, India, Australia, Germany, Switzerland, and the United Kingdom. The study designs consisted of cross-sectional (n=6), cohort (n=3), and case-control (n=2) methodologies. Sample sizes ranged from 43 to 404 participants, with total study populations involving both children and adolescents with T1DM and healthy controls. The age range of participants across these studies varied from 5-19 years.

Most studies defined T1DM diagnosis according to World Health Organization or ADA criteria, typically involving elevated HbA1c (≥6.5%), fasting blood glucose ≥126 mg/dL, or random plasma glucose ≥200 mg/dL in symptomatic individuals. All included studies enrolled children and adolescents with a confirmed diagnosis of T1DM for at least 6-12 months, with several studies requiring diabetes durations of ≥5 years. All lipid profile measurements were conducted in a fasting state (≥8 hours) to ensure comparability.

The inclusion criteria across the studies typically included children and adolescents aged 5-19 years, a confirmed diagnosis of T1DM, a diabetes duration of ≥6-12 months, the availability of fasting lipid measurements, and the absence of acute illness at the time of inclusion. The use of lipid-lowering medications or other systemic therapies, the presence of comorbid conditions affecting lipid metabolism (e.g., hypothyroidism, nephrotic syndrome, chronic renal or liver disease, Down syndrome), acute complications of diabetes [e.g., diabetic ketoacidosis, severe hypoglycemia], the presence of microvascular complications, the use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or hormonal therapies, smoking, pregnancy, and/or obesity were exclusion criteria in some studies. The baseline characteristics of the included studies are presented in Table III.

Table II.I. Results of quality assessment using NOS for cross sectional studies

Cross sectional studies	Selection				Comparability	Outcomes		Total (max 10)	Assessment
	Representative of the sample	Sample size	Non respondents	Ascertainment of the exposure		Assessment of outcomes	Statistical test		
Parthasarathy et al. (12) 2015	*	*	*	**	**	**	*	10	Very good
Angelopoulou et al. (15) 2024	*	-	-	**	-	**	*	6	Satisfactory
Zabeen et al. (16) 2018	*	*	-	**	-	*	*	6	Satisfactory
Prado et al. (14) 2017	*	-	-	**	**	*	*	7	Good
Trigona et al. (17) 2019	*	*	-	**	-	*	*	6	Satisfactory
Wu et al. (13) 2021	*	*	*	**	**	**	*	10	Very good

*: One point, **: Two points, -: Zero points

Table II.II. Results of quality assessment using NOS for case control studies

Cross sectional studies	Selection					Outcomes			Total (Max 9)	Assessment
	Adequacy of case definition	Representativeness of the cases	Selection of controls	Definition of controls	Comparability	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate		
Alakkad et al. (21) 2020	*	*	*	*	*	*	*	-	7	Good
Alwasity et al. (22) 2022	*	*	*	*	*	*	*	-	7	Good

*: One point, **: Two points, -: Zero points

Table II.III. Results of quality assessment using NOS for cohort study studies

Cohort studies	Selection					Outcomes			Total (Max 9)	Assessment
	Representative of exposed cohort	Selection of exposed cohort	Ascertainment of exposure	Outcome not present at the start of study	Comparability	Assessment of outcomes	Length of follow-up	Adequacy of follow-up		
Heier et al. (18) 2017	*	*	*	*	*	*	*	-	7	Good
Mona et al. (19) 2015	*	*	*	*	*	*	*	-	7	Good
Peña et al. (20) 2016	*	*	*	*	**	*	*	*	9	Good

*: One point, **: Two points, -: Zero points
NOS: Newcastle-Ottawa Scale

Table 3. Summary and baseline characteristics of the included studies

Author	Country, Year	Study design	Sample size			Sample age (years)	TC (mg/dL) [Mean ± SD]	
			T1DM	Control	Total		T1DM	Control
Alakkad et al. (21)	Egypt, 2020	Case control	50	25	75	9-19	164.88±39.54	152.22±30.55
Alwasity et al. (22)	Iran, 2022	Case control	52	52	104	6-18	175±55	136±34
Angelopoulou et al. (15)	Greece, 2024	Cross sectional	56	56	112	9-13	166.33±32.72	154.67±15.98
Heier et al. (18)	Norway, 2017	Cohort	293	111	404	8-18	178±31	166±27
Mona et al. (19)	Egypt, 2015	Cohort	N/A	N/A	60	9-16	N/A	N/A
Parthasarathy et al. (12)	India, 2015	Cross sectional	80	54	134	5-17	157±33.5	153.5±27.7
Peña et al. (20)	Australia, 2016	Cohort	77	33	110	10-18	170±42.53	158.54±26.29
Prado et al. (14)	Berlin, 2017	Cross sectional	42	20	62	10-15	164.73±38.28	160.09±39.83
Trigona et al. (17)	Switzerland, 2019	Cross sectional	32	42	74	6-17	170.39±17.70	160±11.87
Wu et al. (13)	London, 2021	Cross sectional	48	19	67	12-17	155.84±31.32	121.42±25.9
Zabeen et al. (16)	India, 2018	Cross sectional	N/A	N/A	422	10-18	N/A	N/A

Table 3. Continued

Author	TG (mg/dL) [Mean ± SD]		HDL (mg/dL) [Mean ± SD]		LDL (mg/dL) [Mean ± SD]		Results
	T1DM	Control	T1DM	Control	T1DM	Control	
Alakkad et al. (21)	85.85±49.50	82.50±42.22	49.78±17.98	47.28±11.33	98.60±35.80	91.55±26.70	Not significant
Alwasity et al. (22)	140±35	74±25	59±19	53±15	93±51	68±30	Lipid abnormalities (TC, TG, LDL) were significantly higher in diabetic patients than in the control group
Angelopoulou et al. (15)	53.33±16.74	58.33±20.54	NA	NA	89.00±31.20	83±15.98	The median TC was significantly higher in diabetic children compared to the control group
Heier et al. (18)	62±44.80	62±44.80	70±15	66±15	97±27	89±27	Reduced HDL function in children and young adults with T1DM compared to the control subjects (p<0.001)
Mona et al. (19)	N/A	N/A	N/A	N/A	N/A	N/A	Dyslipidemia was significantly more frequent among T1DM children and adolescents compared to the control subjects (39/60, 65% vs. 11/39, 28.2%, p<0.001). The most frequent type of dyslipidemia was high LDL and low HDL in the dyslipidemic group
Parthasarathy et al. (12)	71±26.5	71.5±30.5	48.2±13.1	53.1±11.9	95.3±27.7	84.5±26.4	Children and adolescents with T1DM had an abnormal lipid compared to the control group
Peña et al. (20)	36.73±34.02	33.64±13.53	63.03±12.76	58±13.53	92.80±34.80	81.20±20.10	Not significant
Prado et al. (14)	32.86±12.76	38.67±7.34	43.31±10.44	40.21±10.44	102.86±38.28	101.70±46.01	Not significant
Trigona et al. (17)	46.05±20.61	50.58±10.88	56.45±6.6	54.37±5.64	104.7±15.59	96.67±10.68	Not significant
Wu et al. (13)	78.82±27.45	53.14±37.19	57.23±10.82	49.88±16.24	89.32±27.84	67.28±14.69	T1DM showed higher levels of TC, LDL, TG compared with the control group
Zabeen et al. (16)	N/A	N/A	N/A	N/A	N/A	N/A	More than half (65%) of the children and adolescents with T1DM had dyslipidemia

TC: Total cholesterol, TG: Triglycerides, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, SD: Standard deviation, T1DM: Type 1 diabetes mellitus, N/A: Not applicable

Meta-Analysis Results

Four lipid profile parameters were compared between T1DM and healthy children: TC, TG, HDL-C, and LDL-C. All four parameters were higher in T1DM children than in the control groups, with three showing statistical significance. TC levels were found to be significantly higher in T1DM children, with substantial heterogeneity observed [MD=14.31 (8.39, 20.43), p<0.00001; I^2=62%, p=0.007]. TG levels were also found to increase in T1DM children, but statistically insignificantly. These findings had the highest heterogeneity across all studies [MD=8.62 (-0.41, 21.25), p=0.18; I^2=94%, p=0.18]. In contrast, HDL-C were found to have significantly higher levels in T1DM children, with substantial heterogeneity observed [MD=2.66 (0.08, 5.23), p=0.04; I^2=56%, p=0.03]. LDL-C levels were found to be significantly higher in T1DM children, with the lowest heterogeneity across the studies [MD=10.99 (6.99, 14.76), p<0.00001; I^2=23%, p=0.24]. Forest plots are shown in Figures 2.1 to 2.4. Sensitivity analyses were performed in order to assess the influence of individual studies, and the overall findings remained robust. Funnel plots for each result are shown in Figures 2.5 to 2.8.

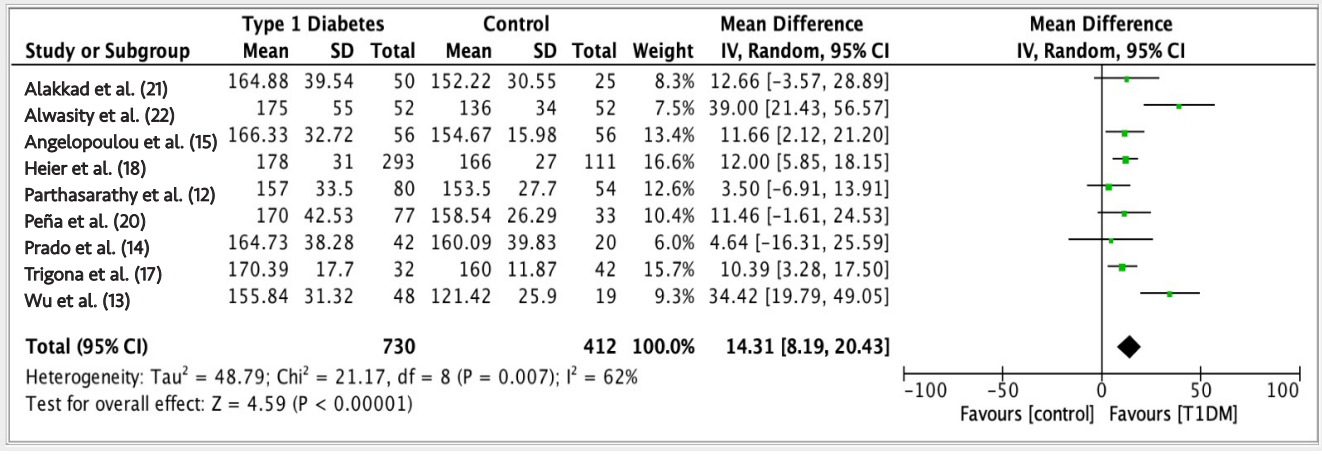

Figure 2.1. Meta-analysis forest plot of TC in children and adolescents with T1DM versus healthy controls
TC: Total cholesterol, SD: Standard deviation, T1DM: Type 1 diabetes mellitus, CI: Confidence interval

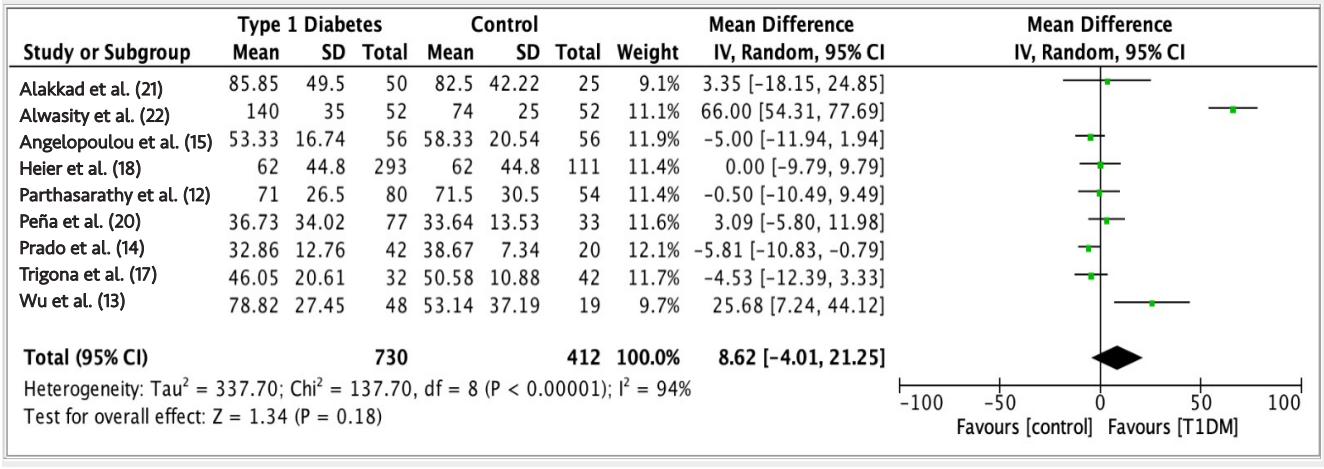

Figure 2.2. Meta-analysis forest plot of TG in children and adolescents with T1DM versus healthy controls
TG: Triglycerides, SD: Standard deviation, T1DM: Type 1 diabetes mellitus, CI: Confidence interval

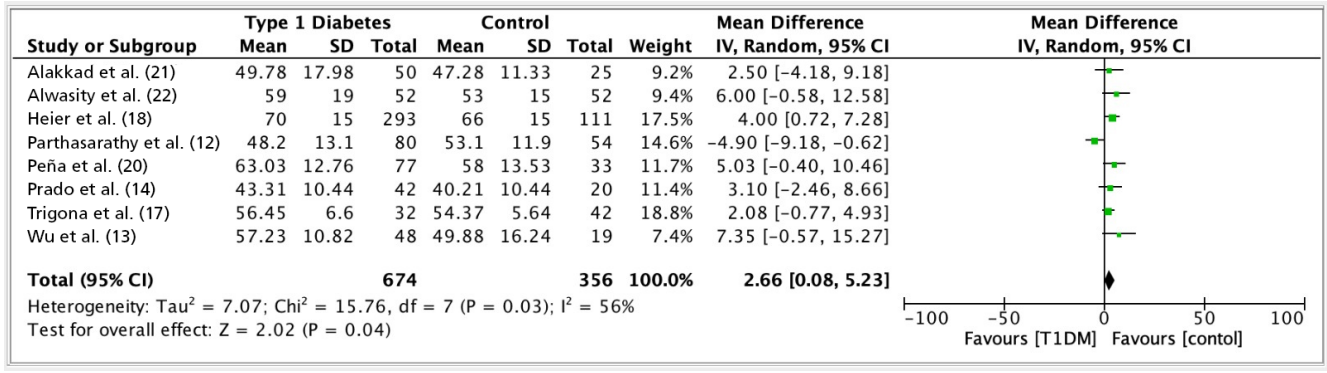

Figure 2.3. Meta-analysis forest plot of HDL-C in children and adolescents with T1DM versus healthy controls
HDL-C: High-density lipoprotein-cholesterol, SD: Standard deviation, T1DM: Type 1 diabetes mellitus, CI: Confidence interval

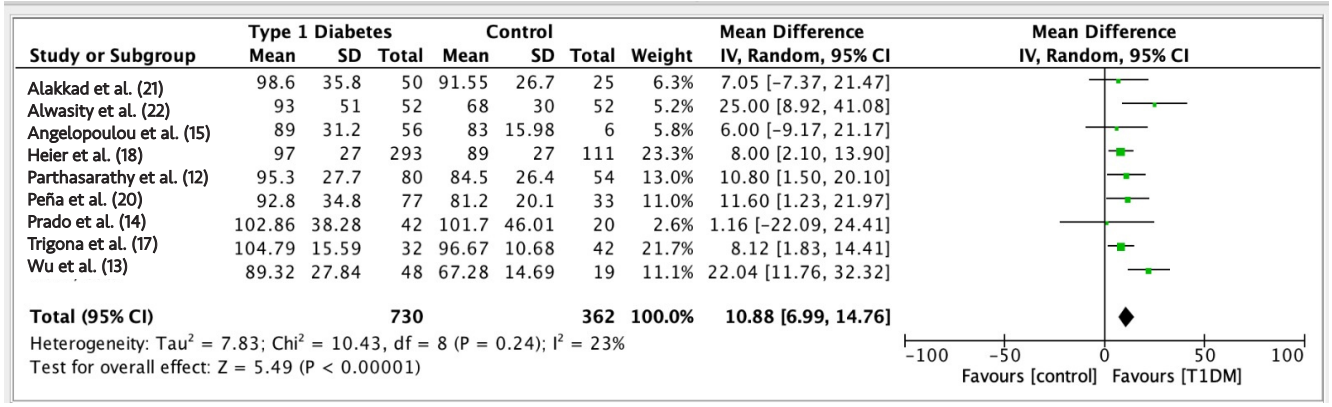

Figure 2.4. Meta-analysis forest plot of LDL-C in children and adolescents with T1DM versus healthy controls
LDL-C: Low-density lipoprotein-cholesterol, SD: Standard deviation, T1DM: Type 1 diabetes mellitus, CI: Confidence interval

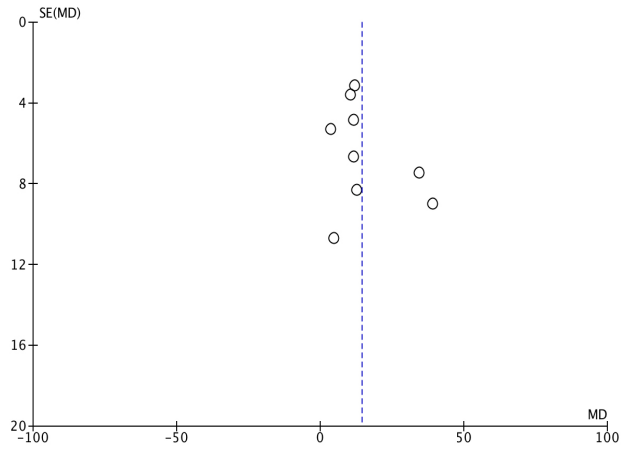

Figure 2.5. Funnel plot of TC in children and adolescents with T1DM versus healthy controls
TC: Total cholesterol, T1DM: Type 1 diabetes mellitus, MD: Mean difference

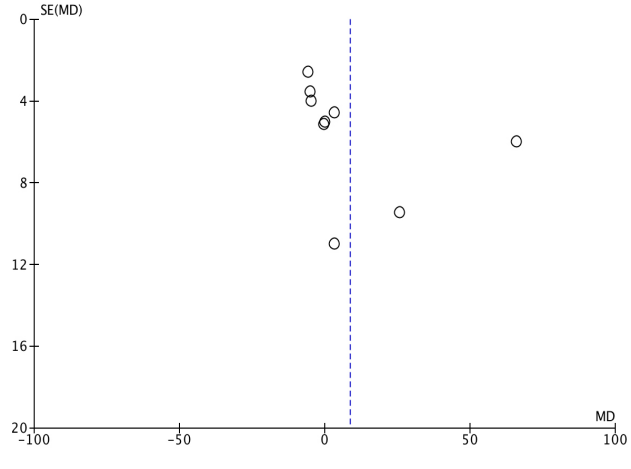

Figure 2.6. Funnel plot of TG in children and adolescents with T1DM versus healthy controls
TG: Triglycerides, T1DM: Type 1 diabetes mellitus, MD: Mean difference

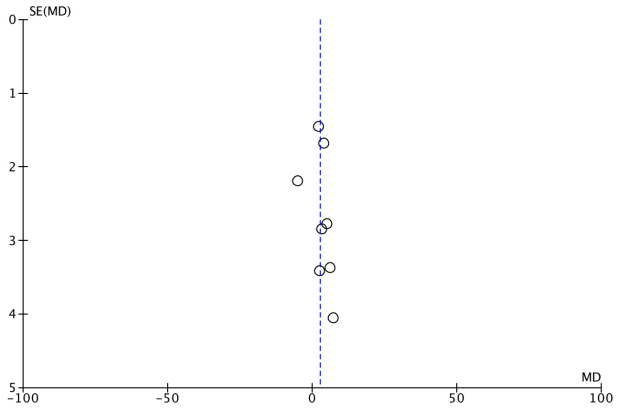

Figure 2.7. Funnel plot of HDL-C in children and adolescents with T1DM versus healthy controls
HDL-C: High-density lipoprotein-cholesterol, T1DM: Type 1 diabetes mellitus, MD: Mean difference

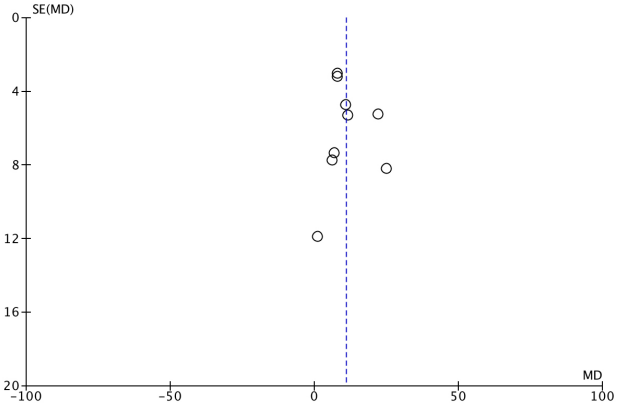

Figure 2.8. Funnel plot of LDL-C in children and adolescents with T1DM versus healthy controls
LDL-C: Low-density lipoprotein-cholesterol, T1DM: Type 1 diabetes mellitus, MD: Mean difference

Discussion

In this meta-analysis of the pediatric population with T1DM, we found that all four lipid parameters, namely TC, TG, HDL-C and LDL-C, were higher in pediatric T1DM patients compared with the control groups. Among these, TC, LDL-C and HDL-C were significantly elevated, while TG did not differ significantly and demonstrated the greatest between-study heterogeneity. These findings confirm that dyslipidemia in T1DM begins early in life, long before the onset of overt CVD, and so they support the importance of routine lipid monitoring from childhood (23,24).

The finding of elevated TC and TG levels in this study was in line with previous studies (25). Indeed, a study by Fagundes Melo et al. (24) 2014 found TC and TG were the main altered lipid parameters. A positive correlation was found between TC and TG with respect to age and the duration of disease (10). The level was reported to increase according to the time of the disease. Poor glycemic control is the key.

The elevation of LDL-C was statistically significant with the lowest heterogeneity across studies. LDL-C is the primary atherogenic lipoprotein, and its elevation in childhood carries lifelong implications, as cumulative LDL-C exposure is a major determinant of premature coronary artery disease (26). Mechanistically, chronic hyperglycemia induces non-enzymatic glycation of apoB-containing lipoproteins, reducing their clearance through LDL-C receptors and leading to prolonged circulation times. In addition, hepatic alterations associated with relative insulin deficiency or fluctuating replacement, such as increased VLDL secretion, further augment LDL-C burden (27,28). These mechanisms explain the robustness of LDL-C elevation in pediatric T1DM despite insulin therapy. Recent cohort data from Brazilian children and adolescents further confirm the high prevalence of LDL-C abnormalities in T1DM, highlighting their relevance in diverse populations (24).

The finding of significantly elevated HDL-C levels in T1DM requires cautious interpretation. Although traditionally considered protective, there is evidence that higher HDL-C in T1DM does not necessarily confer cardiovascular benefit. Studies in adolescents have shown that, despite normal-to-high HDL-C levels, markers of vascular dysfunction, such as impaired flow-mediated dilation remain present, suggesting that HDL particles in T1DM may be dysfunctional (29).

Our results suggest that LDL-C remains the most reliable and clinically actionable lipid marker in pediatric T1DM. Although higher HDL-C levels are traditionally considered protective, their role in this population is less clear, and potential dysfunction may limit the expected benefits. Clinicians should therefore interpret elevated HDL-C with caution, while recognizing that further studies are needed in order to clarify its clinical significance. These findings reinforce the need for early and routine dyslipidemia screening and aggressive LDL-C reduction strategies in pediatric T1DM, in line with contemporary guidelines, while also highlighting the limitations of standard lipid panels in capturing the complexity of dyslipidemia in this group. Future research should employ advanced lipidomic approaches, including nuclear magnetic resonance-based lipid profiling, in order to characterize qualitative alterations in lipoprotein subclasses and particle functionality. Such

high-resolution techniques may help elucidate the true nature of dyslipidemia in pediatric T1DM, which cannot be fully captured by conventional fasting lipid panels.

Study Limitations

This systematic review and meta-analysis provides an up-to-date synthesis of the available studies examining lipid profiles in children and adolescents with T1DM. Several limitations should be acknowledged. First, substantial heterogeneity was observed, particularly in triglyceride outcomes, likely reflecting differences in study design, sample size, disease duration, glycemic control, and insulin regimens. Second, as most of the included studies were observational, causal relationships between T1DM and lipid abnormalities could not be established. Third, data on important confounding factors such as pubertal status, body mass index, and socioeconomic background, which may have influenced lipid outcomes, were inconsistently reported. Finally, hereditary dyslipidemias, which are often polygenic and inherited in an autosomal dominant manner, may also have contributed to the variability in lipid profiles but they were not captured in this analysis.

Future Studies

Future research should prioritize standardized reporting of lipid outcomes, stratified by age, pubertal status, glycemic control, and insulin therapy, in order to reduce heterogeneity and allow more precise comparisons. Longitudinal cohort studies are needed to clarify temporal relationships between glycemic control, lipid abnormalities, and vascular outcomes. Randomized controlled trials evaluating the impact of early lipid-lowering interventions, including statins or lifestyle modifications, in pediatric T1DM would provide critical evidence to guide clinical practice. Additionally, more detailed investigations into HDL functionality, beyond conventional concentration-based measurements, are warranted in order to determine whether the observed increases in HDL-C truly confer cardiovascular protection in this population.

Conclusion

Children and adolescents with T1DM exhibit early dyslipidemia, with significantly higher TC, LDL-C, and HDL-C compared to healthy controls. The early onset of these abnormalities highlights a potential increased risk of CVD. However, given the observational nature of the included studies and variability across populations, these findings should be interpreted with caution. While HDL-C was found to be elevated, its functional implications remain uncertain and requires further investigation. Overall, our results support the importance of early lipid screening and careful LDL-C monitoring in pediatric T1DM, but future studies are needed in order to clarify the role of HDL and to establish evidence-based preventive strategies.

Ethics

Informed Consent: Informed consent was not required for this study because it is a systematic review and meta-analysis based on previously published data.

Footnotes

Authorship Contributions

Concept: M.O., J.C., T.D., Design: M.O., J.C., T.D., Data Collection or Processing: M.O., J.C., T.D., Analysis or Interpretation: M.O., J.C., T.D., Literature Search: M.O., J.C., T.D., Writing: M.O., J.C., T.D.

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Original Article

The Effects of Curcumin on Inflammatory and Oxidative Stress Biomarkers in Pediatric Patients on Regular Hemodialysis: A Randomized Placebo-controlled Trial

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ABSTRACT

Aim: Curcumin is a Chinese plant known for its anti-inflammatory, antioxidant, and anti-tumour activity. Its efficacy and safety in children with end-stage renal disease (ESRD) have not yet been established. This study aimed to evaluate curcumin's effects on inflammatory and oxidative stress biomarkers in children on regular hemodialysis (HD), and to investigate the effects of curcumin supplementation in children with ESRD undergoing regular HD.

Materials and Methods: This randomized, placebo-controlled, double-blind, pilot study was conducted on 28 children with ESRD on regular HD. This study was conducted between March 2022 and December 2022 at a pediatric HD unit. The patients were randomly assigned to either one gram of curcumin (the active group) or a starch-based placebo once a day (the placebo group), with both groups having 14 patients. Patient history, organ function assessment, tumor necrosis factor (TNF) as an inflammatory biomarker, malondialdehyde (MDA) as an oxidative stress factor, and coagulation biomarkers such as prothrombin time, partial thromboplastin time, and international normalized ratio were assessed and followed for 6 months.

Results: At 3 months, the curcumin group showed a significant reduction in MDA levels when compared to the placebo group (median 4.97 vs. 13.60 nmoL/mL, p=0.001). TNF-α levels had declined significantly within the curcumin group at 6 months (p=0.030). A significant decrease in uric acid levels was also observed at 3 months in the curcumin group (p=0.008). Hemoglobin levels showed a modest but statistically significant increase at 6 months (p=0.0232). No significant changes were noted in high sensitivity C-reactive protein, estimating glomerular filtration rate, creatinine, alanine transaminase, or coagulation parameters when compared to the placebo.

Conclusion: Curcumin may have potential benefits in pediatric patients on HD due to its considerable effects in decreasing inflammatory as well as oxidative stress biomarkers.

Keywords: Curcumin, chronic kidney diseases, hemodialysis, inflammatory biomarkers, pediatrics

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Introduction

Curcumin or Turmeric is a natural Chinese plant known for its anti-inflammatory, antioxidant, and anti-tumour activity. The chemical structure of curcumin is 1,7-bis (4-hydroxy-3-methoxyphenyl)-1, 6-heptadiene-3, 5-dione and it has shown substantial biological activity in treating several diseases (1). The root tuber of Curcuma Aromatica Salisb and the rhizome of Curcuma longa L. (Zingiberaceae) have proven efficacy in improving blood circulation and eradicating blood stasis (2,3). The anti-inflammatory activity of curcumin occurs by inhibiting the differentiation of myeloid protein 2-Toll-like receptor 4 co-receptor pathways, proinflammatory cytokines, such as tumour necrosis factor-alpha (TNF-alpha), nuclear factor kappa-B, and interleukin (IL)-1beta, or by the activation of peroxisome proliferator-activated receptor-gamma (4).

Pediatric chronic kidney disease (CKD) is an irreversible decline in renal function which progressively moves towards end-stage renal disease (ESRD) (5). Some European countries recommend hemodialysis (HD) for children older than 3 years (6). The global prevalence of CKD in children and adolescents has been increasing between 1990 to 2019. Furthermore, the age-standardized prevalence rate of CKD in children and adolescents increased globally, with an average annual percentage change of 0.46% (7). The prevalence of pediatric CKD ranges from 55-60 to 70-75 pmarp in some European countries (8). The global burden of CKD disease in Egyptian children under 18 years of age on HD increased by 2% in 2017 (9).

The efficacy and safety of curcumin in adult patients with renal diseases have been demonstrated and a significant impact on reducing the inflammatory and antioxidant biomarkers has been noted (10-14). However, there was a lack of literature on assessing its efficacy or safety in pediatric populations (12,15). Accordingly, this study aimed to evaluate the effects of curcumin supplements on inflammatory and oxidative stress biomarkers in pediatric ESRD patients who were being treated with regular HD.

Materials and Methods

Study Design and Participants

This randomized, placebo-controlled, double-blind, pilot study was conducted on 28 children with ESRD on regular HD. This study was conducted between March 2022 and December 2022 in a single Pediatric Hemodialysis Unit. Ethical approval for this study was obtained from the Research Ethics Committee of the Ain Shams University Faculty of Medicine (approval number: FMASU MD 181/2021, date: 15.09.2021). Written informed consent was obtained from the parents or caregivers of the participants after explaining the study aim and procedures, with their right to withdraw from this study at any time agreed upon in advance. Furthermore, the confidentiality of the patients' information obtained during this study was guaranteed.

The patients were randomly assigned to either a curcumin group (the active group) or a starch-based placebo group, each consisting of 15 patients, using a simple randomization technique performed by a free online random sample allocator available at GraphPad. Those patients with the following criteria were included: aged between 10 and 18 years of both genders, patients weighing at least 30 kilograms (as accepted for the dosing of available capsules of the supplement), patients with ESRD receiving regular HD for at least 6 months before enrollment, and patients whose parents or legal guardians agreed to sign a written informed consent for study participation. Patients were excluded if they had bleeding disorders, chronic liver disease, diabetes mellitus, or any autoimmune diseases. In addition, patients were excluded if they had been receiving corticosteroids, immunosuppressants, antioxidant supplements, including vitamin E, ascorbic acid, omega-3 fatty acids, or L-carnitine within a 3-month period before study enrollment. Those patients who demonstrated bleeding signs or symptoms as a side effect during the curcumin administration course were immediately excluded from this study and were followed up until full recovery.

Procedures and Assessment of Variables

The patients enrolled in this study had three HD sessions weekly, where each session lasted for 3-4 hours. Hemodiafiltration mode was used at least once a week when available. High-flux filters were used during the dialysis sessions. Regarding dialysis access, the majority of the enrolled patients either had fistulas in their arms or Mahurkar catheters. The patients in the curcumin group received a one-gram capsule of curcumin one time per day for 3 consecutive months. The curcumin was in the form of hard gelatin capsules manufactured by Puritan's Pride, Inc., Ronkonkoma, NY 11779 USA. The patients in the placebo group received hard gelatin capsules containing starch with the exact colour of the curcumin capsules provided by Jedco International Pharmaceuticals Company, Cairo, Egypt, once daily for 3 consecutive months. The patients were instructed not to include any curcumin in their food throughout the study period. The selected dose of 1 g/day was chosen as a conservative, well-tolerated regimen based

on previous adult studies on curcumin effectiveness and safety. Our patients were enrolled only if weighing ≥30 kg in order to ensure an appropriate mg/kg exposure range, while maintaining a once-daily schedule in order to support adherence and reduce pill burden (16).

Clinical and laboratory assessments were conducted at baseline, after three months of supplementation, and after six months (three months after supplementation ended) in order to evaluate the relatively longer effects of curcumin. Detailed history regarding previous and/or concurrent medications was collected so as to exclude any interactions with curcumin. Demographic data, presenting symptoms, age of onset, duration of the disease, the etiology of CKD, symptoms of volume overload, symptoms of uremia, heart failure, and any history of bleeding were also recorded. Clinical examination included general examination and blood pressure measurement. Signs of anemia, such as pallor, and tachycardia, and bleeding tendency, such as ecchymotic patches or bleeding from orifices, were recorded.

Laboratory investigations were performed by withdrawing 3-5 mL of venous blood samples once from all patients before the first HD session of the first week at baseline, at 3 months, and at 6 months in order to measure the following: complete blood picture, prothrombin time (PT), international normalized ratio (INR), and partial thromboplastin time (PTT). Urea, creatinine, uric acid, serum alanine transaminase (ALT), and albumin were all tested. The anti-oxidant malondialdehyde level (MDA-SunRed® Biotechnology Catalog No. 201-12-1372) was measured using ELISA. Levels of anti-inflammatory markers, including (TNF-alpha-SunRed® Biotechnology-Catalog No. 201-12-0083) and high sensitivity C-reactive protein (hs-CRP-SunRed® Biotechnology catalog no. 201-121-1806) were also measured by the ELISA technique. The estimated Glomerular Filtration Rate (eGFR) was calculated using the creatinine-based equation (17). All anti-inflammatory and anti-oxidant biomarkers were analyzed via the ELISA technique using a Thermo Scientific Multiscan FC photometer. Study progress and patient compliance were reviewed regularly during medication dispensing every two weeks. Blood samples were collected only when the patients were clinically stable and had been free of any signs or symptoms of acute infection in the week before sampling. The number of capsules was reviewed, and a supply for another two weeks was provided to the patients.

Statistical Analysis

Data were managed and analyzed using SPSS V.28 (IBM Corp., Armonk, NY, USA). Data were either summarized using means and standard deviations in quantitative data or using frequencies and percentages for categorical data. Comparisons between groups were carried out using the Student's t-test for normally distributed variables, while the Mann-Whitney U test was used for non-parametric variables. For comparisons of serial measurements within each group, repeated measures ANOVA was used in normally distributed quantitative variables, while non-parametric Friedman and Wilcoxon signed-rank tests were used for non-normally distributed quantitative variables. In order to compare categorical data, a chi-square (X_2) test was performed. The exact test was used instead when the expected frequency was less than 5. A p value of less than 0.05 was considered statistically significant.

Results

Demographics and Clinical Characteristics

The curcumin group had an equal gender distribution, whereas the placebo group consisted of 28.6% females (p=0.246). The average age was slightly lower in the curcumin group (p=0.070). At baseline, there were no significant differences in weight (p=0.131) or height (p=0.256). After three months of treatment, there there was a slight but statistically insignificant reduction in SBP among both groups (p=0.233). Diastolic blood pressure remained unchanged between the groups (p=1.0). Hemoglobin levels in the curcumin group exhibited a non-significant rise compared to a decrease in the placebo group (p=0.223). Atrophic kidneys and familial/metabolic nephritis were the most common etiologies of ESRD in the study population (Table I).

Anti-inflammatory and Anti-oxidant Biomarkers

TNF levels were comparable in both groups after three months (p=0.462). However, there was a drop in the median TNF levels in the placebo group from 114.90 ng/L to 61.30 ng/L. Similarly, hs-CRP levels were also comparable after three months (p=0.061). A significant decrease in MDA median in the curcumin group [4.97; interquartile range (IQR): 2.21-6.47] was observed, and was significantly less compared to the placebo group (13.60; IQR: 9.87-18.10) after 3 months (p=0.001). Uric acid levels were also comparable after three months (p=0.644 and 0.093, respectively) (Table II and Figure 1).

Kidney, Liver Functions, and Coagulation Profile

At baseline, kidney functions, determined by eGFR, creatinine, and urea, were comparable between the two groups (p>0.05). After 3 months of therapy, the difference

Table I. Demographic and clinical data at baseline and three months in the curcumin and placebo groups

		Curcumin n (%)/Mean (SD)	Placebo n (%)/Mean (SD)	p value
Sex	**Female**	7 (50.0)	4 (28.6)	0.246
	Male	7 (50.0)	10 (71.4)	
Age (years)		13.07±1.54	14.14±1.46	0.070
Weight (kg)		34.00±7.69	30.32±4.34	0.131
Height (cm)		136.43±9.01	132.29±9.86	0.256
SBP at baseline (mmHg)		125.71±21.38	129.64±12.78	0.560
SBP at 3 months (mmHg)		120.71±10.72	125.00±7.60	0.233
DBP at baseline (mmHg)		77.14±16.84	80.00±7.84	0.572
DBP at 3 months (mmHg)		75.71±10.16	75.71±8.52	1
Hb at baseline (gm/dL)		8.89±1.49	8.97±1.80	0.892
Hb at 3 months (gm/dL)		9.29±1.35	8.57±1.69	0.223
Etiology				
Focal segmental glomerulosclerosis		1 (3.6)	1 (3.6)	
Rapidly progressive glomerulonephritis		1 (3.6)	0 (0.0)	
Lupus nephritis		0 (0.0)	1 (3.6)	
Familial/metabolic nephritis		3 (10.7)	4 (14.3)	
Obstructive uropathy		1 (3.6)	0 (0.0)	
Reflux nephropathy		0 (0.0)	1 (3.6)	
Hemolytic uremic syndrome		0 (0.0)	1 (3.6)	
Interstitial nephritis		0 (0.0)	2 (7.1)	
Atrophic kidney		7 (25.0)	4 (14.3)	
Unknown		1 (3.6)	0 (0.0)	

p value of <0.05 was considered statistically significant
SBP: Systolic blood pressure, DBP: Diastolic blood pressure, Hb: Hemoglobin, kg: Kilograms, cm: Centimetres

Table II. Comparison of anti-inflammatory, anti-oxidant biomarkers, and kidney functions between the curcumin and placebo groups

Anti-inflammatory and anti-oxidant biomarkers		Curcumin Median (IQR)/Mean ± SD	Placebo Median (IQR)/Mean ± SD	p value
TNF (ng/L)	**At baseline**	59.20 (52.00-69.50)	114.90 (61.50-133.50)	0.280
	At 3 months	59.01 (47.70-74.90)	61.30 (54.81-166.05)	0.462
hs-CRP (mg/L)	**At baseline**	2.13 (1.24-2.60)	4.00 (2.28-4.74)	0.076
	At 3 months	1.77 (0.92-3.74)	2.95 (1.78-18.00)	0.061
MDA (nmoL/mL)	**At baseline**	10.58 (9.26-14.47)	9.90 (7.18-13.40)	0.603
	At 3 months	4.97 (2.21-6.47)	13.60 (9.87-18.10)	0.001*
Uric acid (mg/dL)	**At baseline**	10.23±2.50	9.86±1.61	0.644
	At 3 months	8.17±2.47	9.50±1.43	0.093

*p value of <0.05 was considered statistically significant
TNF: Tumour necrotizing factor, hs-CRP: High sensitivity C-reactive protein, MDA: Malondialdehyde, IQR: Interquartile range

in kidney function remained insignificant. There was an insignificant difference in liver functions (ALT and albumin) at baseline (p=0.224 and 0.874, respectively) and after three months (p=0.064 and 0.937, respectively). Coagulation profiles, represented by PT, PTT, and INR, were within normal ranges and comparable in both groups at baselines and after three months of therapy (Table III).

Anti-inflammatory and Anti-oxidants in The Curcumin Group Over Time

There were no significant changes in TNF levels from baseline to 3 months (p=0.683); however, a significant decrease in median TNF levels was observed after 6 months, compared to the baseline levels (p=0.030). There was a significant decrease in the median MDA levels detected after 3 months (p=0.004) and 6 months (p=0.026). In contrast, no significant changes in hs-CRP levels were observed over the study period in the curcumin group (p=0.778 and 0.638, respectively). Mean uric acid at baseline was 10.23 (±2.50) compared to 8.17 (±2.47) after 3 months in the curcumin group (p=0.008) (Table IV).

Kidney, Liver Functions, and Coagulation Profile in The Curcumin Group Over Time

In those patients receiving curcumin, Hb levels significantly improved from baseline to 3 months (p=0.063) and at 6 months (p=0.0232). Regarding kidney functions, eGFR, urea, and creatinine levels were comparable across all timepoints. There were no significant changes in liver function tests at 3 months and at 6 months, including ALT (p=0.932 and 1.000, respectively) and albumin (p=0.420 and 0.724, respectively). Coagulation parameters (PT, PTT, and INR) also remained within normal ranges with no significant changes (Table V).

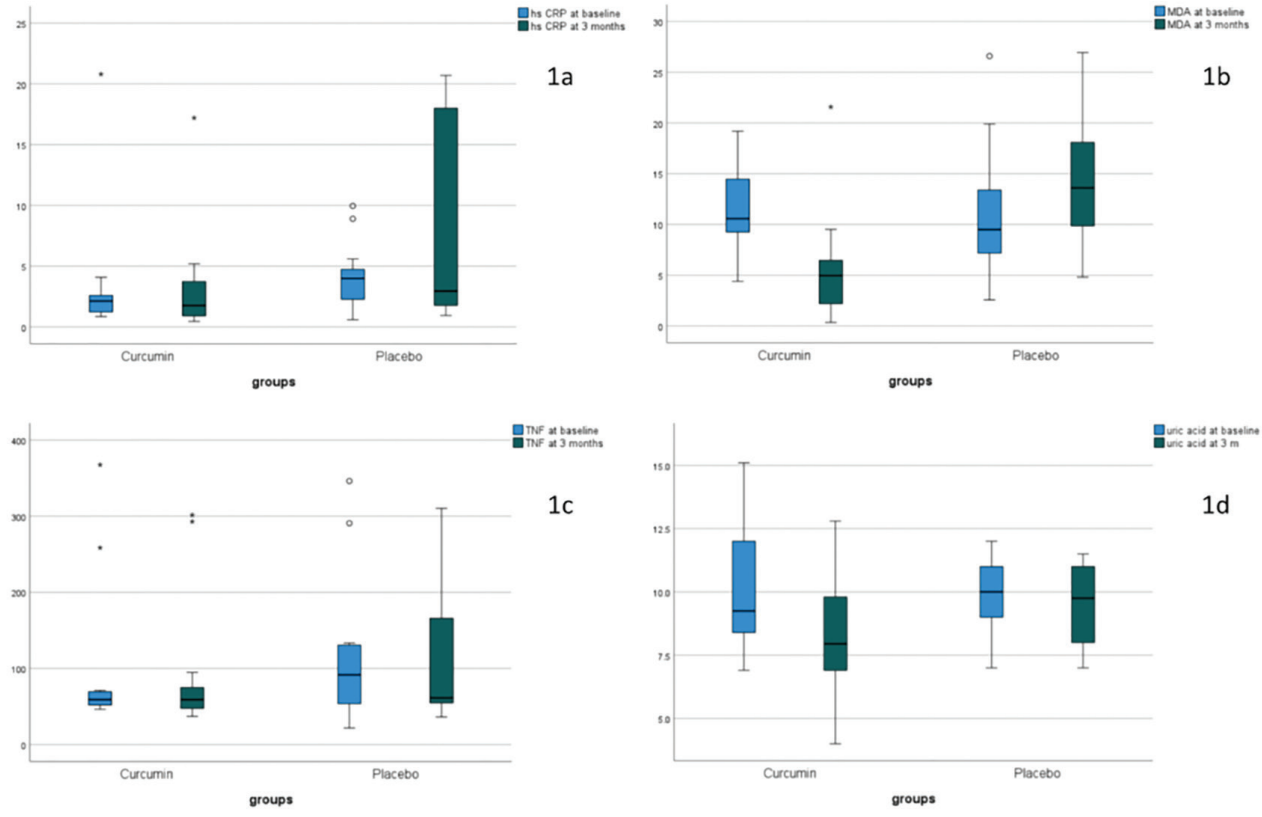

Figure 1. Box plot of anti-oxidant and anti-inflammatory biomarkers in the curcumin versus placebo groups at baseline and after 3 months. **1a)** Box plot of hs-CRP in the curcumin group versus the placebo group at baseline and after 3 months of supplementation (p=0.061), **1b)** Box plot of MDA in the curcumin group versus placebo group at baseline and after 3 months of supplementation (p=0.001), **1c)** Box plot of TNF-alpha in the curcumin group versus placebo group at baseline and after 3 months of supplementation (p=0.462), **1d)** Box plot of uric acid in the curcumin group versus the placebo group at baseline and after 3 months of supplementation (p=0.093)
hs-CRP: High sensitivity C-reactive protein, MDA: Malondialdehyde, TNF: Tumour necrotizing factor

Table III. Comparison of kidney, liver functions, and coagulation parameters between both groups

		Curcumin Mean ± SD	Placebo Mean ± SD	p value
eGFR (mL/min/1.73 m²)	**At baseline**	5.46±0.83	5.29±1.06	0.623
	At 3 months	5.60±0.96	5.49±1.34	0.798
Creatinine (mg/dL)	**At baseline**	10.07±1.39	9.89±1.83	0.765
	At 3 months	9.59±1.33	9.28±2.01	0.630
Urea (mg/dL)	**At baseline**	157.43±38.14	133.64±34.57	0.096
	At 3 months	142.71±33.24	139.07±34.43	0.778
ALT	**At baseline**	31.50±1.95	30.57±1.99	0.224
	At 3 months	32.07±1.86	30.71±1.86	0.064
Albumin (gm/dL)	**At baseline**	4.23±0.39	4.25±0.31	0.874
	At 3 months	4.31±0.53	4.29±0.41	0.937
PT (sec)	**At baseline**	12.94±0.95	12.71±0.81	0.486
	At 3 months	12.41±0.71	12.83±0.81	0.155
PTT (sec)	**At baseline**	34.35±2.70	33.30±3.43	0.376
	At 3 months	34.31±2.18	33.13±2.89	0.231
INR	**At baseline**	1.05±0.07	1.04±0.05	0.520
	At 3 months	1.04±0.05	1.05±0.07	0.520

eGFR: estimated glomerular filtration rate; ALT: alanine transaminase; PT: Prothrombin time; PTT: partial thromboplastin time; INR: international normalized ratio; p value of <0.05 was considered statistically significant

Table IV. Anti-inflammatory and anti-oxidant biomarkers throughout study duration in the curcumin group

	Baseline Median (IQR)/Mean ± SD	3 months Median (IQR)/Mean ± SD	6 months Median (IQR)	p1	p2
TNF (ng/L)	59.20 (52.0-69.5)	59.01 (47.7-74.90)	53.17 (41.2-67.1)	0.683	0.030*
hs-CRP (mg/L)	2.13 (1.24-2.60)	1.77 (0.92-3.74)	2.08 (0.72-2.34)	0.778	0.638
MDA (nmol/mL)	10.58 (9.26-14.47)	4.97 (2.21-6.47)	5.97 (3.60-6.90)	0.004*	0.026*
Uric acid (mg/dL)	10.23±2.50	8.17±2.47	-	0.008*	-

P1 value between baseline and 3 months, P2 value between baseline and 6 months. *A p value less than 0.05 was considered statistically significant
TNF: Tumour necrotizing factor, hs-CRP: High sensitivity C-reactive protein, MDA: Malondialdehyde, Hb: Hemoglobin

Table V. Comparison of kidney, liver functions, and coagulation parameters over time in the curcumin group

	Baseline Mean±SD	3 months Mean±SD	6 months Mean±SD	p1	p2
Hb (g/dL)	8.89±1.49	9.29±1.35	9.17±1.48	0.063	0.0232*
eGFR (mL/min/1.73m²)	5.46±0.83	5.60±0.96	5.56±0.88	1	1
Urea (mg/dL)	157.43±38.14	142.71±33.24	143.21±19.57	0.055	0.16
Creatinine (mg/dL)	10.07±1.39	9.95±1.33	9.94±1.67	0.189	0.763
Albumin (g/dL)	4.23±0.39	4.31±0.53	4.25±0.40	0.420	0.724
ALT (U/L)	31.50±1.95	32.07±1.86	31.57±1.95	0.932	1
PT (Sec)	12.94±0.95	12.41±0.71	12.75±0.72	0.298	0.639
PTT (Sec)	34.35±2.70	34.31±2.18	34.56±0.40	1	1
INR	1.05±0.07	1.04±0.05	1.04±0.05	1	1

Wilcoxon signed rank test. P1 value between baseline and 3 months, P2 value between baseline and 6 months. *A p value of <0.05 was considered statistically significant
eGFR: Estimated glomerular filtration rate, ALT: Alanine transaminase, PT: Prothrombin time, PTT: Partial thromboplastin time, INR: International normalized ratio

Discussion

Evidence from *in vitro* and *in vivo* studies, and clinical trials has shown probable beneficial effects of curcumin in various chronic diseases, including arthritis, pancreatitis, inflammatory bowel disease, chronic anterior uveitis, and tumors (18), diabetes mellitus (19), and CKD (10). This study assessed the effects of curcumin on inflammatory, hematological, and oxidative stress factors, as well as organ function. Our study revealed a significant decrease in MDA in the curcumin group when compared to the placebo group after 3 months of supplementation. Moreover, a significant decrease in TNF after 6 months from baseline assessment was detected. Furthermore, there was a significant decrease in MDA detected after 3 months and 6 months from baseline, as well as in uric acid, among those patients who were on one gram of curcumin per day for 3 months.

Among the fundamental biomarkers released during the inflammatory process in CKD are CRP, IL-6, IL-1, and TNF-α, which directly correlate with CKD progression (20). Our study revealed a significant reduction in TNF by the end of the study. Likewise, previous studies have linked curcumin administration with blocking the initiation of TNF, inhibiting the activation of necrotic factor (NF-κB), as well as hindering cell signaling triggered by TNF in various cell types (21,22). In line with this, curcumin significantly decreased TNF levels by 4.69 pg/mL (CI: -7.10, -2.28, $p<0.001$), as revealed by one meta-analysis, which was found to be correlated with the severity of CKD (23).

Furthermore, our study demonstrated a significant decrease in MDA detected after 3 months and after 6 months. Similarly, a meta-analysis revealed a significant decline in MDA levels in various chronic diseases at curcuminoid doses above 600 mg/d (24). One study, a rat model of chronic obstructive pulmonary disease, revealed that curcumin could reduce oxidative stress through a reduction in MDA and increased production of glutathione peroxidase, superoxide dismutase, and catalase in skeletal muscle mitochondria.

Healthy children typically have plasma MDA levels ranging from 1.49 to 5.87 nmoL/mL (25-27). Our study demonstrated substantially higher baseline levels of MDA (median =10.58 and 9.90 nmoL/mL in the curcumin and placebo groups, respectively). Similarly, reported serum TNF-α levels range from 32.81 to 68.27 ng/L in healthy children (28). Our study showed high TNF-α in children on HD (median =59.20 and 114.90 pg/mL in the curcumin and placebo groups, respectively), supporting the presence of oxidative stress and systemic inflammation among children with ESRD on regular hemodialysis. These comparisons support the pathophysiological burden in this population and the rationale for evaluating anti-inflammatory and antioxidant interventions such as curcumin.

Several studies have demonstrated the efficacy of curcumin in reducing serum levels of creatinine and improving renal function as a result of reactive oxygen species (ROS) inhibition (29-31). ROS are released in diabetic kidney diseases (32), renal oxidative stress (33), and ischemic renal perfusion (34) and these were found to be inhibited by curcumin. Similarly, clinical trials showed curcumin inhibiting xanthine oxidase expression, which triggers uric acid induction in CKD patients during oxidative stress flares (35,36). In our study, curcumin did not impact creatinine levels, albumin, or other kidney functions. However, uric acid significantly decreased after 3 months of therapy. Although trials assessing the efficacy of curcumin on uric acid in patients with renal disorders are lacking, curcumin nanoparticles demonstrated a significant reduction in ankle swelling and uric acid concentrations in mice with uric acid nephropathy (37). In patients with non-alcoholic fatty liver disease, curcumin was found to lower uric acid levels after 8 weeks of treatment ($p<0.001$) (38).

In addition, curcumin upregulated messenger ribonucleic acid (mRNA) and protein expression of the sirtuin family (39), which led to an upsurge in the expression of peroxidase proliferator-activated receptor gamma coactivator 1α randomized clinical trials and lowered the production of ROS (40). Many studies highlighted the anticoagulant effect of curcumin (41,42). One study demonstrated a significant increase in activated partial thromboplastin time and prothrombin time, and inhibition of thrombin and FXa generation (41). Another study revealed an upsurge in protein C levels and partial thromboplastin time levels (42). However, our study did not reveal any significant differences regarding these factors when compared to the placebo.

CRP released during CKD has been associated with erythropoietin resistance, malnutrition, cardiovascular diseases, and mortality (43). Several trials have demonstrated the strong impact of curcumin in inhibiting inflammatory mediators, including hs-CRP (3,15,44-46). One trial revealed that 2.5 grams of curcumin, 3 times a week for 12 weeks, decreased mRNA release of hs-CRP in adult patients undergoing HD (47). In contrast, another study revealed that one gram of curcumin daily for 12 weeks was not enough to achieve an effect on oxidative stress biomarkers such as hs-CRP in HD patients (48), which is in line with our study results where comparing hs-CRP levels in both groups

showed a statistically insignificant decrease after 3 months of therapy. This insignificant finding regarding curcumin in reducing hs-CRP could be due to the low doses of curcumin used in the current study.

Curcumin bioavailability is generally low, and pharmacokinetics could be impacted by interindividual variability, including ethnicity, gender, and the age of patients. Previous multi-ethnic studies in adults showed the impact of age-related disorders on curcumin absorption, distribution, metabolism, and excretion (49,50). Gender has also been suggested to have an influence on curcumin levels, where healthy females were found to have up to 2.1 times higher plasma levels when compared to males (51). However, data related to curcumin bioavailability in pediatric patients with renal disorders or ESRDs remain limited and require future attention and studies. Although no major adverse events were observed in this study, the safety of curcumin in children with ESRD should be further investigated due to its potential interactions with anticoagulants, its effects on platelet function, and its influence on drug metabolism (52). Larger, multicenter studies with extended follow-up durations are needed in order to fully assess its safety before clinical use in this patient population can be recommended.

Study Limitations

This study had some limitations. The sample size is considered to be relatively small to be able to generalize this study's outcomes and draw definitive conclusions. Additionally, this study could not evaluate different responses associated with dose escalation. Those patients receiving antioxidant supplements were excluded at enrollment, and the participating patients were instructed to avoid taking them during the study period. However, it is difficult to ensure that participants did not consume other dietary or over-the-counter antioxidant products. This study also lacked long-term follow-up to assess post-discharge outcomes and any possible later complications. Future studies should focus on larger, multicenter trials with standardized protocols and longer durations in order to better understand the impact of curcumin in ESRD children receiving hemodialysis.

Conclusion

Curcumin may have an anti-inflammatory and antioxidant effect in pediatric patients receiving HD. Future large-scale studies are warranted in order to assess the effective dose, possible interactions, as well as any potential variabilities between HD patients which may affect curcumin efficacy.

Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from the Research Ethics Committee of the Ain Shams University Faculty of Medicine (approval number: FMASU MD 181/2021, date: 15/09/2021).

Informed Consent: A written informed consent was obtained from the parents or caregivers of participants after explaining the study aim and procedures, with their right to withdraw from the study at any time.

Footnotes

Authorship Contributions

Concept: A.H.H., I.M.N.E., S.M.I., S.M.Z., I.Z.E., Design: A.H.H., I.M.N.E., S.M.I., S.M.Z., I.Z.E., Data Collection or Processing: A.H.H., I.M.N.E., S.M.I., S.M.Z., I.Z.E., Analysis or Interpretation: A.H.H., I.Z.E., Literature Search: A.H.H., I.M.N.E., S.M.I., S.M.Z., I.Z.E., Writing: A.H.H., I.M.N.E., S.M.I., S.M.Z., I.Z.E.

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Original Article

Vaccine Hesitancy Regarding Childhood Vaccinations Among Parents

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ABSTRACT

Aim: In Türkiye, vaccine hesitancy has been increasing, with a growing number of parents refusing childhood vaccinations. Understanding the underlying factors of this issue is essential for designing effective interventions. This study aimed to investigate the reasons underlying childhood vaccine hesitancy among parents in Antalya, Türkiye.

Materials and Methods: This cross-sectional study included 172 parents in Antalya who refused at least one childhood vaccine in 2023. Data were collected using a structured questionnaire administered via phone interviews. Descriptive statistics and chi-square tests were performed. In addition, responses to open-ended questions about their reasons for refusal were grouped thematically.

Results: Among the participants, 59.9% had a university-level education, and 69.8% of respondents were mothers. The most common themes influencing hesitancy included perceived adverse events following vaccination, misinformation from social media, and distrust in vaccine contents. A significant proportion (87.8%) stated that the coronavirus disease-2019 (COVID-19) period negatively affected their trust in vaccines. Mothers were significantly more resistant to positive change compared to fathers (p=0.015). Parents aged 34 years and younger were also more resistant to positive change than older parents (p=0.044).

Conclusion: This study highlights that vaccine hesitancy in Antalya is strongly influenced by misinterpretations of adverse events, misinformation originating from social media, and distrust regarding vaccine components. Targeted education on vaccine safety, efforts to address COVID-19 related misinformation, and greater involvement of the fathers in vaccination decisions may help reduce hesitancy. Importantly, while social media is a major driver of misinformation, it may also serve as a powerful tool to strengthen public health communication and awareness.

Keywords: Vaccines, vaccination, vaccine hesitancy, parents, child health, COVID-19, social media

Introduction

Immunization services are essential primary healthcare practices implemented to protect infants, children, and adults from infectious diseases by vaccinating them before the period in which their risk of infection is highest (1). Immunization efforts have prevented 154 million deaths worldwide over the past 50 years. Among those whose lives were saved through immunization, 101 million were infants, and vaccines represent the most important health service for infant health (2). In Türkiye, the primary objective of the Expanded Program on Immunization is to ensure that every newborn is immunized in accordance with the national vaccination schedule against pertussis, diphtheria, tetanus, measles, rubella, mumps, tuberculosis, poliomyelitis, hepatitis B, *haemophilus influenzae* type B, pneumococcus, hepatitis A, and varicella (1).

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The World Health Organization (WHO) defines vaccine hesitancy as "a delay in acceptance or refusal of safe vaccines despite the availability of vaccination services." Vaccine hesitancy is a complex concept and varies depending on time, location, and vaccine type (3). It is an increasingly important public health problem; indeed, in 2019, the WHO listed vaccine hesitancy among the ten global threats to health (4). In Türkiye as well, vaccine hesitancy appears to be rising as a public health concern (5). While the global rate of vaccine hesitancy has been estimated to be 21.1%, this rate has been calculated as being 13% in Türkiye (6).

Antalya, the fifth-largest city in Türkiye, is home to approximately 500,000 children aged 13 years and under. The aim of this study was to identify the reasons for vaccine hesitancy among parents in Antalya and to shed light on possible interventions in order to address this issue.

Materials and Methods

This cross-sectional study included all parents in Antalya in 2023 who refused at least one vaccine dose. In 2023, a total of 971 parents refused at least one childhood vaccine. The sample size was calculated using G*Power; assuming a medium effect size, an alpha error of 0.05, and a statistical power of 0.90, the minimum required sample size was determined to be 143. From among the 971 parents who refused at least one vaccine dose, 216 parents were randomly selected to account for the possibility of refusal to participate.

These parents were contacted using the phone numbers recorded in the national health information systems. It was not known beforehand whether the phone number belonged to the mother or the father. The first number was called initially, and if necessary, the second number was attempted. The parent reached by phone was first informed about the study, and if they agreed to participate, the questions in the structured questionnaire developed by the researchers were administered.

Ethical approval for this study was obtained from the Clinical Research Ethics Committee of Antalya Training and Research Hospital (approval number: 19/13, date: 05.12.2024).

Statistical Analysis

Data were analyzed using IBM SPSS Statistics for Windows, Version 27.0 (IBM Corp., Armonk, NY, USA). Descriptive findings are presented as numbers, percentages, means, and medians. The chi-square test was used for group comparisons, and $p<0.05$ was considered statistically significant. In addition, open-ended questions about the reasons for vaccine hesitancy were asked, and the responses were coded and grouped thematically. The thematic grouping was first conducted independently by the researchers and then finalized together.

Results

A total of 216 parents were initially included in this study. This study was completed with 172 parents. Among the 44 parents who did not participate, 23 (52.3%) could not be reached, 10 (22.7%) refused participation, 7 (15.9%) had initially refused vaccination but were later found to have completed the vaccinations, 2 (4.5%) had language barriers, and 2 (4.5%) had other reasons for non-participation.

Among the children included in this study, 72 (41.9%) were girls and 100 (58.1%) were boys. A total of 169 children (98.3%) were citizens of the Republic of Türkiye, while 2 (1.2%) were citizens of Russia and 1 (0.6%) was a citizen of Germany. The parent interviewed was the mother in 69.8% of cases. In total, 59.9% of the parents had completed a university degree or higher. More than half of the parents had one or two children. The median age of the children was 39.5 months, while the median age of the parents was 35 years (Table I).

Table I. Descriptive characteristics of children and parents

	n	%
Child's gender		
Female	72	41.9
Male	100	58.1
Total	172	100.0
Child's nationality		
Republic of Türkiye	169	98.3
Russia	2	1.2
Germany	1	0.6
Total	172	100.0
Interviewed parent		
Mother	120	69.8
Father	52	30.2
Total	172	100.0
Parental education level		
Literate	1	0.6
Primary school	12	7.0
Middle school	16	9.3
High school	40	23.3
University or above	103	59.9
Total	172	100.0

Table I. Continued		
	n	**%**
Number of children		
1	48	27.9
2	63	36.6
3	49	28.5
4	11	6.4
5	1	0.6
Total	172	100.0
Child's age (months)		
Mean (SD)	51.17 (37.01)	
Median	39.50	
Minimum	19.00	
Maximum	183.00	
IQR	35.75	
Parent's age		
Mean (SD)	35.35 (6.53)	
Median	35.00	
Minimum	22	
Maximum	58	
IQR	8	
SD: Standard deviation, IQR: Interquartile range		

Among the vaccines, the most frequently administered was the 3rd dose of the conjugated pneumococcal vaccine, followed by the 1st dose of the hepatitis B vaccine. The least frequently administered vaccine was the 2nd dose of the oral polio vaccine, followed by the 1st dose of the hepatitis A vaccine (Table II).

In addition, the number of children who received only the hepatitis B vaccine at birth (1st dose of hepatitis B) was 33 (19.2%), while the number of children who had received no vaccination at all was 46 (26.7%).

Table III presents the distribution of responses given to the questions regarding the reasons for vaccine refusal.

Among the responses to the question "Are there any vaccines you particularly do not trust, and if so, which ones?", the most common answer was "all vaccines"; the second most frequent was "combined vaccines", and the third was "COVID-19 vaccines" (Table IV).

The responses of parents who answered "Yes" to the question "Did your concerns about vaccines arise after listening to a particular person/share or after an event?" were categorized into thematic groups. The most frequently recurring theme was "incidents interpreted as adverse events following vaccination by parents" (Table V).

Table II. Vaccination status by vaccine type

Vaccine-dose	Administered (n/%)	Not administered (n/%)	Not due yet (n/%)	Postponed (n/%)	Total (n/%)
Hep B-1	123 (71.5)	49 (28.5)	-	-	172 (100.0)
Hep B-2	83 (48.3)	89 (51.7)	-	-	172 (100.0)
Hep B-3	62 (36.0)	110 (64.0)	-	-	172 (100.0)
BCG	62 (36.0)	110 (64.0)	-	-	172 (100.0)
DaBT-IPV-Hib-1	76 (44.2)	96 (55.8)	-	-	172 (100.0)
DaBT-IPV-Hib-2	67 (39.0)	105 (61.0)	-	-	172 (100.0)
DaBT-IPV-Hib-3	60 (34.9)	112 (65.1)	-	-	172 (100.0)
PCV-1	67 (39.0)	105 (61.0)	-	-	172 (100.0)
PCV-2	58 (33.7)	114 (66.3)	-	-	172 (100.0)
PCV-3	11 (78.6)	3 (21.4)	-	-	14 (100.0)
PCV booster	48 (27.9)	124 (72.1)	-	-	172 (100.0)
MMR-1	49 (28.5)	123 (71.5)	-	-	172 (100.0)
MMR-2	3 (1.7)	80 (46.5)	88 (51.2)	1 (0.6)	172 (100.0)
DaBT-IPV	2 (1.2)	76 (44.2)	93 (54.1)	1 (0.6)	172 (100.0)
OPV-1	53 (30.8)	119 (69.2)	-	-	172 (100.0)
OPV-2	31 (18.0)	141 (82.0)	-	-	172 (100.0)
Hep A-1	30 (18.6)	130 (80.7)	1 (0.6)	-	161 (100.0)
Hep A-2	22 (13.7)	126 (78.3)	11 (6.8)	2 (1.2)	161 (100.0)
Varicella	42 (26.1)	119 (73.9)	-	-	161 (100.0)
Td-booster	-	11 (6.4)	161 (93.6)	-	172 (100.0)

Table III. Responses to questions regarding reasons for vaccine refusal

Question	Yes (n/%)	No (n/%)	Unsure (n/%)
Do you think the contents of vaccines are safe?	16 (9.3)	140 (81.4)	16 (9.3)
Do you think vaccines are beneficial for your child's health?	19 (11.0)	125 (72.7)	28 (16.3)
Do you think vaccines are effective in preventing diseases?	31 (18.0)	117 (68.0)	24 (14.0)
Do you think vaccines are harmful for your child's health?	121 (70.8)	22 (12.9)	28 (16.4)
Are there any vaccines you particularly do not trust?	52 (30.2)	107 (62.2)	13 (7.6)
Do you trust healthcare professionals who recommend vaccination?	86 (50.6)	57 (33.5)	27 (15.9)
Do you trust politicians who recommend vaccination?	11 (6.6)	137 (82.5)	18 (10.8)
Were your religious beliefs influential in not vaccinating your child?	15 (8.8)	152 (89.4)	3 (1.8)
Has social media (Instagram, X, Facebook, etc.) increased your concerns about vaccines?	53 (31.0)	117 (68.4)	1 (0.6)
Did your concerns about vaccines arise after listening to a specific person/share or after an event?	61 (35.7)	108 (63.2)	2 (1.2)
Did COVID-19 vaccines negatively affect your trust in vaccines?	151 (87.8)	20 (11.6)	1 (0.6)
As mother and father, do you share the same opinion about not vaccinating?	157 (91.3)	13 (7.6)	2 (1.2)
If the unadministered vaccine was a Td booster dose, was it the child's decision not to be vaccinated?	3 (27.3)	8 (72.7)	0 (0.0)
Do you receive sufficient information about vaccines from healthcare professionals?	137 (79.7)	31 (18.0)	4 (2.3)
When you need information about vaccines, can you access healthcare professionals to ask questions?	160 (93.0)	8 (4.7)	4 (2.3)
Can your concerns about vaccines change positively?	41 (24.1)	116 (68.2)	13 (7.6)

Table IV. Vaccines that parents particularly distrust

Vaccine	Total number
All	37
Combined vaccines	6
COVID-19 vaccines	4
Vaccines under 1 year of age	3
Measles/MMR vaccine	3
Hepatitis vaccine	3
Tetanus vaccine	3
Varicella vaccine	2
Meningitis vaccine	1
Influenza vaccine	1
HPV vaccine	1
Rotavirus vaccine	1

COVID-19: Coronavirus disease-2019, MMR: Measles-mumps-rubella, HPV: Human papillomavirus

When the parents' answers to the question "Can your concerns about vaccines change positively?" were compared, it was found that mothers, when compared to fathers, statistically significantly more often answered "No" (p=0.015). When divided into two age groups, parents aged 34 and under were statistically significantly more likely to answer "No" when compared to older parents (p=0.044). Those parents whose child had received zero vaccines (i.e., refused all vaccines) were also statistically significantly more likely to answer "No" when compared to the others (p=0.005), while parental education levels did not create a significant difference (p=0.382) (Table VI).

Table V. Parents' responses to the open-ended question "Which event/person/post increased your concerns about vaccines?"

Theme	Total number of responses	Illustrative quotations
Incidents interpreted as adverse events following vaccination by parents	43	"Epilepsy was diagnosed after the combined vaccine administered to my daughter, who is now 8 years old, when she was 18 months old." (F, 36) "Cystic fibrosis developed after the first dose of hepatitis B." (F, 35) "In my first child, autism, valve laxity in the heart, and the prominence of arm veins occurred." (F, 44)
Research, books, articles, scientific sources	34	"I decided on vaccine refusal as a result of expert opinions and my own research." (F, 40) "I researched on the World Health Organization's website and decided not to vaccinate." (F, 54)
Influence of family and social contacts	17	"The neighbor's child contracted the disease despite being vaccinated." (F, 35) "My siblings are healthcare workers; I was influenced by what I heard from them and the people around me, and decided not to vaccinate." (M, 41)
Social media posts	14	"Social media increased my vaccine refusal." (F, 28) "Seeing children who died because of vaccines on social media influenced me." (F, 45)
COVID-19 related experiences	11	"After the COVID-19 vaccines, I lost my trust in vaccines." (F, 44) "COVID-19 vaccines helped us open our eyes more." (F, 22)
Vaccine contents	10	"Due to the mercury in vaccines, they create a perception to force people into vaccination; instead, I prefer cupping therapy." (M, 40)
Distrust in healthcare professionals and physicians	10	"Healthcare professionals are uneducated and cannot provide sufficient information about vaccines. Doctors buy diplomas from other countries." (M, 34)
Personal health experiences	9	"I have regrets from the past. I do not want to listen to healthcare professionals." (F, 39)
Anti-vaccine figures, sources, and conspiracy theories	6	"Yağmur İbiç, Sait Ercan, a professor from a university in Samsun." (M, 34) "I read Soner Yalçın's book Black Box. Rockefeller and Bill Gates cannot know my child's health better than I do." (M, 34)
Distrust in politicians and politics	4	"In general, shares about vaccines supported my vaccine refusal. Politicians do not create trust at all." (M, 46)
Preference for domestic vaccines/distrust in imported vaccines	3	"I do not trust vaccines imported from abroad." (F, 29) "If domestic vaccines are produced and proven reliable, my opinion may change positively." (M, 37)

COVID-19: Coronavirus disease-2019

Table VI. Comparison of parents based on response to the question: "Can your concerns about vaccines change positively?"

	Yes/unsure (n/%)	No (n/%)	Total (n/%)	p value
Parent				
Mother	31 (26.1)	88 (73.9)	119 (100.0)	p=0.015
Father	23 (45.1)	28 (54.9)	51 (100.0)	
Age of parent				
34 and under	21 (25.0)	63 (75.0)	84 (100.0)	p=0.044
35 and above	33 (38.4)	53 (61.6)	86 (100.0)	
Education of parent				
High school or lower	19 (27.9)	49 (72.1)	68 (100.0)	p=0.382
University degree or higher	35 (34.3)	67 (65.7)	102 (100.0)	
No vaccinations				
Yes	7 (15.2)	39 (94.8)	46 (100.0)	p=0.005
No	47 (37.9)	77 (62.1)	124 (100.0)	

Discussion

According to the findings of this research, the majority of participants did not consider vaccines to be safe, and a significant proportion stated that vaccines were harmful to their child's health. It was also determined that social media and the coronavirus disease-2019 (COVID-19) period increased parents' hesitations about vaccines. Incidents perceived as vaccine side effects were found to be the most common theme associated with vaccine hesitancy. It was further identified that the attitudes of female participants and younger participants regarding vaccine hesitancy were more resistant to change when compared to others.

The results of this study show that a considerable proportion of parents did not trust vaccines and believed that vaccines are harmful to their children's health. This finding is consistent with both previous studies conducted in Türkiye and international studies (5,7,8). A global systematic review and meta-analysis reported that distrust in vaccines and the belief that vaccine contents are harmful are among the most common reasons for vaccine hesitancy worldwide (9).

Through thematic analysis of the responses to the open-ended questions, the most frequently stated theme was "incidents interpreted as adverse events following vaccination by the participant." It is known that true adverse events following vaccination, as well as the misinterpretation of unrelated health conditions as vaccine side effects, contribute to vaccine hesitancy (10-12). However, this study demonstrated that parents had low levels of knowledge about vaccine side effects and considered certain health conditions, notably conditions which could not be caused by vaccines, as vaccine-related adverse effects. For example, one participant perceived their child's cystic fibrosis diagnosis as a vaccine side effect. Although the absence of any relationship between autism and vaccines has been consistently demonstrated (13,14), in this study, some parents still attributed their child's autism diagnosis to vaccines. Another study conducted in Türkiye similarly showed that parents interpreted health conditions not caused by vaccines as vaccine side effects (15). These findings highlight the importance of better informing parents about vaccine side effects. Preventing health conditions unrelated to vaccination from being perceived as side effects may reduce the proportion of parents who distrust vaccines or believe vaccine contents are harmful. In another study conducted in Türkiye, when healthcare workers were asked to propose solutions to vaccine hesitancy, the most common suggestion was "informing the public that most vaccine side effects are minor" (16).

In this study, parents were asked whether there were specific vaccines they particularly did not trust. The majority of participants stated that there was no specific vaccine they distrusted more than others. However, among those who did name particular vaccines, the most frequent responses were combined vaccines and COVID-19 vaccines. A study conducted in the United States similarly found that although most parents did not identify a specific vaccine they distrusted, combined vaccines were commonly believed to cause more side effects (8). Another study indicated that the belief that combined vaccines are harmful represents an increasing risk factor for vaccine hesitancy (17). Combined vaccines involve administering two or more vaccines in the same session. Combined vaccines enable timely immunization during the most vulnerable period of infancy and minimize the number of clinic visits needed. Thus, combined vaccines save time and cost and provide a less traumatic vaccination experience for the child. Moreover, combined vaccines have been shown to be as safe as single-dose vaccines (18). During parental education efforts, the safety of combined vaccines should be emphasized and misconceptions should be clarified.

Another prominent finding of this study was that the COVID-19 period and COVID-19 vaccines increased vaccine hesitancy. A total of 87.8% of participants stated that the COVID-19 period negatively affected their trust in vaccines. Similar findings have been reported in both national and international studies (19,20). The COVID-19 pandemic negatively affected public health practices both directly and indirectly. The unexpected and rapidly evolving nature of the pandemic, along with the infodemic which followed, negatively influenced many public health interventions, including immunization efforts. Therefore, correcting the misinformation which emerged during the COVID-19 period should be a priority for public education on immunization.

In today's digital age, the ways in which individuals access health information have also changed. While social media facilitates the flow of information, it also accelerates the spread of misinformation. In this study, a significant proportion of parents stated that social media negatively influenced their views on vaccines. The role of social media in increasing vaccine hesitancy has been repeatedly demonstrated (5,7,21). Although social media contributes to the spread of false or misleading information, its wide reach also offers an opportunity to enhance public knowledge and awareness of public health issues (22). Interestingly, parents

themselves also suggested that social media should be used as a tool to counter vaccine hesitancy (19,23).

The process of vaccine hesitancy, and the thoughts, attitudes, and behaviors of parents within this process, cannot be easily defined by strict boundaries. Individuals fall along a broad continuum between fully accepting all vaccines and completely rejecting them (24). It is important to provide accurate and clear information to individuals within this "gray zone." In this study, one-third of participants answered "Yes" or "Unsure" to the question "Can your concerns about vaccines change positively?". Male participants, when compared to female participants, and participants aged 35 and above, when compared to younger participants, were more open to positive change. The literature shows that vaccine hesitancy is more common among mothers and younger parents (8,25-27). The underlying reasons why mothers and younger parents exhibit more hesitancy and less openness to change should be further explored. The fathers' views regarding vaccine hesitancy were found to be more open to positive change. Including fathers in decisions related to child health and expanding "maternal and child health" to "parental and child health" may support efforts to improve public health outcomes.

Study Limitations

This study had several strengths. The sample size was relatively large and included both mothers and fathers, allowing for a broader understanding of parental perspectives on vaccine hesitancy. The random selection of the participants from all of those parents who refused at least one childhood vaccine in 2023 strengthened the representativeness of the findings. There were also limitations. As the data were collected through phone interviews, the number of questions had to be kept to a limit, which reduced the depth of information. In addition, the thematic analysis used in this study did not constitute a full qualitative research design but was instead applied in order to organize and group open-ended responses. Although the sample was large and randomly selected, its representativeness was limited to one province and did not reflect the entire country; therefore, larger and multi-center studies are needed in order to achieve national representativeness.

Conclusion

This study was conducted with 172 mothers and fathers who had refused at least one childhood vaccine. The majority of the participants stated that they did not trust vaccine contents and that vaccine side effects were the main reason for their hesitancy. Combined vaccines and COVID-19 vaccines were specifically mentioned as the vaccines they distrusted. The COVID-19 period and social media emerged as factors which increased vaccine hesitancy. Fathers, when compared with mothers, were found to be more open to positive changes regarding vaccine hesitancy.

Providing accurate information to the public about vaccine side effects, and addressing the misinformation and misconceptions which arose during the COVID-19 period are essential steps. The influence of social media can be reversed through proper use. Increasing the fathers' involvement in the decision-making process for child immunization may also help reduce vaccine hesitancy.

Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from the Clinical Research Ethics Committee of Antalya Training and Research Hospital (approval number: 19/13, date: 05.12.2024).

Informed Consent: All surgical procedures were performed with written informed consent from the legal guardians.

Footnotes

Authorship Contributions

Concept: A.G.T., H.N.Y., Ç.E.E., G.S., A.Ç., Y.U., S.Y., Ş.Y.A., Design: A.G.T., H.N.Y., Ç.E.E., G.S., A.Ç., Y.U., S.Y., Ş.Y.A., Data Collection or Processing: A.G.T., H.N.Y., Ç.E.E., G.S., A.Ç., Y.U., S.Y., Ş.Y.A., Analysis or Interpretation: A.G.T., H.N.Y., Ç.E.E., G.S., A.Ç., Y.U., S.Y., Ş.Y.A., Literature Search: A.G.T., H.N.Y., Ç.E.E., G.S., A.Ç., Y.U., S.Y., Ş.Y.A., Writing: A.G.T., H.N.Y., Ç.E.E., G.S., A.Ç., Y.U., S.Y., Ş.Y.A.

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Original Article

Disruption of Cerebral Autoregulation Prior to Extracorporeal Membrane Oxygenation Cannulation Contributes to Neurologic Injury in Pediatric Patients

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ABSTRACT

Aim: Neurologic complications are a significant cause of morbidity and mortality for children supported with extracorporeal membrane oxygenation (ECMO). Disruption of cerebral autoregulation (CAR) is associated with neurologic injury for children who require ECMO. The aim of this project was to identify the period of ECMO support which carries the greatest risk of neurologic injury.

Materials and Methods: This retrospective cohort study was conducted in children supported on venovenous or venoarterial ECMO between 2020 and 2023 at a single quaternary center. CAR was measured by assessing the wavelet transform coherence of mean arterial blood pressure and cerebral oximetry. Disruption of CAR was assessed by the time-period of ECMO support and then compared between patients in order to determine the association between impaired CAR and neurologic injury determined by neuroimaging.

Results: A total of 31 neonates and children who received ECMO support were included. Eleven children developed severe neurologic injury (35%). Peak disruption of CAR during the pre-cannulation period correlated with severe neurologic injury (R^2=0.14, p=0.04). Peak disruptions of CAR in the peri-cannulation (R^2=0.004, p=0.7) and post-cannulation periods (R^2=0.04, p=0.28) were not significant. There were no significant differences in laboratory values or anticoagulation between the groups. There were no differences in CAR disruption between the neonates and the children [18.4 (8.6-35) p=0.09] or for extracorporeal cardiopulmonary resuscitation with respect to the other indications for ECMO [17.5 (6.5-35), p=0.5].

Conclusion: Impaired CAR in the 24 hours preceding ECMO support may represent the most critical window for neuroprotection in pediatric ECMO.

Keywords: Extracorporeal membrane oxygenation, neurologic injury, pediatrics, cerebral autoregulation

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Introduction

Extracorporeal membrane oxygenation (ECMO) is a form of cardiopulmonary bypass which provides temporary support to critically ill children whose illness is progressing despite maximal conventional therapies. Advances in ECMO have allowed more children to survive an otherwise fatal illness. However, neurologic injury remains a significant cause of morbidity and mortality. Even with the best care, 15-35% of patients surviving ECMO experience significant neurologic injury (1-7).

The risk factors for neurologic injury are varied and multifactorial. Recent work has identified an association between disruptions in cerebral autoregulation (CAR) and neurologic injury for patients on ECMO (8-10). In a healthy child, the brain maintains stable blood flow over a wide range of blood pressures through a physiologic control system known as CAR. Multiple factors of critical illnesses such as hypoxemia, hypercarbia, and acidemia can cause disruptions in CAR (11,12). Intra-ECMO factors including rapid corrections of CO_2 (13,14), mechanical stress on major blood vessels, and alterations of pulsatile flow patterns also play a role in altered CAR (15,16). The period of ECMO support which confers the greatest risk for neurologic injury is currently unknown.

In this study, we sought to identify the period of ECMO support which confers the greatest burden of impaired CAR and, thus, the risk of the development of neurologic injury. As patients experience rapid changes in physiologic factors during the peri-cannulation period, we hypothesize that this will lead to the greatest disruption of CAR and more severe neurologic injury.

Materials and Methods

Participants

This retrospective cohort study included neonatal and pediatric patients (0 to 18 years) who were supported on ECMO from August 2020 to December 2023 at the Children's Medical Center, Dallas. With University of Texas Southwestern Medical Center Institutional Review Board approval (approval number: STU-2023-0788, date: 28.08.2023), electronic medical record data was extracted for eligible patients. Those patients who had previously received ECMO support or did not have neurologic imaging within 30 days of decannulation were excluded from this study. Those patients who did not have near-infrared spectroscopy (NIRS) data or blood pressure data for the 4 hours prior to cannulation through to 72 hours after cannulation were excluded from the analysis. The reasons for ECMO intervention were varied and consisted of persistent pulmonary hypertension of the newborn (PPHN), cardiogenic shock, extracorporeal cardiopulmonary resuscitation (eCPR), septic shock and acute respiratory distress syndrome (ARDS). All patients were cared for in the pediatric or cardiac intensive care unit. Clinical management was under the purview of the patient's primary intensivist and followed institutional guidelines. Cannulation was performed by the general and cardiovascular surgical teams.

Data Collection

Patient demographics, ECMO factors and laboratory data were obtained from the electronic medical records. All patients received continuous hemodynamic monitoring which included mean arterial pressure measured through an indwelling arterial catheter. Cerebral tissue oxygen saturation (rSO_2) was measured on the forehead using Near Infrared Spectroscopy (17-21). Both signals were sampled every 5 seconds and recorded throughout the ECMO run, except during patient transportation for imaging or other procedures. Laboratory testing pre- and during ECMO followed institutional standards. For this study, the extracted data included bilirubin, blood gas parameters (pH, pO_2, and pCO_2), lactate, platelet, fibrinogen, hemoglobin, plasma-free hemoglobin, and daily mean anticoagulant dose.

Neuroimaging Assessment and Scoring

It is standard care at our institution that post-ECMO magnetic resonance imaging (MRI) is obtained within 30 days of decannulation. If there is concern of an acute change in neurologic status during the ECMO run, an emergent computed tomography (CT) is often obtained. Intra- and post-ECMO neuroimaging of the recruited subjects were scored using a previously validated categorical scale (22,23) which is predictive of functional neurodevelopmental outcome (10,24). The neuroradiologists who carried out the scoring were blinded to the clinical course and study findings. This scoring system divided intracranial injuries into three categories: hemorrhagic, ischemic and ventricular dilation. Injuries were assigned numeric scores based on their severity and weighted with an a priori assumption of the risk of neurologic sequelae. In the case that a patient had both intra-ECMO CT and post-ECMO MRI, the CT imaging was analyzed for scoring purposes. Neuroimaging scores were grouped into two categories: no/minimal injury (score 0 to 8) or severe injury ($\geq$9). A cut-off score of $\geq$9 was selected as prior work had demonstrated this correlates with unfavorable neurocognitive outcomes in pediatric patients (24).

Autoregulation Measurement

Wavelet transform coherence (WTC) is an advanced data analysis tool in the time-frequency domain for studying

non-stationary time series and the relationship between two synchronous time series. WTC has been used to assess CAR by calculating the coherence metrics between mean arterial blood pressure (MAP) and cerebral oximetry (rSO_2 from NIRS) (10,25-27). In principle, WTC provides two key parameters: (1) cross-wavelet coherence magnitudes between the two signals across time and frequency, and (2) phase information between the two signals, indicating whether they are in phase (moving together), anti-phase (moving in opposite directions), or lead-lag relationships. As a WTC approach utilizes nonstationary signals and analyzes signals across time and frequency, it is better at assessing the dynamic changes in CAR compared to other methodologies (27). These WTC results are typically visualized as a color-coded time-frequency plot (known as a scalogram), where coherence values range from 0 (no correlation) to 1 (strong correlation), and arrows indicate the phase relationship between the two signals. In this study, 0 represents the lowest impaired CAR burden and 1 represents complete coherence of the wavelets, i.e., the highest disrupted CAR burden. In this study, we focused on the pressure-passive state which signifies impaired autoregulation and leads to high in-phase coherence between MAP and rSO_2 fluctuations (27).

In addition, this study followed a new analysis strategy in order to quantify time-resolved percentage time of significant coherence (trSC in %) (27). Yu et al. al. (27) provides a narrative explanation of a WTC computational package using a graphical flowchart for clinicians, and it also introduces a novel method which allows quantification of temporal changes in trSC (%) in order to examine CAR impairment during the pre-, peri-, and post-cannulation periods in the selected patient population. Specifically, a temporal window, such as 30 or 60 min (1 h), was chosen in a pre-selected frequency or scale range [scale=1/(Morlet-wavelet frequency)] within the time-frequency WTC scalogram. Then, the averaged percentage time of the significant coherence (across both time- and scale-ranges) was obtained for each temporal window to form time-dependent WTC indices as CAR burden (27).

Peak and averaged autoregulation disruption were calculated for each patient in three time periods: pre-cannulation (-24 h to 0 h), peri-cannulation (0 h to +12 h) and post-cannulation (+12 h to +72 h); where hour zero denotes the time of cannulation. Peak and median autoregulation disruption was then compared for the injury group vs no/minimal injury group.

Statistical Analysis

Demographics, ECMO factors, laboratory parameters and outcomes were compared for patients in the injury and no/minimal injury groups. Continuous variables were analyzed with Student's t-test if normally distributed or Wilcoxon-Mann-Whitney univariate analysis for non-normally distributed variables and are expressed as median with 25^{th}-75^{th} interquartile ranges. Regression analysis was performed in order to evaluate the relationship between autoregulation disruption and neuroimaging scores. A p value of <0.05 was considered statistically significant.

Results

A total of 153 neonates and children received ECMO during the study period. As shown in Figure 1, patients were excluded if they did not receive neuroimaging within 30 days of decannulation or if cerebral oximetry data was missing for any of the study time periods. Thirty-one patients were included in the final analysis.

The predominant diagnosis in the neonates was PPHN, and in the children, it was eCPR followed by ARDS. The predominant ECMO type was venoarterial (VA) (n=25, 81%). As shown in Table I, 11 patients (35%) had severe neurologic injury, with similar incidence in the children and the neonates. All severe injuries were observed in those patients supported on VA ECMO and the predominant indication for ECMO in the injury group was eCPR. There were no significant differences in the laboratory values between the groups. All patients received a loading dose of heparin prior to cannulation and daily mean heparin doses were similar between the groups. Survival was similar between the groups with 85% of patients surviving to hospital discharge in the no/minimal injury group and 72% surviving to hospital discharge in the severe injury group.

Autoregulation disruption was calculated in peaks and averages for the no/minimal injury and severe injury groups. As shown in Table II, this was further stratified into the pre-cannulation period (-24 h to 0 h), the peri-cannulation period (0 h to 12 h) and the post-cannulation period (+12-72 h). It should be noted that the pre-cannulation time period varied between -4 h and -24 h. There were no significant differences when comparing the averages of disrupted autoregulation between the time periods and the development of neurologic injury (pre-cannulation: R^2=0.07, p=0.15, peri-cannulation: R^2=0.02, p=0.43, post-cannulation: R^2=0.08, p=0.12). However, there was a statistically significant correlation between peak autoregulation disruption in the pre-cannulation period and development of neurologic injury for those with severe injury (R^2=0.14, p=0.04) (Figure 2). As seen in Table III, there were no significant differences in peak CAR disruption between neonates versus children (p=0.09) or between eCPR versus other indications (p=0.32).

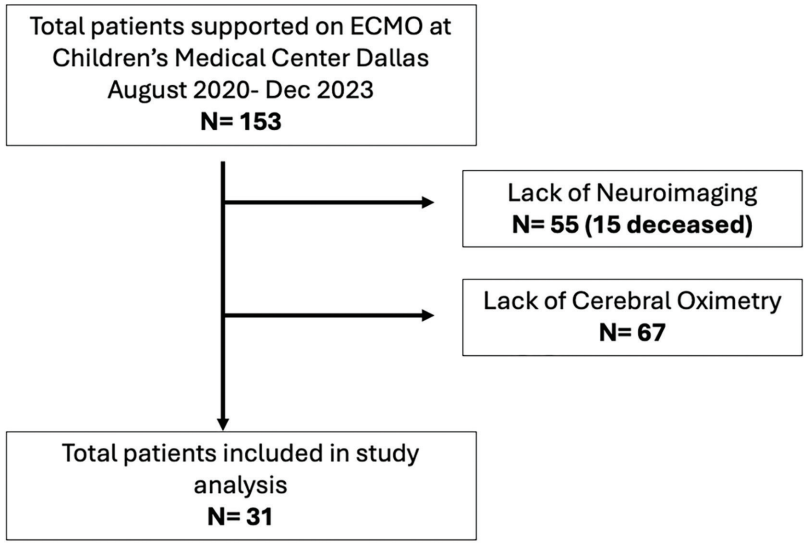

Figure 1. Flowchart of patient identification, inclusion and exclusion. Patients were excluded if neuroimaging was not completed within 30 days of decannulation. Fifteen patients died prior to obtaining neuroimaging. Sixty-seven patients did not have cerebral oximetry values for all periods of ECMO support and therefore were removed from the study analysis
ECMO: Extracorporeal membrane oxygenation

Table I. Admission characteristics, ECMO factors, laboratory parameters of the study cohort (n=31)		
Patient group, n	**No injury, n=20**	**Severe injury, n=11**
Age groups		
Neonates n=12	35% (7)	45% (5)
Children n=19	65% (13)	55% (6)
Gender		
Male n=19	55% (11)	73% (8)
Female n=12	45% (9)	27% (3)
Primary diagnosis		
PPHN n=4	10% (2)	18% (2)
Septic shock n=4	10% (2)	18% (2)
ARDS n=7	35% (7)	0
eCPR n=9	20% (4)	45% (5)
Cardiac n=7	25% (5)	18% (2)
Type of ECMO		
VV n=6	30% (6)	0
VA n=25	70% (14)	100% (11)
Worst laboratory values prior to ECMO cannulation, median (25%-75% interquartile range)		
Highest bilirubin (mg/dL)	0.9 (0.4-6.6)	1.4 (0.75-3)
Lowest pH	7.15 (7.1-7.20)	7.18 (7.1-7.22)
Lowest PaO_2 (mmHg)	53.5 (37.5-70)	65 (51.5-107.5)
Highest pCO_2 (mmHg)	66.5 (58.75-102.3)	56 (51.5-75.5)
Highest lactate (mmol/L)	4.15 (1.9-6.8)	8.3 (4.85-14.5)

Table I. Continued

Patient group, n	**No injury, n=20**			**Severe injury, n=11**		
Maximum changes of arterial blood gas from pre-ECMO to 24 h on ECMO, median (25%-75% interquartile range)						
Increase in pH	0.24 (0.19-0.28)			0.18 (0.155-0.28)		
Increase in pO_2 (mmHg)	164 (34.75-299)			94 (63.5-115.5)		
Decrease in pCO_2 (mmHg)	24.5 (17.25-47.8)			17 (13.5-38)		
Decrease in lactate (mmol/L)	2.05 (0.89-3.99)			5 (2.3-10)		
Intra-ECMO laboratory values, median (25%-75% interquartile range)						
	Day 1	**Day 2**	**Day 3**	**Day 1**	**Day 2**	**Day 3**
Hb (g/dL)	9.55 (87.7-10.4)	10 (9.5-10.8)	9.9 (9.3- 10.5)	9.4 (8.65-9.8)	9.5 (8.9-10.45)	9.2 (8.75-10.6)
Daily lowest platelet (thousand/mm^3)	92.5 (64-142)	88 (78-113)	80 (72-126)	79 (48.5-110)	85 (67.5-108.5)	80 (63.5-109)
Daily lowest fibrinogen (mg/dL)	164 (150-241)	230 (152-302)	298 (180-376)	144 (123.5-177)	235 (160-270)	284 (227-327)
Daily highest plasma free Hb (mg/dL)	35 (30-55)	50 (40-85)	60 (50-80)	70 (70-110)	85 (37.5-135)	50 (40-60)
PTT	88 (59.3-107)	102 (78.8-154)	86.5 (74-149)	114 (86-173)	93 (66-111)	90 (75-109.5)
Mean heparin dose during ECMO (un/kg/hr)	22.5 (20-28)	27 (22.5-32.3)	28 (19-36.5)	20 (20-28)	20 (18-28)	20 (18-29)
Survival to discharge (yes)	85% (17)			72% (8)		

ECMO: Extracorporeal membrane oxygenation, VV: Venovenous, VA: Venoarterial, PTT: Partial thromboplastin time, PPHN: Persistent pulmonary hypertension of the newborn, ARDS: Acute respiratory distress syndrome, eCPR: Extracorporeal cardiopulmonary resuscitation

Table II. Peak CAR disruption across ECMO time periods and demographic groups

	Peak CAR disruption Median (IQR)	**p value**
Neonate vs. child	18.4 (8.6-34.9)	0.09
VV vs. VA ECMO	7.5 (0.4-25)	0.32
eCPR vs. other	17.5 (6.5-34.9)	0.53
Pre-cannulation	13.5 (13.5-25.9)	0.03
Peri-cannulation	5.9 (5.7-20.2)	0.85
Post-cannulation	35 (26.7-34.2)	0.29

ECMO: Extracorporeal membrane oxygenation, VV: Venovenous, VA: Venoarterial, IQR: Interquartile range, CAR: Cerebral autoregulation, eCPR: Extracorporeal cardiopulmonary resuscitation

Table III. Comparison of CAR disruption in the pre-cannulation period across demographic groups		
	Peak CAR disruption Median (IQR)	**p**
Age		0.09
Neonate	6.0 (0.75-35)	
Child	18 (8.6-34.9)	
Type of ECMO		0.32
VV	7.5 (0.43-24.88)	
VA	16.5 (6-34.91)	
eCPR		0.53
Yes	7.5 (5.2-31.4)	
No	17.5 (6.5-34.9)	

ECMO: Extracorporeal membrane oxygenation, VV: Venovenous, VA: Venoarterial, IQR: Interquartile range, CAR: Cerebral autoregulation, eCPR: Extracorporeal cardiopulmonary resuscitation

Discussion

The current study investigated the relationship between impaired CAR and the development of severe neurologic injury in pediatric ECMO patients. The mean burden of impaired CAR did not vary across ECMO time periods and was not associated with neurologic injury. However, shorter (1 hr) periods of highly impaired CAR were more common in the pre-cannulation period and were associated with severe neurologic injury. This aligns with our clinical understanding that shorter periods of more profound clinical instability may confer greater risk of injury than modest physiologic derangements over longer time periods. Further, we found no significant differences in ventilator, laboratory or anticoagulation parameters between the severe and no/minimal injury groups, implying that other factors may play an important role in the development of neurologic injuries acquired on ECMO.

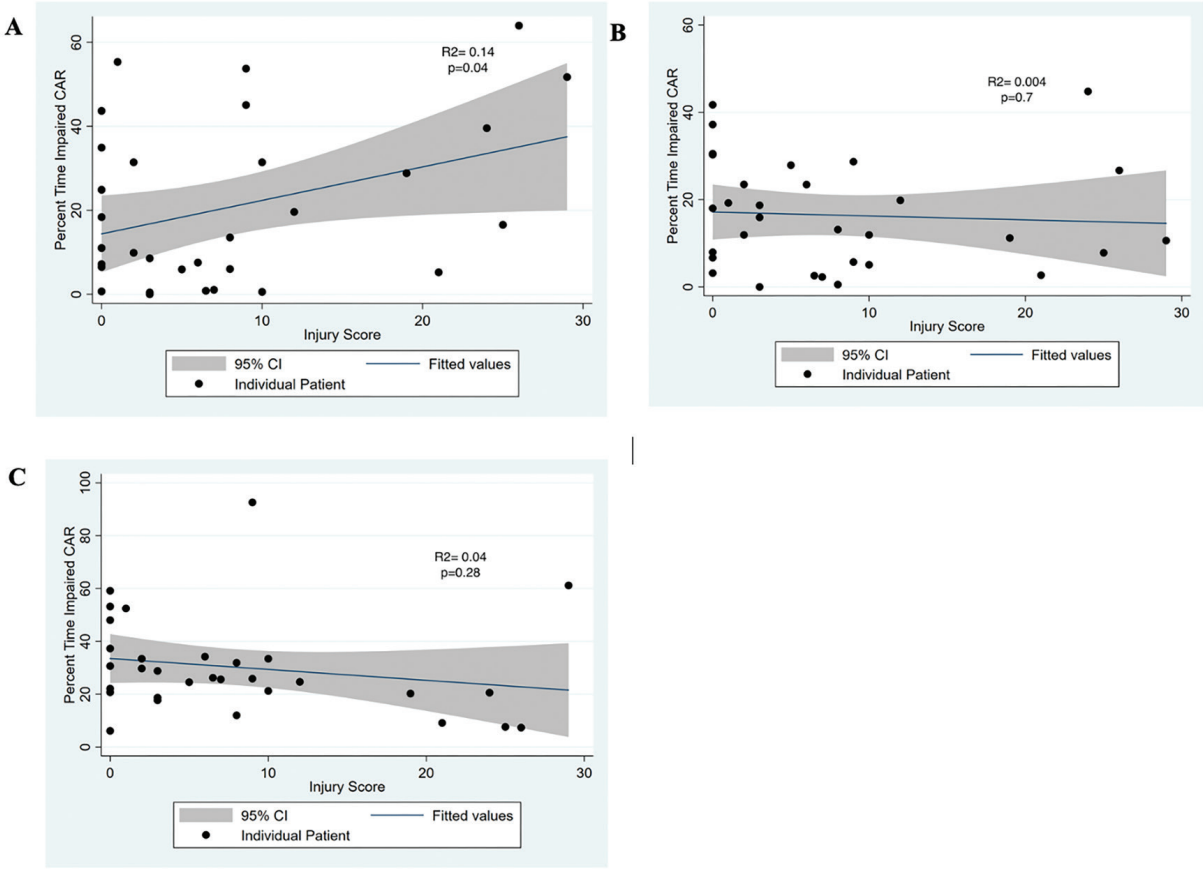

Figure 2. Association between the percentage of time with impaired CAR and the development of neurologic injury seen on neuroimaging in the **A)** pre-cannulation (-24 h to 0 h), **B)** peri-cannulation (0 h to 12 h), **C)** post-cannulation (12h to 72h) period of ECMO support. Neurologic injury scores range from 0-30 with scores >9 correlating with severe neurologic injury. There was a statistically significant correlation between peak autoregulation disruption in the pre-cannulation period and the development of neurologic injury seen on neuroimaging for those with severe injury (R2=0.14, p=0.04)
ECMO: Extracorporeal membrane oxygenation, CAR: Cerebral autoregulation, CI: Confidence interval

CAR was measured by performing a WTC analysis of MAP and cerebral oximetry as a surrogate for cerebral blood flow. This methodology has been utilized in pediatric patients supported on ECMO, pediatric cardiac arrest and neonatal hypoxic ischemic encephalopathy (10,26,27). Our results compliment these prior studies through utilization in a larger cohort of ECMO patients. Additionally, we utilized WTC in shorter time windows in order to analyze peak periods of impaired CAR. Consistent with prior reports, we found that disruption of CAR correlates with the development of severe neurologic injury for pediatric patients on ECMO (8-10,12,20,26). It has been previously reported that the majority of acute neurologic events occur within the first 24 hours of ECMO initiation, and this is a critical time for CAR disruption (8). Several mechanisms have been proposed to explain this phenomenon including alterations in the pulsatile blood flow pattern (16) and the rapid correction of carbon dioxide which occurs with ECMO initiation (9,13,14). However, prior to cannulation, all patients experienced critical illnesses which themselves are risk factors for CAR disruption and neurologic injury (28-32). To the best of our knowledge, this is the first study to investigate the time-period of maximal disruption of CAR and its impact on the development of neurologic injury for pediatric patients supported on ECMO.

We initially suspected that CAR would be maximally disrupted during the peri-cannulation period given the rapid changes in physiologic status during the cannulation process. However, our data supports the idea that disrupted CAR in the 24 hours preceding ECMO support confers the greatest risk of developing severe neurologic injury. This finding is likely reflective of the patient's underlying critical illness. Cerebral blood flow and cerebrovascular reactivity can be profoundly deranged in various pathophysiologic states such as sepsis (32), severe hypoxemia or acidemia (33). Similarly, in this study, patients with sepsis, PPHN, and congenital heart disease had profound disruption of CAR in the pre-cannulation period. Notably, most patients with severe injury were those who were cannulated with ongoing cardiopulmonary resuscitation. CPR may overlap between the pre- and peri-cannulation periods, making interpretation of peak impaired CAR between time periods difficult to assess in these patients. Clearly, patients cannulated during cardiopulmonary resuscitation are at particular risk for disrupted CAR and neurologic injury. Cessation of forward blood during cardiac arrest can lead to hypoxic ischemic brain injury and cytotoxic edema. CAR is often dysfunctional or absent following cardiac arrest (29,30) and the rapid restoration of cerebral blood flow by VA-ECMO may exacerbate reperfusion injury (28). Overall, the eCPR population represents a high-risk group which requires particular attention in clinical practice and future studies.

It has been well reported that rapid fluctuations of $PaCO_2$ can cause disruption of CAR leading to hemorrhagic injury (9,13,14). In an ELSO registry review, Shah et al. (13) found that pediatric patients who experienced a relative decrease of >30% in ΔCO_2 or had a relative increase ΔMAP >50% immediately following ECMO initiation had increased rates of neurologic complications and hospital mortality. Conversely, the patients in this study experienced a relative decrease of ~25% ΔCO_2 and there was no significant difference in blood gas parameters or maximal correction of blood gas parameters during the peri-cannulation period between the injury and no/minimal injury groups. This may explain why disruptions of CAR in the peri-cannulation period were not found to correlate with severe neurologic injury. Future studies should seek to replicate these findings across multiple sites in order to account for practice variations.

Study Limitations

This study was limited to retrospective data from a single center with a small sample size. These limitations may have confounded study results and also limit its generalizability. The primary outcome of neurologic injury defined by neuroimaging resulted in the exclusion of many patients as the neuroimaging was inconsistently obtained. Due to critical illness or death, certain patients with neurologic injury may not have received imaging. Thus, the risk of omitting an important cohort of patients who suffered neurologic injury from this analysis was present. Additionally, there was often a delay between obtaining imaging and the occurrence of dysregulation, possibly confounding the results. Furthermore, excluding those patients who did not have cerebral oximetry or blood pressure data available may have created a selection bias for children who were more severely ill. Variables were pre-selected, but due to sample size limitations, only univariate analyses were performed. In addition, in certain populations, such as those patients who were cannulated for eCPR, it was difficult to delineate whether the disruption in autoregulation was contributory versus being a response to the cerebral injury.

Conclusion

The 24 hours preceding ECMO support represents a critical window for neuroprotection in pediatric patients. This provides physicians with an opportunity to adapt management strategies in order to avoid periods of impaired CAR which may contribute to subsequent neurologic injury. The current study, along with prior work, demonstrates the value of continual assessment of CAR for pediatric ECMO patients. In the future, bedside interpretation of CAR may be key to improved cerebral protection before and during ECMO support.

Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from the University of Texas Southwestern Medical Center Institutional Review Board (approval number: STU-2023-0788, date: 28.08.2023).

Informed Consent: Retrospective cohort study.

Footnotes

Authorship Contributions

Concept: C.C., D.B., L.R., E.S., Design: C.C., D.B., L.R., E.S., Data Collection or Processing: C.C., S.I., H.L., M.T., D.B., L.R., E.S., Analysis or Interpretation: C.C., S.I., H.L., S.S., M.M., D.B., L.R., E.S., Literature Search: C.C., E.S., Writing: C.C., S.I., H.L., S.S., M.M., M.T., D.B., L.R., E.S.

Conflict of Interest: The authors declare that there is no conflict of interest regarding this study.

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Original Article

Managing Bone Health in Pediatric Celiac Disease: Effects of a Gluten-free Diet and Calcium-vitamin D Therapy

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ABSTRACT

Aim: Celiac disease is an autoimmune disease affecting individuals of all ages, causing damage to the small intestines upon consuming gluten. This study aimed to assess changes in bone mineral density among children with celiac disease following dietary intervention and treatment compared to their pre-intervention levels, and also to determine the frequency of metabolic bone disease at the time of diagnosis.

Materials and Methods: This study included pediatric patients with biopsy-proven celiac disease who underwent dual-energy X-ray absorptiometry at diagnosis and after 12 months. Anthropometric measurements, serum calcium, phosphorus, alkaline phosphatase, parathyroid hormone, and 25-hydroxyvitamin D levels were recorded. Lumbar spine (L1-L4) bone mineral density was measured using a dual-energy X-ray device. Anthropometric measurements, dual-energy X-ray absorptiometry results, and biochemical laboratory findings were evaluated before and after treatment. All patients received standardized vitamin D (400-2,000 IU/day based on their deficiency status) and calcium supplementation (age-appropriate daily intake 800-1,300 mg/day) based on their baseline deficiency status, and their adherence to a gluten free diet was verified by clinical improvement and negative anti-tissue transglutaminase IgA at follow-up.

Results: Sixty children (36 female, 24 male; mean age 8.82±3.90 years) were included in this study. At the initial evaluation, low bone mineral density was identified in 25% of the patients. During follow-up, some patients demonstrated worsening dual-energy X-ray absorptiometry findings despite adherence to the diet. Further assessment revealed that these patients had vitamin D deficiency and were non-compliant with the prescribed supplementation.

Conclusion: These findings highlight the critical role of dietary management and appropriate supplementation in managing celiac disease, emphasizing the necessity for dual-energy X-ray absorptiometry screening at diagnosis and follow-up.

Keywords: Bone mineral density, calcium, celiac disease, malabsorption, vitamin D

Introduction

Celiac disease (CD) is an autoimmune disorder in which gluten exposure leads to immune-mediated damage of the small intestine in genetically susceptible individuals. Once manifested, CD becomes a lifelong condition, and the only effective treatment is a gluten-free diet (GFD) (1). The global prevalence of CD is approximately 1% (2).

Classical symptoms include failure to thrive, chronic diarrhea, and weight loss; however, many patients present with fatigue, bloating, constipation, abdominal pain, or metabolic

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bone disease (MBD) (3). The mechanisms underlying MBD in CD are multifactorial and not fully understood. Proposed contributors include autoimmune activity, circulating inflammatory cytokines, and impaired absorption of key nutrients such as vitamin D, magnesium, phosphorus, and calcium (4). Local and systemic inflammation, particularly involving tumor necrosis factor-α, interleukin-1 (IL-1), and IL-6, affects bone metabolism in children with CD. Alterations in the RANK/RANKL/OPG pathway have been reported, with CD patients demonstrating elevated OPG and RANK levels and a reduced OPG/RANKL ratio, which correlates with spine bone mineral density (BMD) and IL-6 levels. The clinical relevance of OPG autoantibodies remains unclear due to conflicting findings (5,6).

MBD, a potential complication of CD, encompasses disorders which disrupt bone mineral homeostasis (7). It may be asymptomatic or present with bone pain, vertebral compression, or long-bone and vertebral fractures. Diagnosis relies mainly on dual-energy X-ray absorptiometry (DXA), the gold standard for assessing bone mineral content (BMC) and BMD. BMC reflects the mineral amount in a specific region, while BMD is calculated by dividing BMC by bone area. Although DXA is recommended for monitoring children at risk of MBD, such as those receiving long-term parenteral nutrition (8), there are no specific guidelines for routine BMD assessment in pediatric CD cases.

Children with CD, who are at increased risk for impaired bone health, require careful evaluation in order to prevent MBD and guide appropriate treatment. The primary aim of this study was to assess changes in BMD after dietary and medical intervention compared with baseline values. The secondary aim was to determine the frequency of MBD at diagnosis in children with CD.

Materials and Methods

Patients were eligible for inclusion if they had a biopsy-proven diagnosis of CD and were between 2 and 17 years of age at the time of this diagnosis at Sivas Numune Hospital, Clinic of Pediatric Gastroenterology, Hepatology, and Nutrition, between the dates of January 2021 and June 2023. The inclusion criteria also required the availability of baseline laboratory tests, DXA measurements, and at least one follow-up evaluation.

Exclusion criteria included the presence of chronic systemic diseases (e.g., endocrine disorders, renal disease, inflammatory disorders) which may affect bone metabolism, the use of medications known to influence BMD, incomplete medical records, or a lack of follow-up DXA evaluation.

Adherence to a GFD was confirmed by clinical assessment and negative anti-tissue transglutaminase immunoglobulin A (anti-TTG IgA) levels at follow-up. Only those patients with confirmed compliance were included in the longitudinal analysis.

The diagnosis of patients was based on positive celiac serology results and histopathological findings from upper gastrointestinal endoscopy, where biopsy specimens were scored according to Marsh classification as being 2 or 3.

Serum levels of calcium, phosphorus, magnesium, alkaline phosphatase (ALP), parathyroid hormone (PTH), and 25-hydroxyvitamin D3 [25(OH)D3], as well as BMD z-score results at the time of diagnosis, were reassessed after 1 year of adherence to a GFD. Serum 25(OH)D3 levels below 20 ng/mL were considered indicative of vitamin D deficiency.

We conducted DXA scans. Measurements of the lumbar spine included L1-L4. The DXA scans of the spines were analyzed in order to determine BMD (g/cm^2). L1-L4 z-scores were determined using standard deviation (SD) values of areal BMD (g/cm^2) for Turkish children, adjusted for height-age and gender. Patients with a BMD z-score ≤-2 SD were categorized as the low BMD group, those with z-scores between -1 and -2 were categorized as the high-risk of low BMD group, and those with z-scores ≥-1 were categorized as the normal group in L1-L4 measurement area. Following baseline evaluation of BMD and serum 25(OH)D3 levels, all patients received individualized supplementation. Those patients with vitamin D deficiency [25(OH)D3 <20 ng/mL] were prescribed 1,000-2,000 IU/day of vitamin D, while those with normal levels received 400-800 IU/day. Calcium supplementation was provided according to age-specific daily requirements (4-8 years: 800 mg/day; 9-18 years: 1,300 mg/day). Supplementation was adjusted based on follow-up biochemical results and administered under the guidance of a pediatric endocrinologist.

Anthropometric measurements including weight, height, body mass index (BMI), and z-scores for these parameters at the time of diagnosis and during follow-up were retrieved from the patient records. Weight, height, and BMI z-score values were computed using the tool provided by the Turkish Pediatric Endocrinology and Diabetes Association (CHILD METRICS, https://www.ceddcozum.com/).

This study was approved by the Sivas Cumhuriyet University Non-Interventional Clinical Research Ethics Committee (approval number: 2024-02/20, date: 22.02.2024), and informed consent was obtained from the parents of each pediatric patient.

Statistical Analysis

Statistical analysis was conducted using the SPSS-IBM, version 22 (SPSS Inc., Chicago, Illinois, USA). All eligible patients were included in the analysis. Comparisons between the initial visit and follow-up visit were conducted using the Chi-square test for gender, Paired Samples t-test (mean±SD) for normally distributed countable variables, and Wilcoxon test [median (min-max)] for non-normally distributed countable variables.

Correlations between BMD z-sores, anthropometric and biological parameters were evaluated using Pearson's rank correlation coefficient in the high-risk of low BMD and the low BMD groups. A value of $p<0.05$ was considered statistically significant.

Results

Sixty children with CD participated in this study. The mean age of the children was 8.82±3.90 years. The youngest child was 2.44 years old, and the oldest was 16.23 years old. Of the children included, 36 (60%) were female, and 24 (40%) were male.

The initial and follow-up median weights of the patients were 22.12 kg (range: 11.45-70.75) and 25.35 kg (range: 15.50-68.90), respectively. The initial and follow-up mean heights of the patients were 124.82±21.61 and 132.75±20.35 cm, respectively. The initial and follow-up median BMI of the patients were 15.69 (range: 12.41-28.34) and 16.80 g/cm^2 (range: 14.05-28.3), respectively. A statistically significant differences were found between these data. Over the course of a year adhering to a GFD, there was a notable increase observed in weight, height, and BMI measures. However, there was no statistically significant difference found between the z-score of weight, height, and BMI. The anthropometric measurements of the patients which were recorded at diagnosis and at follow-up are presented in Table I.

At the initial visit and follow-up visit, the levels were as follows: calcium levels were 9.73±0.55 and 9.91±0.38 mg/dL, phosphorus levels were 4.84±0.81 and 4.68±0.50 mg/dL, magnesium levels were 1.99±0.12 and 1.97±0.20 mg/dL, ALP levels were 195.21±74.02 and 209.55±86.35 U/L, PTH levels were 37.60 (range: 11.40-176.60) and 26.85 (range: 10.10-96.60) pg/mL, and 25(OH)D3 levels were 17.55±7.37 and 22.56±8.79 ng/mL, respectively. Among these laboratory parameters, only the 25(OH)D3 levels were found to be statistically significantly higher at the follow-up visit when compared to the initial visit levels (p=0.024). The laboratory measurements of the patients at diagnosis and at follow-up are presented in Table II.

Table I. Anthropometric measurements of the patients at diagnosis and at follow-up

	Initial visit	Follow-up visit	p value
Weight (kg)	22.12 (11.45-70.75)*	25.35 (15.50-68.90)*	**<0.001**
Weight z-score	-0.83±1.19	-0.68±1.15	0.300
Height (cm)	124.82±21.61	132.75±20.35	**<0.001**
Height z-score	-0.96±0.94	-0.79±0.95	0.101
BMI	15.69 (12.41-28.34)*	16.80 (14.05-28.3)*	**0.0010**
BMI z-score	-0.52±1.18	-0.22±1.11	0.147

Paired Samples t-test (mean±SD), *Wilcoxon test [median (min-max)], p value <0.05 significant
BMI: Body mass index, kg: Kilogram, cm: Centimeter, SD: Standard deviation, min-max: Minimum-maximum

Table II. Laboratory measurements of the patients at diagnosis and at follow-up

	Initial visit	Follow-up visit	p value
Calcium (mg/dL)	9.73±0.55	9.91±0.38	0.250
Phosphorus (mg/dL)	4.84±0.81	4.68±0.50	0.715
Magnesium (mg/dL)	1.99±0.12	1.97±0.20	0.224
ALP (U/L)	195.21±74.02	209.55±86.35	0.134
PTH (pg/mL)	37.60 (11.40-176.60)*	26.85 (10.10-96.60)*	0.050
25(OH)D3 (ng/mL)	17.55±7.37	22.56±8.79	**0.024**

Paired samples t-test (mean ±SD), *Wilcoxon test [median (min-max)], p value <0.05 significant
ALP: Alkaline phosphatase, PTH: Parathyroid hormone, 25(OH)D3: 25-hydroxyvitamin D3, SD: Standard deviation, min-max: Minimum-maximum

The mean L1-L4 BMD z-scores of the patients at the initial visit and follow-up visit were calculated as -1.09 ±1.08 and -0.79±1.29, respectively, and no statistically significant difference was found. The BMD z-score results of the patients at the time of diagnosis and at follow-up are presented in Table III.

When the patients were categorized into 3 groups based on their L1-L4 BMD z-score, we found 24 (40%) patients were in the normal group, 21 (35%) patients were in the high-risk of low BMD group, and 15 (25%) patients were in the low BMD group at their initial visit. At the follow-up visit, there were 27 (45%) patients in the normal group, 21 (35%) patients in the high-risk of low BMD group, and 12 (20%) patients in the low BMD group (Table IV).

During the follow-up visit, analysis of BMD z-scores revealed that 3 patients improved from the high-risk of low BMD group to the normal group, and 3 patients progressed from the low BMD group to the normal group.

In the high-risk of low BMD group, there was no correlation between BMD z-scores and the other anthropometric or biochemical parameters. In the low BMD group, a strong positive correlation was observed between BMD z-scores and calcium levels (r-value=0.975, p=0.005).

Table III. The bone mineral density results of the patients at diagnosis and at follow-up

	Initial visit	Follow-up visit	p value
L1-L4 BMD z-score	-1.09±1.08	-0.79±1.29	0.098

Paired samples t-test (mean ±SD), p<0.05 significant
BMD: Bone mineral density, SD: Standard deviation

Table IV. Distribution of bone mineral density measurements in lumbar region (L1-L4)

	Normal group: n (%) (-1<Z-score<1)	Low bone mineral density group: n (%) (-2<Z-score<-1)	High-risk group of low bone mineral density: n (%) Z-score<-2
Initial visit	24 (40)	21 (35)	15 (25)
Follow-up visit	27 (45)	21 (35)	12 (20)

Discussion

Our study shows that children newly diagnosed with CD have significantly reduced BMD, and although a GFD combined with calcium–vitamin D supplementation improves biochemical parameters, short-term recovery of BMD remains limited. These findings emphasize the importance of early DXA assessment and close monitoring of vitamin D status during follow-up in children with CD.

CD is a chronic immune-mediated disorder caused by gluten ingestion, leading to mucosal damage and nutrient malabsorption. It is associated with HLA-DQ2/DQ8 molecules which activate T lymphocytes and trigger autoimmune injury, resulting in villous atrophy (1,9). CD affects individuals of all ages; in our cohort, 60% were female and 40% male, with ages ranging from 2.44 to 16.23 years, which is consistent with previous studies (2,10,11).

CD is increasingly recognized as an important cause of MBD. Malabsorption of calcium and vitamin D contributes to secondary hyperparathyroidism and reduced bone mineralization. Osteopenia, osteoporosis, and fractures are well-known skeletal complications (12). In our study, 25% of the children had low BMD and 35% were at high risk at diagnosis, supporting earlier findings reporting osteoporosis rates between 27.5% and 44% (11,12). Consistent with these observations, Zacay et al. (13) demonstrated an increased risk of fractures among children with CD, both before and after diagnosis, indicating that impaired bone quality may precede diagnosis and may persist despite treatment. After GFD and supplementation, BMD improved modestly, with 20% having low BMD and 35% remaining high risk. Similar improvements have been described in other studies (14-17). In line with our findings, a recent systematic review and meta-analysis by Oliveira et al. (18) reported that GFD significantly increases both BMD and BMC in children and adolescents with CD, although values often remain lower than those of healthy controls.

While no correlation was identified between BMD z-scores and other parameters in the high-risk group, significant positive correlations were found between BMD z-scores and calcium levels (r=0.975, p=0.005) in the low BMD group. These findings may indicate that children presenting with low BMD may particularly benefit from targeted nutritional and therapeutic interventions to improve bone outcomes. Trovato et al. (19) similarly reported no correlation between anti-TTG IgA levels and BMD z-scores, although some studies report conflicting results, likely due to differing patient populations (20,21).

Vitamin D-dependent intestinal calcium absorption is essential for bone mineralization. In our cohort, 25(OH)D3 levels significantly increased at follow-up, likely reflecting supplementation and GFD adherence.

Bone turnover is affected by numerous biological and environmental factors beyond malabsorption. Given the limited sunlight exposure in our geographic region, vitamin D levels may not adequately improve with diet alone; therefore, supplementation appears necessary. Geographic variation should be considered when planning supportive therapy in CD.

Although improvements in height, weight, and BMI were observed, rapid linear growth may outpace bone mineralization, delaying measurable improvements in BMD. Increased needs for calcium and vitamin D, time required for bone matrix formation, and growth plate maturation may explain the slow normalization of bone parameters.

Study Limitations

This study was limited by its small sample size, single-center design, and short follow-up period. In particular, the 1-year follow-up may be insufficient to fully assess changes in pediatric BMD, as bone mineralization can require longer periods to show significant improvement. Additionally, physical activity, sunlight exposure, pubertal stage, and adherence to supplementation were not fully evaluated and may have influenced outcomes.

Conclusion

Adequate intake and absorption of calcium, phosphorus, and vitamin D are essential for maintaining bone health, especially in CD where malabsorption may occur. Regular DXA evaluation and appropriate preventive or therapeutic strategies are crucial. DXA should be performed at diagnosis and periodically thereafter in order to effectively monitor bone health in children with CD.

Ethics

Ethics Committee Approval: This study was approved by the Sivas Cumhuriyet University Non-Interventional Clinical Research Ethics Committee (approval number: 2024-02/20, date: 22.02.2024).

Informed Consent: Informed consent was obtained from the parents of each pediatric patient.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: E.K.T., S.E., Concept: E.K.T., S.E., Design: E.K.T., S.E., Data Collection or Processing: E.K.T., S.E., Analysis or Interpretation: E.K.T., S.E., Literature Search: E.K.T., S.E., Writing: E.K.T., S.E.

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Original Article

Evaluating Kidney Length as an Early Indicator for Surgical Decision-making in Congenital Ureteropelvic Junction Obstruction

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ABSTRACT

Aim: Diagnosing ureteropelvic junction obstruction (UPJO) is challenging due to the lack of a definitive test. The "increase in hydronephrosis" is an important but ambiguous sign, so multiple sonographic parameters are used together for evaluation. We aimed to assess kidney length change as an early indicator of increasing hydronephrosis and investigated whether monitoring patients with kidney length nomograms can aid in its follow-up.

Materials and Methods: This study included patients with high-grade hydronephrosis due to UPJO who had undergone at least three sonograms between 2012 and 2022. Kidney long-axis diameters in consecutive sonograms were plotted on a nomogram curve, and deviation from the individual's percentile was considered as an abrupt length increase.

Results: A total of 128 patients (84 operated on and 44 managed conservatively) were included. In initial sonography, 23 patients in the pyeloplasty group and 13 patients in the non-obstructive dilatation (NOD) group were already above the 97th percentile. An abrupt increase in length was observed in 63 patients, with 57 (94%) in the pyeloplasty group and 6 (19%) in the NOD group. Regarding the timing of surgery, 33 patients underwent surgery at a median of 7 (3-11.5) months after the abrupt increase, as there was no significant change in either anteroposterior diameter (p=0.076) or parenchymal thickness (p=0.240) at that time.

Conclusion: Our study revealed a notable abrupt increase in kidney length in most UPJO patients who underwent pyeloplasty. Our findings suggest the potential for an objective criterion using the change in kidney length in the decision for surgery.

Keywords: Hydronephrosis, ureteropelvic junction obstruction, renal length, ultrasonography, pyeloplasty

Introduction

Ureteropelvic junction obstruction (UPJO) is the most prevalent congenital obstruction within the urinary tract. The diagnosis of UPJO remains challenging due to the absence of a single diagnostic test (1). Ultrasonography advancements have allowed for earlier and more frequent detections of hydronephrosis. However, hydronephrosis does not always indicate obstruction, making diagnosis challenging (2).

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While an "increase in hydronephrosis" is an important sign of obstruction, defining it poses challenges. Various grading systems have been established in order to address this issue, yet they all have limitations (3). Consequently, several sonographic parameters are used together in order to evaluate hydronephrosis. Among these, renal pelvis anteroposterior diameter (APD) and parenchymal thickness (PT) have come forward as they offer easy monitoring and provision of data for comparison in follow-up. However, multiple studies have illustrated their insufficiency in decision-making regarding UPJO (4).

Kidney length serves as a numerical parameter in renal ultrasonography primarily used to assess kidney growth rather than specifically for evaluating hydronephrosis. We hypothesized that an abrupt change in kidney length could be an early sign of worsening hydronephrosis. This retrospective study investigated kidney length change as a potential parameter in assessing increased hydronephrosis in patients with UPJO.

Materials and Methods

Study Design and Setting

This retrospective case-control study was conducted across two tertiary care hospitals in İzmir, Türkiye. Ethical approval was obtained from the Ege University Medical Research Ethics Committee under (decision number: 23-6.1T/31, date: 22.06.2023). The hospital records of all of those patients followed with high-grade hydronephrosis due to UPJO between 2012 and 2022 were retrospectively reviewed.

Follow-up Protocol

All patients with high-grade congenital hydronephrosis undergo serial urinary sonograms, along with at least one Mercapto Acetyl Glycine scintigraphy with an F+20 protocol, which may be repeated when necessary. These renal scans also confirm no loss of function in the kidney. Voiding cystourethrogram is performed to rule out vesicoureteral reflux in those patients undergoing surgery or in those experiencing febrile urinary tract infections. Indications for surgical intervention are determined according to European Association of Urology/ European Society for Pediatric Urology guidelines. Therefore, high grade hydronephrosis along with increased APD is the primary finding for surgical decision-making using US (1).

Data Collection

The hospital records of those patients with high-grade hydronephrosis and no ureteric dilatation were reviewed. High-grade hydronephrosis was defined as urinary tract dilatation (UTD) grade 3 or Society of Fetal Urology (SFU) Grades 3 and 4. Only patients with at least three consecutive sonograms reporting all sonographic parameters were included.

Exclusion criteria:

- Patients who had undergone surgery within the first two months of life

- Patients with less than three sonograms with all data being required

- Patients with concomitant urologic abnormalities potentially affecting hydronephrosis or renal length (known vesicoureteral reflux, neurogenic bladder, duplex kidney, solitary kidney)

- Patients with lower grades of hydronephrosis (UTD grades 1 or 2)

The sonographic parameters assessed included long-axis length of the kidney, hilar APD of the renal pelvis APD, PT, and the grade of hydronephrosis (UTD/SFU). The data reviewed included age at diagnosis, age at admission, if they had surgery for UPJO, age at surgery for UPJO (if applicable), and repetitive sonographic measurements of the hydronephrotic kidney.

The patients were categorized into two groups: the pyeloplasty group (comprising those patients who had undergone surgery for UPJO) and the non-obstructive dilatation (NOD) group (comprising those patients who were followed non-operatively).

Procedure

All sonographic measurements (renal length, UTD/SFU grade, APD, and PT) were documented in a database for analysis. Renal pelvis APDs measured at the hilum were considered for evaluation.

Renal length changes were assessed using nomograms in order to distinguish them from normal kidney growth. The long-axis lengths of the kidney over repetitive studies were plotted on a nomogram curve. The nomogram by Obrycki et al. (5) was used after permission from the authors. This nomogram was selected for being the only nomogram providing monthly lengths in infancy. An abrupt upward movement on the curve resulting in crossing a major percentile line was considered to be a significant increase in length (Figure 1, star). Small deviations (<5.5 mm) were deemed as misinterpretations and not classified as a sharp increase in length (Figure 1, arrowhead). This threshold (5.5 mm) was chosen to overcome interobserver variability in measuring kidney lengths in children (6).

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics 23.0 (IBM Corp., Armonk, NY, USA). Data distribution was evaluated using histograms and the Kolmogorov-Smirnov test. Normally distributed data are reported as (means ± standard deviation) while non-normally distributed data are presented as medians (Q1-Q3). Wilcoxon, Paired samples t-test, and Mann-Whitney U tests were employed as appropriate and are specified within each result throughout the text. The level of significance was set at $p<0.05$.

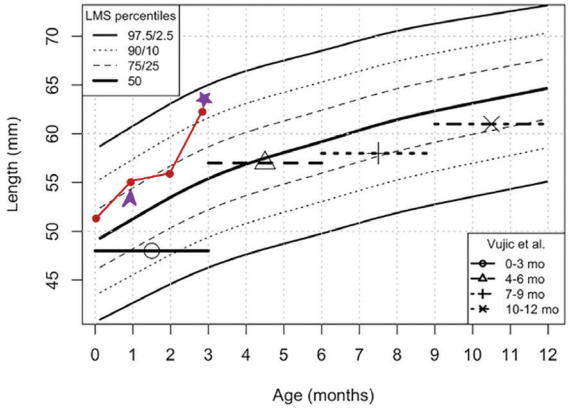

Figure 1. A sample nomogram curve of a hydronephrotic kidney made by marking the long axis lengths of the kidney in repetitive studies in follow-up. An incline which was regarded as a sharp incline in length (star), and one deemed as a misinterpretation (arrowhead) are marked to show how the evaluations were made

Table I. Characteristics of the study group

	Pyeloplasty group	Non-obstructive dilatation group	p value
Number of patients with kidney length over 97th percentile starting from the first sonography (%)	23/84 (28%)	13/44 (30%)	0.796*
Number of patients with a sudden incline in length/number of patients excluding the ones over 97th percentile (%)	57/61 (94%)	6/31 (19%)	p<0.001*
Median age (Q1-Q3) at first sonography	2 (0-14)	0 (0-3)	0.076#
Median age (Q1-Q3) during the sonography with a sudden incline in length	6 (2-27)	1 (0-3)	0.004#

*:Pearson chi-square test, #:Mann-Whitney U test

Results

A total of 323 patients followed with congenital hydronephrosis suggestive of UPJO were identified during the study period. After applying the exclusion criteria, 128 patients and 604 sonograms were included in this study. Among these, 84 patients had undergone surgery for UPJO (pyeloplasty group), and 44 patients were managed conservatively (NOD group).

Reviewing the renal lengths with regards to percentiles, 23 of patients in the pyeloplasty group (28%) and 13 patients in the NOD group (30%) already had kidney lengths above the 97th percentile, making it impossible to assess any percentile change in those instances. After excluding these cases, an abrupt increase in kidney length, according to the defined criterion above, was observed in 63 patients (63/92, 69%). Among them, 57 were in the pyeloplasty group (57/61, 94%) and 6 were in the NOD group (6/31, 19%) with a statistically significant difference between the groups (Pearson chi-square, $p<0.001$) (Table I).

The time elapsed between the abrupt change in kidney length and the time of surgery was also examined. The median age when an abrupt increase in kidney length was detected was 5 months (Q1-Q3: 2-22) and the median age at the operation was 15 months (Q1-Q3: 6-35). The surgery was prompted due to a noticeable increase in hydronephrosis by the sonography which also showed an abrupt increase in length in 24 cases (42%). The remaining 33 patients underwent surgery at a median of 7 months (Q1-Q3: 3-11.5) after the initial detection of the sharp increase.

There was no significant change in either renal pelvis APD (Wilcoxon test, $p=0.076$) or PT (Wilcoxon test, $p=0.240$) at the sonography when the increase was observed; however, there was a statistically significant change in kidney length (Wilcoxon test, $p<0.001$) (Table II).

Discussion

Most indications for surgery in UPJO rely on ultrasonography; however, several studies have demonstrated the limitations of each parameter used in accurately selecting those patients requiring surgical intervention (4). Renal length is often not assessed in this regard. To the best of our knowledge, there are only three studies investigating any relationship between renal length and UPJO and none of these suggest it as being an early indicator of surgery as our study does.

Koff et al. (7) proposed using contralateral compensatory kidney growth as a sign of obstruction. The major criticism for his study was possible late surgery when contralateral

Table II. Sonographic measurements of the hydronephrotic kidney (anteroposterior diameter of the renal pelvis, renal parenchymal thickness, and long axis length) comparing the first sonography at admission and the one with a sudden incline in kidney length. Pelvis anteroposterior diameter was measured at the hilum. Parenchymal thickness was depicted as the ratio of the parenchymal thickness of the hydronephrotic kidney to the contralateral one

	First sonography	Sonography with a sudden incline	p value
Median (Q1-Q3) renal pelvis anteroposterior diameter (mm)	17 (12-22)	20 (15-25)	0.076*
Median (Q1-Q3) renal parenchymal ratio	0.86 (0.62-1)	0.66 (0.50-0.97)	0.240*
Median (Q1-Q3) kidney length (mm)	59 (53-70)	73 (65-83)	<0.001*

*:Wilcoxon test

hypertrophy had already occurred. Kelley et al. (8) actually studied the value of parenchymal measurements of the hydronephrotic kidney and revealed a correlation between greater kidney length and an increased likelihood of requiring surgery. Another study which was recently published used the difference of length between the two kidneys as an evaluation of kidney length and it showed a significant decrease in this difference following pyeloplasty (9).

Similar to the findings of the study by Gharpure et al. (9), we think a significantly larger kidney length can be an additional warning sign for obstruction. However, a single measurement or comparing both kidneys can be misleading. While kidney length increases gradually by 2-3 mm per year during adolescence, it undergoes rapid changes in the first two years of life, making interpretation of kidney length difficult in infancy (10). A solution for this is to compare the diseased and the healthy kidney as Gharpure et al. (9) did but kidney length can differ between both kidneys even in the healthy children as has been shown in several studies (10,11). Kadioglu (12) addressed this issue by defining normal values for renal and bladder sonography in healthy children in Türkiye. He found that the left kidney was longer and had a thicker parenchyma, with particularly significant differences between both kidneys at ages 2 and 5 months - a critical time period when decisions for surgery are often made for UPJO patients (12).

Therefore, we used a nomogram giving monthly changes in the first year of life (5) and defined a criterion as an unexpected upward movement on the curve resulting in crossing a major percentile line, which we termed a "sharp increase in length" in order to ensure an objective evaluation. We observed an interesting abrupt change in kidney length in a significant group of patients before surgery when all preoperative assessments were plotted on a kidney-length nomogram. There was no concurrent change either in PT or renal pelvis APD at the time of kidney length change which supports the hypothesis that it might be used as an earlier indicator.

Our findings suggest the potential for establishing an objective criterion regarding kidney length in decision-making for UPJO. The notable prevalence of patients with kidney lengths exceeding the 97th percentile in the study group also raises the possibility that such individuals may have experienced this significant increase in kidney length prior to the sonograms included in our study, potentially even during prenatal development.

Study Limitations

The major limitation of our study was its retrospective nature, which resulted in non-standardized sonographies conducted at different intervals, performed in various centers, and by different individuals. In order to mitigate this bias, we disregarded small deviations which did not persist in subsequent sonograms, as these could be attributed to the lack of standardization in image acquisition. Nonetheless, these sonograms were considered suitable for patient evaluation and surgical decision-making, making them appropriate for this study. Additionally, as in most studies about UPJO, the reliance on surgical intervention as the primary outcome measure introduces uncertainty as we cannot definitively know what would have happened if surgical intervention had not been performed but no ethical study (prioritizing patient well-being) can solve this issue regarding our current knowledge.

Conclusion

Our study revealed a possible correlation between kidney length change and the need for surgery in UPJO patients. One obstacle in utilizing nomograms was the high proportion of patients already over the major percentile lines, limiting the effectiveness of our criterion. Developing a nomogram tailored specifically for hydronephrotic kidneys

and initiated from the antenatal follow-up may represent a step towards addressing this issue and provide more robust data concerning renal length in decision making for UPJO.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Ege University Medical Research Ethics Committee under (decision number: 23-6.1T/31, date: 22.06.2023).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.T., Ö.B.Y., M.C., D.S., B.T.K., A.T., İ.U., Concept: S.T., A.T., İ.U., Design: S.T., Ö.B.Y., A.T., İ.U., Data Collection or Processing: S.T., Ö.B.Y., M.C., D.S., B.T.K., Analysis or Interpretation: S.T., Ö.B.Y., M.C., D.S., B.T.K., A.T., İ.U., Literature Search: S.T., Ö.B.Y., M.C., D.S., B.T.K., A.T., İ.U., Writing: S.T.

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Original Article

Transdiagnostic Impact of Temperament on Symptom Severity and Quality of Life in Preschoolers with Neurodevelopmental Disorders

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ABSTRACT

Aim: Previous research has indicated that children with autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) often display differences in temperament. However, the relationship between temperament and both symptom severity and quality of life in preschoolers remains poorly understood.

Materials and Methods: Temperament was assessed in 27 preschoolers with ADHD and 27 with ASD, and the results were compared with those of 27 typically developing peers. For this purpose, the Children's Behavior Questionnaire-Short Form and the Pediatric Quality of Life Inventory were administered. ASD symptom severity was measured using the Childhood Autism Rating Scale, while ADHD symptom severity was evaluated with the Parent Assessment of Preschool Behavior Scale.

Results: In the ADHD group, symptom severity was positively associated with extraversion and negatively associated with effortful control. Higher levels of negative affectivity and higher extraversion were linked to poorer Pediatric Quality of Life scores. In the ASD group, greater effortful control correlated with both lower symptom severity and higher overall quality of life.

Conclusion: Our findings suggest that temperament traits in preschoolers with ASD and ADHD are associated with both symptom severity and quality of life. Given the limited sample size of this study, longitudinal studies are needed in order to confirm and expand upon these results.

Keywords: Attention deficit disorder with hyperactivity, autism spectrum disorder, child, preschool, neurodevelopmental disorders, quality of life, temperament

Introduction

Autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) are the two most prevalent neurodevelopmental disorders (NDDs) in childhood (1,2). NDDs in early childhood are characterized by heterogeneous clinical manifestations. Although these disorders fall into distinct diagnostic categories, they share a high degree of symptom overlap (3). Although symptom severity is an important prognostic indicator, the heterogeneity of NDDs cannot be fully explained by disorder-specific features (4). Recent evidence suggests that transdiagnostic factors, which vary across individuals independent of categorical

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diagnoses, may hold additional prognostic value beyond baseline symptom severity. Among these, temperament has been identified as an important factor contributing to the heterogeneity of NDDs (5,6).

Temperament is generally conceptualized as a biologically rooted tendency involving the regulation and reactivity of emotional, attentional, and motor processes (7). Despite multiple theoretical perspectives, researchers generally agree that temperament emerges early, is neurobiologically based, remains stable across early childhood, and exhibits consistency across contexts (8). According to Rothbart's widely accepted model, temperament from infancy to late childhood can be described along three major dimensions (9,10). The first dimension, surgency/extraversion, reflects how children respond to potential rewards and is associated with approach behaviors, high activity levels, and positive emotions. The second dimension, negative affectivity, captures the tendency to experience distress and other negative emotions, such as fear, sadness, frustration, and difficulty being soothed. The third dimension, effortful control, represents the child's capacity to regulate attention, manage impulses, and maintain goal-directed behavior. Surgency and negative affectivity (considered as being reactive dimensions) emerge within the first year, whereas effortful control (a regulatory dimension) becomes apparent in the second year as children develop greater conscious awareness (11).

It has been shown that temperament in neurotypical individuals may have both direct and indirect effects on development, including social-emotional, behavioral and psychopathological outcomes across the lifespan (12). Additionally, the idea that temperamental traits may be related to differences in psychopathology has guided several studies. While some studies have focused on predicting clinical symptoms and disorders, others have investigated the link between temperament and psychopathological symptoms (13). Increasing evidence has shown that temperament characteristics not only influence psychosocial adjustment in children with NDDs, but also interfere with interventions and exacerbate functional impairment with subsequent behavioral problems (14).

Examining individual characteristics within the framework of NDDs can enhance the understanding of how symptoms emerge and may also inform the selection of more suitable therapeutic strategies. The present study aimed to examine the relationship between temperament and two contributors to heterogeneity: symptom severity and quality of life.

The hypotheses tested in this study were:

- Hypothesis 1: Children with NDDs display temperamental characteristics which differ from those of their typically developing peers.

- Hypothesis 2: Temperamental traits in children with NDDs are associated with the severity of their symptoms.

- Hypothesis 3: Temperamental differences among children with NDDs are associated with variations in their quality of life.

Materials and Methods

Participants

Three groups were included in this study: preschool-age patients with ASD (n=27) and ADHD (n=27), both diagnosed according to DSM V, and a control group (n=27). All participants were followed at the 2-6 age polyclinic of the department of child and adolescent psychiatry. Their mean age in months was 54.3 months for the ASD group, 58.9 months for the ADHD group and 51.1 months for the control group. There were no significant differences in age or gender across the groups. The diagnoses of the participants were made by two different clinicians, each evaluating the participants independently. Patients with developmental delays, intellectual disabilities, or accompanying neurological-genetic diseases were excluded from this study. Additionally, those who met the criteria for both ASD and ADHD were also excluded. The Childhood Autism Rating Scale (CARS) was applied by the clinician in order to determine the severity of ASD symptoms. The Attention Deficit Hyperactivity Disorder and Disruptive Behavior Disorder Preschool Period Screening and Evaluation Scale was completed by the parents to determine ADHD severity. The Child Behavior Questionnaire-Short Form (CBQ-SF) was completed by the parents to determine temperament characteristics, and the Pediatric Quality of Life Inventory (PedsQL) was completed by parents in order to assess quality of life. A power analysis using G*Power 3.1 (bivariate normal model, 95% confidence, 80% power, H_0 correlation =0.46) indicated that each group required at least 27 participants (15).

Socio-demographic Data Form

The socio-demographic data form was developed by the researchers in order to collect demographic information and was completed by the clinician following parent interviews.

Parent Assessment of Preschool Behavior Scale: PARPS

The PARPS consists of 10 items rated by parents on a four-point Likert scale (0=never to 3=always). Total

scores range from 0 to 30, with higher scores indicating greater behavioral concerns. The scale demonstrates strong internal consistency, with a Cronbach's alpha of 0.92 (16).

The Children's Behavior Questionnaire-short Form (CBQ-SF)

The CBQ-SF, a shortened version of the original CBQ, is a caregiver-report instrument designed to evaluate temperament in children between the ages of 3 and 7 years (17,18). This seven-point Likert-type scale can measure 15 temperament dimensions: activity level, attentional focus, frustration-anger, discomfort, soothability, fear, high-intensity pleasure, low-intensity pleasure, impulsivity, inhibitory control, perceptual sensitivity, sadness, shyness, smiling, and laughter (18).

For analytical purposes, the CBQ-SF is grouped into three overarching temperament dimensions: negative affectivity, extraversion/surgency, and effortful control (18). Extraversion/surgency reflects tendencies toward approach behaviors, positive anticipation, and higher levels of motor and cognitive activity. Negative affectivity refers to the child's propensity to experience negative emotions, while effortful control encompasses the ability to regulate attention, inhibit impulses, and maintain goal-directed behavior. A Turkish adaptation study reported a Cronbach's alpha of 0.78 for the overall scale (19).

Pediatric Quality of Life Inventory (PedsQL)

The PedsQL measures health-related quality of life in children aged 2-18 years. It consists of 23 items, each rated on a 5-point Likert scale ranging from 0 (never) to 4 (almost always). It consists of four domains: physical functioning (8 items), emotional functioning (5 items), social functioning (5 items), and school functioning (5 items). From these domains, three standardized summary scores can be generated: the Total Quality of Life Score, the Physical Health Summary Score (calculated from the physical functioning items), and the Psychosocial Health Summary Score (derived from emotional, social, and school functioning items) (20).

Psychometric studies have demonstrated good reliability. Psychometric studies report Cronbach's alpha values of 0.88 (child) and 0.90 (parent) for the total score, 0.80 (child) and 0.88 (parent) for physical health, and also 0.83 (child) and 0.86 (parent) for psychosocial health (21).

Childhood Autism Rating Scale (CARS)

CARS is widely used to assess ASD symptom presence and severity in children aged 2 years and above. It is designed to classify symptom severity (ranging from mild to severe ASD) using quantifiable ratings derived from direct clinical observations.

The instrument consists of 15 items which cover a broad range of functional domains, including: interpersonal relations, imitation, emotional response, use of body and objects, adaptability to change and restricted interests, visual and auditory responses, reactions to taste, smell and touch, levels of fear or nervousness, verbal and non-verbal communication, activity level, intellectual response (consistency and quality), and overall impressions. Each item is scored on a 0-4 scale, with higher scores indicating more severe impairment; ratings are based on the frequency, intensity, distinctiveness, and duration of the observed behaviors.

Ethical Considerations

Ethical committee approval for this study was obtained from Ege University Faculty of Medicine Medical Research Ethics Committee (approval number: 22-12.2T/37, date: 29.12.2022).

Statistical Analysis

Statistical analyses were performed using SPSS version 27.0.1. Descriptive statistics are expressed as mean ± standard deviation. Group comparisons were conducted using One-Way analysis of variance for normally distributed variables, followed by post-hoc multiple comparison tests when appropriate. Correlation analyses were performed using Spearman's rank correlation coefficient in order to examine associations between temperament dimensions, symptom severity, and quality of life. A p value of <0.05 was considered statistically significant.

Results

The quality of life of the participants was assessed using the PedsQL by a parent proxy report. Emotional functioning scores were significantly lower in the ADHD group when compared to the control group ($p=0.012$). Social functioning scores were significantly lower in the ASD group compared to the ADHD group and the control group ($p<0.001$). School functioning, psychosocial functioning, and total PedsQL scores were significantly lower in both the ASD and ADHD groups when compared to the control group ($p=0.004$; $p<0.001$; $p=0.001$) (Table I).

The temperament of the children was measured using the CBQ-SF. There was no significant difference between the groups in negative affectivity and effortful control. However, extraversion/surgency scores were significantly higher in the ADHD group compared to the control group (Table II).

Table I. Comparison of PedsQL scores between groups

	Groups			
	Control (n=27)	**ASD (n=27)**	**ADHD (n=27)**	**p value**
PedsQL				
Physical health	88.5±14.6	86.7±12.2	86.1±13.0	0.783
Emotional functioning	79.3±16.3[a]	67.4±19.1[a,b]	65.0±19.2[b]	**0.012**
Social functioning	92.2±14.0[a]	70.0±22.7[b]	81.9±16.1[a]	**<0.001**
School functioning	92.1±8.4[a]	79.5±16.9[b]	80.3±18.4[b]	**0.004**
Psychosocial health	85.8±10.9[a]	70.3±15.6[b]	73.7±14.8[b]	**<0.001**
Total score	87.6±8.6[a]	76.8±11.4[b]	78.9±12.8[b]	**0.001**

Descriptive statistics are expressed as arithmetic mean ± standard deviation
Similar letters in the same row indicate statistical similarities and different letters indicate differences
Bold p-values indicate statistical significance (p<0.05)
PedsQL: Pediatric Quality of Life Inventory, ASD: Autism spectrum disorder, ADHD: Attention-deficit/hyperactivity disorder

Table II. Comparison of CBQ-SF scores between groups

	Groups			
	Control (n=27)	**ASD (n=27)**	**ADHD (n=27)**	**p value**
CBQ-SF				
Activity level	5.19±1.98	5.29±0.82	5.66±0.97	0.407
Anger/frustration	3.81±1.07	4.31±1.23	4.52±1.19	0.079
Approach/positive anticipation	4.95±0.67[a]	5.33±0.91[a,b]	5.77±0.63[b]	**0.001**
Attentional focusing	4.58±0.96[a]	3.42±0.79[b]	3.21±1.20[b]	**<0.001**
Discomfort	3.73±1.13	3.99±1.23	4.41±0.97	0.081
Low intensity pleasure	4.97±0.81	4.27±1.29	4.39±1.17	0.051
Fear	3.99±1.09	4.28±1.48	4.12±1.19	0.719
Soothability	4.68±0.88	5.07±0.95	5.21±0.91	0.095
Impulsivity	4.28±0.85[a]	4.65±0.76[a,b]	5.22±1.15[b]	**0.002**
Inhibitory control	4.99±0.75	4.75±1.23	4.19±1.34	**0.032**
High intensity pleasure	5.27±0.66	5.63±0.82	5.62±0.81	0.157
Perceptual sensitivity	5.60±0.87	5.85±0.91	6.11±0.93	0.135
Sadness	4.47±0.73	4.18±0.96	4.57±0.94	0.238
Shyness	3.42±0.96	3.74±1.45	3.25±1.54	0.398
Smiling and laughter	5.45±0.87	5.10±0.94	5.17±0.89	0.318
Negative affectivity	4.19±0.52	4.20±0.67	4.40±0.49	0.317
Extraversion/surgency	4.50±0.55	4.82±0.47	5.02±0.45	**0.001**
Effortful control	5.18±0.50	4.95±0.61	4.86±0.66	0.127

Descriptive statistics are expressed as arithmetic mean ± standard deviation
Similar letters in the same row indicate statistical similarities and different letters indicate differences
Bold p-values indicate statistical significance (p<0.05)
CBQ-SF: Child Behavior Questionnaire-Short Form, ASD: Autism spectrum disorder, ADHD: Attention-deficit/hyperactivity disorder

Table III. The correlation analysis of CBQ-SF with symptom severity and PedsQL in the ADHD and ASD groups

		CBQ-SF		
		Negative affectivity	**Extraversion/surgency**	**Effortful control**
		r	**r**	**r**
ADHD	**ADHD score**	0.161	0.398*	-0.387*
	PedsQL total	-0.425*	-0.475*	0.095
ASD	**CARS score**	-0.377	0.034	-0.441*
	PedsQL total	0.332	-0.268	0.421*

r: Spearman correlation coefficient
*=p<0.05
CBQ-SF: Child Behavior Questionnaire-Short Form, ASD: Autism spectrum disorder, ADHD: Attention-deficit/hyperactivity disorder, CARS: Childhood Autism Rating Scale, PedsQL: Pediatric Quality of Life Inventory

Correlation analysis indicated that, within the ADHD group, negative affectivity (r=0.425) and extraversion (r=0.475) were inversely related to the total PedsQL score (p<0.05). Conversely, effortful control demonstrated a positive correlation with the total PedsQL score in the ASD group (r=0.421, p<0.05) (Table III).

Discussion

Compared to the growing literature on differences in neurotypical individuals, surprisingly little research has addressed the role of temperament in children with ASD and ADHD. However, in the present study, the temperament dimensions of preschool children with ADHD, ASD, and neurotypical children were evaluated, and the associations of these dimensions with disease severity and quality of life were assessed.

In the current study, those children with ADHD had higher extraversion/surgency levels than neurotypical children; however, no significant group differences were observed in negative affectivity or effortful control. Studies of 175 children with ASD (mean age =10.3 years) and 84 children with ADHD (mean age =10.1 years) reported higher negative affectivity, reduced effortful control, and lower surgency in ASD, whereas children with ADHD showed higher scores for effortful control than those children in the community sample (22,23). In a study directly comparing 27 children with ASD, 27 children with ADHD, and 27 neurotypical children, the clinical groups scored lower than neurotypical children on effortful control. Although effortful control was useful in distinguishing neurotypical children from the clinical groups, it was found to be less effective in distinguishing ADHD from ASD (15). In a systematic review synthesizing the existing evidence on temperament in relation to ASD, it was found that children and adolescents with ASD show distinct temperamental profiles when compared to their typically developing peers and other clinical groups without ASD, marked by elevated negative affectivity, reduced surgency, and diminished effortful control at higher-order levels (4).

Since temperament has been considered an influential factor in problematic behaviour among typically developing children, its association with quality of life and symptom severity in children with NDDs has attracted research interest (24). It has been widely reported that high extraversion is associated with increased externalizing behaviours and fewer internalizing problems, whereas high negative affectivity is associated with an increased risk of internalizing problems (25-28). Effortful control generally reflects the ability to control, regulate, or inhibit behaviors. Throughout development, low levels of effortful control have been reported to be strongly associated with internalizing and externalizing psychopathologies (29,30). In the present study, we observed a positive correlation between ADHD symptom severity and extraversion/surgency and a negative correlation with effortful control. High levels of extraversion/surgency (impulsivity and unsoothability) and low levels of effortful control (poor attentional focus and low inhibitory control) may increase the symptom severity in ADHD. In the present study, negative affectivity and extraversion were negatively correlated with the quality of life in those patients with ADHD. Reduced effortful control (e.g., difficulties in distributing attention, diminished attentional focus, limited attentional shifting, and reduced adaptability) together with elevated negative affect (e.g., greater disorganization, heightened reactivity, increased distress, and lower agreeableness) may negatively influence parent-reported quality of life by impairing functioning in children with ADHD.

In the current study, we found that effortful control was positively associated with the quality of life and negatively

associated with symptom severity in those patients with ASD. This finding is consistent with those of previous studies. Previous research has shown that the developmental course of ASD symptoms may differ depending on variability in temperamental domains, with higher levels of effortful control often associated with fewer symptoms (31). Our results support earlier work linking effortful control with social functioning, empathy, and positive peer perception (32,33). Furthermore, more severe ASD symptoms appear to be related to greater difficulties in behavioral regulation, and lower levels of effortful control may negatively impact overall quality of life.

This study explored temperament-based heterogeneity in ASD and ADHD. Considering temperament characteristics in the assessment of those children with NDDs may help tailor individualized interventions and treatments. Further research is required in this field based on the data obtained in this study.

Study Limitations

This study was the first to examine temperament characteristics and quality of life in preschoolers with ADHD. Its limitations include the small sample size, its cross-sectional design, the single-center nature of this study, and the reliance on parent-report measures for temperament and quality of life.

Conclusion

The present study demonstrates that temperament traits are meaningfully associated with both symptom severity and quality of life in preschool children with ASD and ADHD. In particular, extraversion/surgency and effortful control appear to play a key role in symptom expression and functional outcomes across diagnostic groups. These findings support the importance of a transdiagnostic, temperament-informed perspective in the clinical assessment of NDDs. Considering individual temperament profiles may contribute to more personalized intervention strategies. Future longitudinal studies with larger samples are needed in order to confirm and extend these findings.

Ethics

Ethics Committee Approval: Ethical committee approval for this study was obtained from Ege University Faculty of Medicine Medical Research Ethics Committee (approval number: 22-12.2T/37, date: 02.01.2023).

Informed Consent: Participants and their parents were informed about the study, and written informed consents were obtained.

Footnotes

Authorship Contributions

Concept: S.E., Design: N.B.Ö., Data Collection or Processing: Z.İ.E., Analysis or Interpretation: S.E., Z.İ.E., Literature Search: S.E., N.B.Ö., Writing: S.E., Z.İ.E., N.B.Ö.

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Original Article

Inflammation-Driven Iron Deficiency in Obese Children: The Role of Hepcidin and IL-6

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ABSTRACT

Aim: Obesity and iron deficiency represent two of the most prevalent nutritional disorders worldwide. Obesity is accompanied by chronic low-grade inflammation, with elevated circulating levels of pro-inflammatory cytokines, particularly interleukin 6 (IL-6). Obesity-related inflammatory pathways promote hepatic hepcidin synthesis, with IL-6 serving as a central mediator of hepcidin transcription under inflammatory conditions. Hepcidin is the principal regulator of intestinal iron absorption, and its increased expression contributes to impaired iron availability in obese individuals. This study aimed to examine the association between obesity and iron deficiency and to clarify the role of hepcidin in iron homeostasis among obese children.

Materials and Methods: This case-control study enrolled 50 children with obesity [body mass index (BMI) >95th percentile] and 50 healthy non-obese children (BMI between the 5th and 95th percentiles), aged 8-18 years. The evaluated parameters included hemoglobin (Hb), mean corpuscular volume (MCV), serum iron, ferritin, total iron-binding capacity, transferrin saturation (TS), as well as serum hepcidin and IL-6 levels.

Results: Obese children had significantly lower serum iron, Hb, MCV, ferritin, and TS (all $p<0.05$), and higher hepcidin and IL-6 levels ($p=0.024$ and $p=0.032$, respectively), compared to the controls. Hepcidin levels were directly correlated with IL-6 ($p<0.001$) and BMI standard deviation scores ($p=0.019$). Inverse correlations were observed between hepcidin and iron ($p=0.024$), hepcidin and Hb ($p=0.001$), and hepcidin and MCV ($p=0.02$).

Conclusion: Chronic inflammation of obesity and elevated hepcidin levels result in the low iron states in obese children.

Keywords: Obesity, hepcidin, interleukin-6, iron deficiency

Introduction

Obesity is characterized by the excessive accumulation of adipose tissue which adversely affects health outcomes. Over recent decades, it has emerged as one of the most important public health challenges worldwide and is recognized by the World Health Organization as a global epidemic (1). Obesity develops through both adipocyte hypertrophy and hyperplasia, leading to an expansion of adipose tissue mass (2). Obesity substantially increases susceptibility to metabolic complications which include insulin resistance, abnormalities in lipid metabolism, and the development of hypertension. Emerging evidence suggests that obesity also contributes to disturbances in iron metabolism, leading to iron deficiency anemia (IDA) (3).

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Iron plays a fundamental role in human biology by supporting cellular energy pathways, erythropoiesis, and immune competence. In addition, it is required for heme synthesis, enzymatic reactions such as cytochrome P450 activity, deoxyribonucleic acid replication and repair, and normal neurodevelopment (2). The relationship between hepcidin, obesity, and iron metabolism is complex and multifaceted, involving various metabolic and inflammatory pathways.

In obesity, chronic low-grade inflammation is associated with increased circulating hepcidin levels, which in turn contributes to disturbances in systemic iron regulation (4). Increased hepcidin activity limits intestinal iron uptake and restricts iron mobilization from storage sites, which can reduce iron availability even when total body iron stores are preserved (5,6). Studies have shown that obese individuals, including children and adolescents, exhibit higher hepcidin levels compared to their normal-weight counterparts. Higher hepcidin levels have been shown to be associated with elevated concentrations of pro-inflammatory cytokines, including interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) (7-9). This inflammatory response is primarily driven by dysfunctional adipose tissue, which secretes pro-inflammatory cytokines which in turn stimulate hepcidin production (10,11).

The present study was designed to examine the association between serum hepcidin and IL-6 concentrations and markers of iron status in children with obesity.

Materials and Methods

Ethical Consideration

This study was prepared based on a thesis into research into childhood obesity causing IDA which was completed in 2012. The study received approval from the Ethics Committee of Marmara University Faculty of Medicine (approval no.: MAR-AEK-09-2010-0066, date: 28.09.2010).

Study Population

A total of 100 children between 8 and 18 years of age were enrolled, including 50 children with obesity and 50 age-matched healthy controls. Recruitment was conducted through the well-child and pediatric outpatient clinics of Marmara University Faculty of Medicine Hospital. Written informed consent was obtained from both the participants and their legal guardians.

Obesity was classified using age- and sex-specific body mass index (BMI) percentiles, with values above the 95th percentile and a corresponding BMI standard deviation score (SDS) greater than +2 SD based on local growth references (12). The obese group consisted of children with no known systemic, endocrine, neurologic, or chronic diseases and who were not on any medications. The control group included healthy children matched for age and sex, whose BMI values ranged between the 5th and 95th percentiles according to age- and sex-specific reference standards.

Exclusion criteria for both groups included: (1) the use of iron supplements within the past six months; (2) the presence of an active infection; (3) the presence of any inflammatory condition (e.g., inflammatory bowel disease, autoimmune disease) or a history of cancer therapy within the past year; (4) the presence of any significant risk factors for iron deficiency (e.g., chronic blood loss from heavy menstruation or gastrointestinal bleeding, or adherence to a vegetarian diet); and (5) the presence of any known disorders of erythrocyte function (e.g., thalassemia, lead poisoning, sickle cell disease, or sideroblastic anemia).

Instruments and Laboratory Methods

Each participant underwent a detailed medical evaluation. All blood samples for hematologic indices and biochemical parameters were collected in the morning after an overnight fast in order to minimize potential diurnal and dietary variations. Complete blood count, including hemoglobin (Hb) and mean corpuscular volume (MCV), was performed on a Beckman Coulter LH 780 analyzer. Serum iron and total iron-binding capacity were assessed using a colorimetric method on the Roche Cobas C 502 analyzer, while ferritin concentrations were determined by an electrochemiluminescence immunoassay on the Roche Modular Analytics E170 platform. Transferrin saturation (TS) was calculated as [serum iron ÷ total iron binding capacity (TIBC)] × 100. For inflammatory markers, serum samples were frozen at -20 °C until analysis. Serum hepcidin concentrations were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (DRG® Hepcidin ELISA, DRG Diagnostics, Germany) according to the manufacturer's instructions. The analytical sensitivity of the assay was approximately 0.9 ng/mL, with a detection range of 0-80 ng/mL. The intra-assay coefficient of variation was below 8%, whereas the inter-assay coefficient of variation remained below 10%. Serum IL-6 levels were determined using a commercially available ELISA kit (eBioscience®, Vienna, Austria) following the manufacturer's protocol. The analytical sensitivity of the assay was approximately 0.9 pg/mL, with a detection range of 2-200 pg/mL. Both intra-assay and inter-assay coefficients of variation were below 10%. For both assays,

all samples were analyzed in duplicate and measured within the same assay run in order to minimize analytical variability.

Statistical Analysis

All statistical evaluations were carried out with GraphPad Prism software (version 5.00; GraphPad Software, San Diego, CA, USA). Continuous variables were summarized using appropriate descriptive measures, including means with SDs or medians with interquartile ranges, depending on the data distribution.

Comparisons between groups were performed according to the data distribution. The Mann-Whitney U test was applied for non-normally distributed variables, including IL-6 and hepcidin, whereas normally distributed continuous variables were analyzed using the independent samples t-test. Categorical variables were evaluated with the chi-square test. Associations between variables were examined using Pearson's correlation coefficient for normally distributed data and Spearman's rank correlation coefficient for variables with non-normal distributions, including hepcidin and IL-6. Statistical significance was defined as a p value below 0.05.

Results

The study population comprised 50 children and adolescents with obesity and 50 healthy non-obese controls. The median age was comparable between the obese and control groups [12.0 (8.0-18) vs. 12.1 (8.3-18) years], with a similar male distribution in both groups (60% vs. 52%). No significant differences were observed between the groups with respect to age or sex. The group comparisons of the demographic characteristics, anthropometric measurements, and iron-related parameters are summarized in Table I. The mean BMI-SDS of the obese group was 2.6±0.4 versus -0.6±0.9 for the non-obese group. Compared with the healthy controls, the children with obesity had significantly reduced serum iron (p=0.024), Hb (p=0.001), MCV (p=0.02), ferritin (p<0.05), and TS levels (p<0.05). Conversely, the children with obesity showed significantly elevated IL-6 and hepcidin concentrations compared with the controls (p=0.024 and p=0.032, respectively) (Figure 1). TIBC was much higher in the obese group compared with the control group (p=0.001). Although ferritin levels were significantly lower in the obese group compared with the controls (p=0.03), mean ferritin values in both groups remained within the age-appropriate reference ranges. Hepcidin levels were strongly and positively associated with IL-6 concentrations (p<0.0001). Figure 2 supporting the hypothesis that chronic inflammation in obesity stimulates hepcidin production. Hepcidin concentrations demonstrated significant negative associations with serum iron (p=0.024), Hb (p=0.001), and MCV (p=0.02), indicating that elevated hepcidin levels contribute to impaired iron availability and anemia in obese children (Table II). No significant

Table I. Anthropometrical and biochemical features of the obese group versus the control group

		Control		Obese	p value
Age		12.9±2.9		12.7±2.7	0.767
Sex					
Girls	20	40%	24	48%	0.420
Boys	30	60%	26	52%	
BMI (kg/m^2)		17.98±2.09		30.85±3.63	0.0001
BMI-SDS		-0.60±0.92		2.60±0.47	<0.0001
Ferritin (ng/mL)		35.97±13.62		29.59±15.26	0.03
Serum iron (ug/dL)		93.78±28.17		69.28±23.59	0.0001
TIBC (mg/dL)		363.16±40.4		402.56±43.17	0.0001
Transferrin saturation (%)		26.24±8.9		17.45±6.35	0.0001
Hb (g/dL)		13.05±0.84		12.63±0.89	0.019
MCV (fL)		84.65±2.78		82.68±3.46	0.002
Hepcidin (ng/mL)		8.61±1.97		11.12±5.48	0.024
IL-6 (pg/mL)		1.99±0.80		3.09±3.99	0.032

BMI: Body mass index, SDS: Standard deviation score, TIBC: Total iron binding capacity, Hb: Hemoglobin, MCV: Mean corpuscular volume, IL-6: Interleukin-6

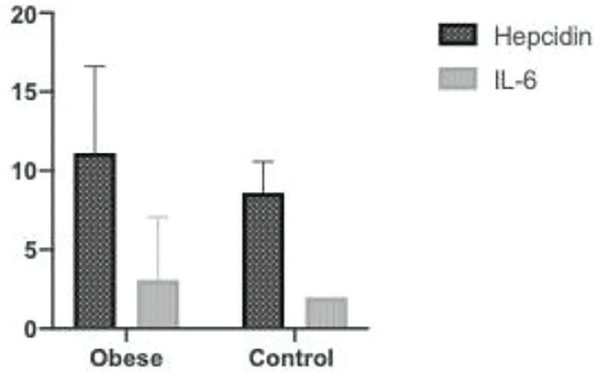

Figure 1. Comparisons of serum hepcidin and IL-6 between the two group
IL-6: Interleukin-6

Table II. Correlations between IL-6, serum hepcidin and iron profiles in all children

		IL-6	Hepcidin
Ferritin	r	-0.076	-0.155
	p	0.452	0.122
Iron	r	**-0.219**	**-0.226**
	p	**0.03 2**	**0.024**
TIBC	r	-0.039	0.091
	p	0.704	0.369
Hemoglobin	r	**-0.236**	**-0.328**
	p	**0.018**	**0.001**
MCV	r	**-0.221**	**-0.233**
	p	**0.029**	**0.02**
TS	r	0.015	-0.042
	p	0.881	0.674

IL-6: Interleukin-6, TIBC: Total iron binding capacity, MCV: Mean corpuscular volume, TS: Transferrin saturation

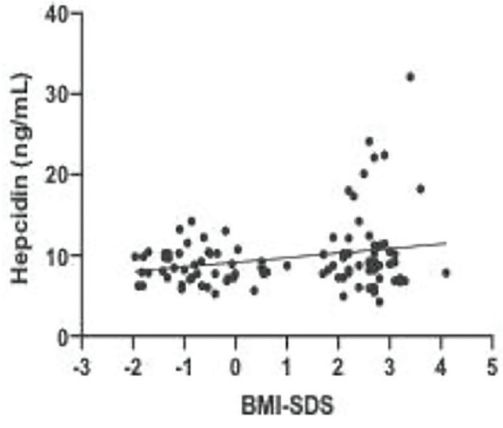

Figure 3. Correlation between BMI-SDS and serum hepcidin
BMI: Body mass index, SDS: Standard deviation score

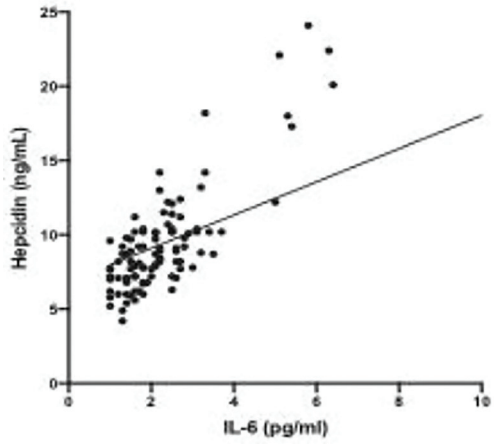

Figure 2. Correlation between serum hepcidin and IL-6
IL-6: Interleukin-6

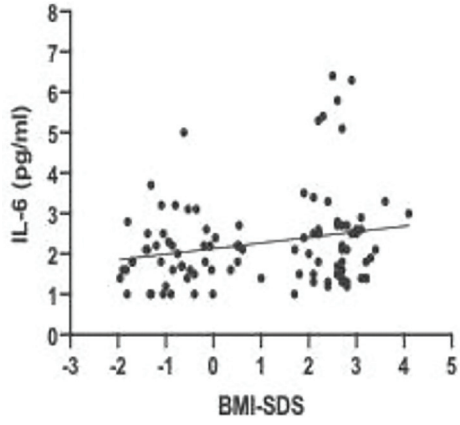

Figure 4. Correlation between BMI-SDS and serum IL-6
BMI: Body mass index, SDS: Standard deviation score, IL-6: Interleukin-6

correlations were observed between TS and either hepcidin (p=0.674) or IL-6 (p=0.881). Positive correlations between BMI-SDS and hepcidin (p=0.001) and also between BMI-SDS and IL-6 (p=0.03) are shown in Figures 3 and 4. Hepcidin and IL-6 were negatively correlated with Hb, MCV and iron levels (Table II).Higher BMI-SDS values were associated with increased IL-6, hepcidin, and total iron-binding capacity levels, while inverse relationships were observed with Hb, serum iron, and MCV (Table III). Separate subgroup analyses showed no statistically significant associations between any inflammatory markers, including hepcidin and IL-6, and iron-related parameters in either the obese group or the non-obese group.

Table III. Correlations between BMI-SDS and serum Hepcidin, IL-6, and iron profiles in all children

		BMI-SDS
IL-6	r	0.2098
	p	0.0361
Hepcidin	r	0.2339
	p	0.0192
Iron	r	-0.3659
	p	0.0002
TIBC	r	0.4219
	p	<0.0001
Hemoglobin	r	-0.3625
	p	0,0002
MCV	r	-0.3010
	p	0.0023
Table III. Continued		
		BMI-SDS
TS	r	-0.4451
	p	<0.0001
Ferritin	r	-0.1638
	p	0.1033

BMI: Body mass index, SDS: Standard deviation score, IL-6: Interleukin-6, TIBC: Total iron binding capacity, MCV: Mean corpuscular volume, TS: Transferrin saturation

Discussion

Iron plays a critical role in fundamental biological processes across almost all forms of life, and disturbances in iron balances have widespread clinical implications. According to global health data, iron deficiency remains the most prevalent nutritional disorder worldwide (13). In childhood obesity, contributing factors include genetic predisposition, imbalanced diet, reduced physical activity with lower myoglobin synthesis, and increased iron needs due to greater blood volume (14). However, studies have shown no major differences in dietary iron intake or in enhancers/inhibitors of absorption between obese and non-obese children, suggesting diet alone does not explain the higher prevalence of deficiency (15).

The inverse association between adiposity and iron status was initially described by Wenzel et al. (16) in 1962; obese adolescents had significantly lower mean serum iron than their non-obese peers. Later studies supported this observation. In the Third National Health and Nutrition Examination Survey, data from 9,698 children aged 2-16 years were analyzed, revealing that 10.2% of participants had BMI values exceeding the 95th percentile. Within this subgroup, iron deficiency prevalence was 6.2% in children aged 2-5 years and 9.1% in those aged 12-16 years (17). In an Iranian study of 1,675 university students, Hb and MCV decreased with rising BMI (18). The authors concluded that overweight children and adolescents have a higher prevalence of iron deficiency than their normal-weight peers, consistent with our findings. Moafi et al. (18) also noted that anemia risk increased with age, whereas we found no correlation between serum iron and age (p=0.7).

Cepeda-Lopez et al. (19) demonstrated that iron deficiency in obesity is driven not only by low dietary intake but also by inflammation. Previous studies have reported that, even with comparable dietary iron intake, obese women exhibit significantly reduced serum iron levels compared with their non-obese counterparts (p=0.014). In contrast, obese children have been shown to display increased TIBC (p<0.001), suggesting the presence of a compensatory mechanism. C-reaktif protein (CRP) levels were about fourfold higher in obese participants, reflecting chronic inflammation which may impair iron metabolism. Similarly, the obese children in our study had lower serum iron levels and higher total iron-binding capacity than the non-obese children. Richardson et al. (20) demonstrated that obese children aged 2-19 years (BMI >95th percentile) had lower serum iron, Hb, ferritin, and TS than age-matched controls, in findings which parallel those observed in our cohort.

Adipose tissue contributes to chronic low-grade inflammation through the secretion of cytokines such as IL-1, IL-6, and TNF-α, as well as adipokines including leptin, adiponectin, hepcidin, and resistin (21). IL-6 and hepcidin levels were significantly increased in the obese children relative to the controls in our study. IL-6–mediated activation of the Janus kinase/signal transducer and activator of transcription signaling cascade plays a central role in the regulation of hepcidin expression. In obesity, chronic inflammation elevates IL-6, stimulating hepatic hepcidin production, a mechanism important for iron homeostasis, but which also contributes to iron deficiency (22). In the overall cohort, IL-6 levels were positively associated with hepcidin, whereas hepcidin showed an inverse relationship with serum iron, supporting inflammation-mediated hepcidin regulation of iron metabolism. However, when correlation analyses between inflammatory markers (IL-6 and hepcidin) and iron parameters were performed separately within the obese and non-obese groups, no significant associations were identified. This pattern suggests that obesity-related disturbances in iron metabolism may primarily reflect

a group-level difference between obese and non-obese children rather than a simple linear association at an individual level.

Chronic inflammation in obesity is thought to disrupt iron homeostasis by reducing intestinal absorption and increasing iron sequestration in macrophages and the reticuloendothelial system (23). In anemia of inflammation, bone marrow and iron stores are usually adequate, yet serum iron levels remain low (24). Ferritin levels may be normal or elevated in this context, reflecting both iron storage and its role as an acute-phase reactant (25). However, in childhood obesity, the interpretation of ferritin is complex due to the coexistence of low-grade chronic inflammation and disturbances in iron homeostasis. Obesity-related inflammation may increase hepcidin and restrict iron availability through the hepcidin–ferroportin axis without necessarily inducing a proportional increase in ferritin (26,27). Accordingly, studies on ferritin in obesity are heterogeneous: some report impaired iron status with higher hepcidin and reduced iron absorption despite comparable ferritin levels (8), whereas others demonstrate lower ferritin concentrations in obese children, particularly when true iron deficiency predominates (28). In our study, mean Hb, MCV, iron, TS, and ferritin were all significantly lower in the obese group, although ferritin values remained within age-appropriate normal ranges.

Weight reduction improves hepcidin levels and iron status in obesity by reducing chronic inflammation. In a randomized controlled trial, young women with obesity and IDA showed significant reductions in serum hepcidin levels, accompanied by increases in Hb and ferritin following diet-induced weight loss (29). Similarly, obese children participating in a weight loss program exhibited decreased hepcidin concentrations, which were correlated with lower leptin and IL-6 levels, highlighting the role of reduced inflammation in improving iron absorption (30).

Elevated hepcidin in obesity alters iron distribution and contributes to IDA, particularly in children, who often respond poorly to oral iron intake due to persistently high hepcidin (31). Thus, standard supplementation may be insufficient, and strategies targeting inflammation or modulating hepcidin may be required.

Study Limitations

This study had several limitations, including its single-center design and relatively small sample size, which may restrict the generalizability of the results. Dietary intake and physical activity were not evaluated in detail, and additional inflammatory markers such as CRP or adipokines, which could have provided a more comprehensive picture, were not measured. These factors should be considered when interpreting the results, and future multicenter longitudinal studies are needed in order to confirm and expand our observations.

Conclusion

Our study shows that obesity-related inflammation, reflected by elevated IL-6 and hepcidin, contributes to iron deficiency in children with obesity. These findings underscore the need for a comprehensive approach to management which addresses both nutritional and inflammatory factors. Weight control and anti-inflammatory strategies may help reduce hepcidin overexpression and improve iron availability. Future studies are warranted in order to explore targeted interventions to lower chronic inflammation or inhibit hepcidin activity, thereby restoring normal iron metabolism in this vulnerable group.

Ethics

Ethics Committee Approval: This study was prepared on the basis of the thesis on the research of childhood obesity causing IDA, completed in 2012. The study received approval from the Ethics Committee of Marmara University Faculty of Medicine (approval no.: MAR-AEK-09-2010-0066, date: 28.09.2010).

Informed Consent: Written informed consent was obtained from both the participants and their legal guardians.

Footnotes

Authorship Contributions

Concept: D.H., A.B., Design: D.H., B.Y., A.B., Data Collection or Processing: D.H., Analysis or Interpretation: D.H., B.Y., A.B., Literature Search: D.H., B.Y., A.B., Writing: D.H., A.B.

Conflict of Interest: The authors declare that they have no competing interests.

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Original Article

Inflammatory Markers in Adolescents with Polycystic Ovary Syndrome: Association with Androgen Levels

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ABSTRACT

Aim: Polycystic ovary syndrome (PCOS) is increasingly recognized as a systemic disorder associated with metabolic abnormalities and chronic inflammation. In this study, we aimed to investigate the relationship between androgen levels and inflammatory markers in adolescents with PCOS.

Materials and Methods: Eighty-nine patients with PCOS were analyzed retrospectively. Inflammatory markers, including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII), were assessed. Androgen levels and metabolic parameters were also evaluated.

Results: The inflammatory markers were not significantly associated with androgen levels or hyperandrogenism. No significant differences in NLR, PLR, or SII were observed between adolescents with and those without hyperandrogenism or between patients with obesity and those without obesity (all $p>0.05$). Body mass index (BMI) and BMI-standard deviation scores were not correlated with inflammatory markers. In contrast, homeostasis model assessment of insulin resistance showed a weak but statistically significant positive correlation with SII.

Conclusion: Our findings demonstrate that inflammatory markers, including NLR, PLR, and SII, were not significantly associated with androgen levels. Furthermore, these markers did not differ according to the presence of obesity or hyperandrogenism.

Keywords: Polycystic ovary syndrome, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte, systemic immune-inflammation index

Introduction

Polycystic ovary syndrome (PCOS) represents a significant global health concern which affects approximately 10-13% of females worldwide (1). It is characterized by a heterogeneous clinical presentation, including hyperandrogenism, ovulatory dysfunction, and polycystic ovaries in ultrasound (1). Since PCOS often begins during adolescence, early recognition of its clinical and biochemical features is essential in preventing

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long-term metabolic and reproductive complications. In adolescents, the diagnosis of PCOS is challenging due to the physiological overlap between normal pubertal development and PCOS-related features, such as menstrual irregularity and acne (1,2).

Regardless of age and body mass index (BMI), women with PCOS have an increased risk of developing cardiovascular disease, impaired glucose metabolism, metabolic syndrome, Type-2 diabetes, and obstructive sleep apnea (1-3).

In addition to its hormonal irregularities, PCOS is increasingly recognized as a systemic disorder associated with metabolic abnormalities and chronic inflammation (4,5). The relationship between PCOS and chronic inflammation is complex and remains unclear (5).

Routinely measured biochemical and hematological markers, as well as their derived ratios, can be used to assess systemic inflammation in various diseases (6-10).

Previous studies have demonstrated elevated levels of inflammatory markers, such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), mean platelet volume (MPV), high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-a) and systemic immune-inflammation index (SII) in women with PCOS (4,5,11-15).

However, studies focusing on adolescents with PCOS are limited, despite the critical time of adolescence for early metabolic and cardiovascular risk assessment. Therefore, the aim of our study was to evaluate inflammatory markers in adolescents with PCOS, and to assess the associations between hyperandrogenism and systemic inflammation in this population.

Materials and Methods

Study Design and Patients

We retrospectively analyzed 108 patients with PCOS followed and treated at the Clinic of Pediatric Endocrinology, University of Health Sciences Türkiye, İzmir Dr. Behçet Uz Children's Diseases and Surgery Training and Research Hospital, between January 2023 and December 2025. Patients with missing data and those with chronic or other endocrine disorders were excluded, resulting in 89 patients included in the final analysis. This study was conducted in accordance with the Declaration of Helsinki, and approved by the University of Health Sciences Türkiye, İzmir Dr. Behçet Uz Children's Diseases and Surgery Training and Research Hospital Non-Interventional Research Ethics Committee (approval number: 2026/01-06, date: 15.01.2026). Informed consent was obtained from all subjects and parents involved in this study. Written informed consent was obtained from the patients and parents to publish this paper. All patients were followed up in our pediatric endocrinology clinic at a tertiary referral hospital in Western Türkiye. In accordance with international adolescent-specific guidelines, PCOS diagnosis required the presence of persistent menstrual irregularity for a period of at least 2 years from the time of menarche and hyperandrogenism (clinical or biochemical), following the exclusion of other causes of hyperandrogenism, such as Cushing syndrome or congenital adrenal hyperplasia. Ovarian morphology was excluded from the diagnostic criteria, as polycystic ovarian morphology is common during normal pubertal development and lacks diagnostic specificity in adolescents (1,16). A structured questionnaire was used to systematically evaluate all clinical and laboratory data. The standard deviation scores (SDS) of weight, height, and BMI were calculated based on Turkish children's reference values (17). Obesity was defined as a BMI-SDS >2, according to established pediatric growth references (18).

Hormonal and Biochemical Measurements

All laboratory assessments were performed before the initiation of any medical treatment for PCOS. Hormone analyses including luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, dehydroepiandrosterone sulfate (DHEA-S), 17-hydroxyprogesterone (17-OHP), 11-deoxycorticosterone (11-DOC), 21-deoxycorticosterone (21-DOC), 1,4-androstenedione (1,4-AS), total testosterone and sex hormone-binding globulin (SHBG) were performed in the follicular phase of the menstrual cycle after overnight fasting. The free androgen index (FAI) was calculated using the following formula: Total testosterone/SHBG×100. Hyperandrogenism was defined as a FAI >6 and/or DHEA-S >200 µg/dL and/or the presence of clinical hyperandrogenism, which is in accordance with previous recommendations and the published literature (1,16,19).

Based on peripheral blood cell counts, systemic inflammation markers were calculated; SII, NLR, and PLR. The calculations were as follows;

- SII = (neutrophils x platelets)/lymphocytes,
- NLR = neutrophils/lymphocytes,
- PLR = platelets/lymphocytes.

Statistical Analysis

Statistical analyses of the data were performed using the SPSS software package for Windows (Ver. 25.0; SPSS Inc., Chicago, IL, USA). The distribution of the data was evaluated using the Shapiro-Wilk test. For numerical comparisons, Student's t-test or Mann-Whitney U tests were used to assess differences between the two groups according to the normal distribution of the measured parameters. Categorical variables were analyzed with the chi-square (χ^2) test. Data are presented as mean±SD or median and interquartile range (IQR, 25th-75th percentiles). The relationship between inflammatory markers and androgens was analyzed using Spearman correlation tests. In all statistical tests, p values <0.05 were considered as statistically significant.

Results

A total of 108 patients with PCOS were initially evaluated. Patients with missing data and those with chronic or other endocrine disorders were excluded, resulting in 89 patients included in the final analysis. The mean age at presentation was 15.4±1.3 years. Irregular menstrual cycles were the most common presenting symptom (92.1%), followed by hirsutism (32.5%), obesity (4.4%), acne (2.2%), and dysmenorrhea (1.1%). The median BMI was 24.27 kg/m^2 (IQR: 21.52-29.36), with a median BMI-SDS of 1.21 (IQR: 0.11-2.41). Based on BMI-SDS criteria, 43.8% of the patients were classified as obese. The demographic, clinical, and laboratory characteristics of the patients at presentation are summarized in Table I.

Table I. The demographic, clinical, and laboratory characteristics of the patients

Age (years)	15.41±1.33
Weight, SDS*	1.21±1.91
Height, SDS*	-0.07±1.03
BMI	24.27 (21.52-29.36)
BMI-SDS	1.21 (0.11-2.41)
Obesity (%)	43.8
Glucose (mg/dL)	89 (86-92)
Insulin	15.59 (11.91-21.53)
HOMA-IR	3.03 (1.67-4.32)
Triglyceride (mg/dL)	87.55 (63-122)
Total cholesterol (mg/dL)	154.20 (137.65-171.82)
LDL (mg/dL)	80 (67-100)
HDL (mg/dL)	52.00 (43.50-58.75)

*Normal distribution (Shapiro-Wilk test)
Data are given as mean±SD or median (IQR: 25th-75th percentile).
SDS: Standard deviation score; BMI: Body mass index; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance, LDL: Low-density lipoprotein HDL: high-density lipoprotein, IQR: Interquartile range

The hormonal characteristics of the study population at presentation are summarized in Table II. Gonadotropin levels showed a median LH concentration of 8.10 U/L (IQR: 5.58-11.90) and a mean FSH concentration of 5.65±1.40 U/L, with a median LH/FSH ratio of 1.43 (IQR: 0.99-2.02). Median levels of total testosterone, FAI, and DHEA-S were 37.52 ng/dL (IQR: 29.20-56.00), 7.63 (IQR: 0-12.94), and 263.50 µg/dL (IQR: 198.12-325.50), respectively. Levels of adrenal androgens, including 17-OHP, 11-DOC, and 21-DOC, are also presented in Table II. Hyperandrogenism was identified in 73% of the adolescents with PCOS.

The median values of inflammatory markers SII and NLR were 520.80 (IQR: 364.57-659.70) and 1.62 (IQR: 1.28-2.24), respectively, while the mean PLR was 121.88±30.54. Spearman correlation analysis revealed no statistically significant associations between androgen levels and inflammatory markers, including NLR, PLR, and SII (all p>0.05) (Table III). In addition, inflammatory markers did not differ significantly between those adolescents with and those without hyperandrogenism (all p>0.05) (Table IV).

No significant correlations were observed between BMI and BMI-SDS and inflammatory markers, including NLR, PLR, and SII (all p>0.05). Moreover, inflammatory markers did not differ significantly between adolescents with PCOS according to obesity status (all p>0.05) (Table V). homeostasis model assessment of insulin resistance

Table II. Hormonal data of the patients

LH (U/L)	8.10 (5.58-11.90)
FSH* (U/L)	5.65±1.40
LH/FSH ratio	1.43 (0.99-2.02)
Estradiol (ng/dL)	36.15 (29.85-47.55)
Total testosterone (ng/dL)	37.52 (29.20-56.00)
DHEA-S (µg/dL)	263.50 (198.12-325.50)
11-DOC (ng/dL)	37.92 (22.79-74.67)
21-DOC (ng/dL)	2.38 (1.69-3.70)
17-OHP (ng/mL)	0.71 (0.40-1.39)
1,4-AS (ng/mL)	3.29 (2.19-4.93)
FAI	10.58 (5.5-16.68)

*Normal distribution (Shapiro-Wilk test)
Data are given as mean±SD or median (IQR: 25th-75th percentile)
LH: Luteinizing hormone; FSH: Follicle-stimulating hormone; DHEA-S: Dehydroepiandrosterone sulfate; 11-DOC: 11-deoxycorticosterone; 21-DOC: 21-deoxycorticosterone; 17-OHP: 17-Hydroxyprogesterone; 1,4-AS: 1,4-androstenedione; FAI: Free androgen index, SD: Standard deviation, IQR: Interquartile range

Table III. Spearman correlation coefficients between inflammation markers and androgen levels

	NLR		PLR		SII	
	Spearman r'	p value	Spearman r'	p value	Spearman r'	p value
Total testosterone	-0.010	0.931	-0.019	0.872	0.041	0.722
DHEA-S	-0.054	0.651	-0.007	0.955	-0.024	0.840
11-DOC	-0.154	0.350	0.141	0.392	-0.100	0.544
21-DOC	-0.277	0.088	-0.108	0.511	-0.271	0.095
17-OHP	0.029	0.813	0.005	0.965	0.007	0.955
1,4-AS	-0.039	0.741	-0.021	0.862	0.028	0.817
FAI	-0.133	0.272	-0.106	0.384	-0.235	0.051

p<0.05 indicates a statistically significant correlation
DHEA-S: Dehydroepiandrosterone sulfate; 11-DOC: 11-deoxycorticosterone; 21-DOC: 21-deoxycorticosterone; 17-OHP: 17-hydroxyprogesterone; 1,4-AS: 1,4-androstenedione; FAI: Free androgen index, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, SII: Systemic immune-inflammation index

Table IV. Inflammatory markers in adolescents with PCOS, comparison according to hyperandrogenism

	Total	Hyperandrogenism (+) (n=65)	Hyperandrogenism (-) (n=24)	p value
SII	520.80 (364.57-659.70)	486.16 (373.15-652.08)	556.59 (340.94-657.36)	0.900
NLR	1.62 (1.28-2.24)	1.61 (1.27-2.23)	1.87 (1.28-2.23)	0.707
PLR*	121.88±30.54	122.51±29.82	120.37±32.48	0.597

*Normal distribution (Shapiro-Wilk test)
p<0.05 indicates statistically significant
SII: Systemic immune-inflammation index, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, PCOS: Polycystic ovary syndrome

Table V. Inflammatory markers in adolescents with PCOS: comparison between patients with and without obesity

	Total	Obese (n=39)	Non-obese (n=50)	p value
SII	520.80 (364.57-659.70)	513.60 (402.51-718.50)	534.01 (341.55-651.67)	0.372
NLR	1.62 (1.28-2.24)	1.66 (1.35-2.39)	1.61 (1.24-2.13)	0.260
PLR*	121.88±30.54	117.89±28.95	125.69±31.03	0.268

*Normal distribution (Shapiro-Wilk test)
p<0.05 indicates statistically significant
SII: Systemic immune-inflammation index, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, PCOS: Polycystic ovary syndrome

(HOMA-IR) showed a weak but statistically significant positive correlation with SII (r=0.234, p=0.038), whereas no significant correlations were observed between HOMA-IR and NLR or PLR.

Discussion

In this study, we investigated the relationship between androgen levels and inflammatory markers in adolescents with PCOS. Our findings demonstrate that inflammatory markers, including NLR, PLR, and SII, were not significantly associated with androgen levels. Furthermore, these markers did not differ according to the presence of obesity or hyperandrogenism.

Low-grade chronic inflammation has been increasingly recognized as a component of PCOS pathophysiology in adult populations (4,11,12,14,15). Previous studies have reported elevated levels of inflammatory markers, including hs-CRP, NLR, PLR, MPV, SII, SIRI and cytokines in women with PCOS compared to healthy controls, supporting the concept of an inflammatory environment of the disease (4,5,11,13,14). However, most data are from adult cohorts, in whom long-term metabolic abnormalities, obesity, and IR are more prevalent.

In the largest population-based study evaluating SII in children and adolescents, which included 4,134 children aged 6-19 years, the mean SII was reported as 355.71 (IQR:

255.15-492.00), while children with obesity exhibited higher SII values (10). Notably, the median SII observed in our cohort of adolescents with PCOS [528 (IQR: 366.88-655.69)] was higher than the general pediatric population and it was comparable to the levels reported in children with obesity. This finding suggests that adolescents with PCOS may exhibit a degree of low-grade systemic inflammation similar to that observed in pediatric obesity.

In previous studies, BMI has been consistently shown to be associated with inflammatory markers, particularly the SII (10,12,20). Furthermore, elevated inflammatory markers have also been reported in children with obesity, especially among those exhibiting features of metabolic syndrome (21). In contrast, we found no significant associations between BMI or BMI-SDS and inflammatory markers. Moreover, there were no significant differences in NLR, PLR, or SII between adolescents with PCOS according to their obesity status. This suggest that obesity alone may not be enough to trigger systemic inflammation in adolescence. It is likely that the duration of obesity and metabolic stress plays a critical role, with inflammatory consequences becoming more significant the longer the disease is present in adulthood.

IR plays a central role in the pathophysiology of PCOS and is strongly associated with its clinical manifestations. Consequently, women with PCOS are at increased risk of metabolic syndrome, type 2 diabetes mellitus, cardiovascular disease, and possibly higher cardiovascular mortality (1,4). In our study, in contrast to the lack of association with obesity, HOMA-IR demonstrated a weak but statistically significant positive correlation with SII. This suggests that IR may be a key factor in the early development of systemic inflammation in adolescents with PCOS.

While Bulu et al. (11) reported a significant positive association between PLR and HOMA-IR, we did not observe a similar relationship in our adolescent PCOS cohort, suggesting potential differences in inflammatory responses according to age.

Studies conducted in adult populations have suggested inflammation could be correlated with circulating androgens (5,22,23). In their review, Dey et al. (5) highlighted the association of both hematological inflammatory markers and pro-inflammatory cytokines with hyperandrogenism. In a retrospective cross-sectional study including women aged 18-40 years diagnosed with PCOS, inflammatory markers, particularly SII differed significantly across PCOS phenotypes with most elevated in phenotypes characterized by hyperandrogenism. In addition, correlation analyses indicated positive associations of NLR and SII with total testosterone and FAI (13). Similarly, Padder et al. (24) reported that hyperandrogenic PCOS phenotypes exhibited significantly higher levels of inflammatory cytokines. In another study, NLR was identified as an inflammation marker in patients with PCOS, exhibiting a positive correlation with free testosterone and 1,4-AS levels (25). In contrast, a study evaluating 392 women with hirsutism found no significant relationship between circulating androgen levels and NLR values (26). Similarly, our findings demonstrate that inflammatory markers were not significantly associated with hyperandrogenism or androgen levels. The lack of significant differences in inflammatory markers between adolescents with and those without hyperandrogenism further underscores the complexity of PCOS pathophysiology during adolescence. Pubertal hormonal fluctuations and physiological changes in androgen production may prevent the identification of the relationship between androgen concentrations and systemic inflammation at this age. This may partly explain why associations observed in adult women with PCOS are not consistent in the adolescent cohort.

Study Limitations

This study had certain limitations. Firstly, it was a retrospective, single-center study, which may limit its generalizability. Secondly, the absence of a healthy control group limits comparisons with those adolescents without PCOS. Although our sample size was comparable to previous adolescent PCOS studies, limited statistical power may have reduced the ability to detect subtle associations. In addition, age-related hormonal variability during adolescence, including pubertal fluctuations in androgen production and dynamic changes in sex hormone-binding globulin levels, may further obscure potential relationships between circulating androgen concentrations and systemic inflammation. Additionally, inflammatory status was assessed using hematological inflammatory markers rather than cytokine-based markers.

Conclusion

In conclusion, inflammatory markers in adolescents with PCOS appear to be independent of androgen excess and obesity, while IR may represent an early driver of low-grade systemic inflammation. Although elevated inflammation markers have been linked to systemic inflammation in chronic diseases and shown to be increased in women with PCOS in previous studies, its clinical relevance in adolescents with PCOS remains less clear. Early identification and diagnosis of PCOS during adolescence are of critical

importance, given the strong association of PCOS with long-term metabolic abnormalities.

Ethics

Ethics Committee Approval: This study was approved by the University of Health Sciences Türkiye, İzmir Dr. Behçet Uz Children's Diseases and Surgery Training and Research Hospital Non-Interventional Research Ethics Committee (approval number: 2026/01-06, date: 15.01.2026).

Informed Consent: Informed consent was obtained from all subjects and parents involved in this study. Written informed consent was obtained from the patients and parents to publish this paper.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Ö.K., G.A.K., İ.M.E., Ö.N., H.A.K., B.Ö., Concept: Ö.K., B.Ö., Design: Ö.K., Data Collection or Processing: Ö.K., N.P., G.A.K., İ.M.E., Ö.N., H.A.K., Analysis or Interpretation: Ö.K., Literature Search: Ö.K., Writing: Ö.K., B.Ö.

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Original Article

Sleep Quality and Associated Respiratory Problems in Mucopolysaccharidosis: A Cross-sectional Study based on Parent Reports

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ABSTRACT

Aim: Mucopolysaccharidoses (MPS) are a group of lysosomal storage disorders characterized by the accumulation of glycosaminoglycans (GAGs) in various tissues. Particularly, the accumulation of GAGs in the soft tissues of the head and neck region contributes to obstructive respiratory problems and sleep disturbances. This study aimed to evaluate sleep-related respiratory symptoms in patients with different subtypes of MPS.

Materials and Methods: This study included 25 patients diagnosed with MPS. The patients were evaluated in terms of their MPS subtypes, age, gender, duration of enzyme replacement therapy (ERT), and sleep questionnaire scores. Sleep-related respiratory problems were assessed using the "Pediatric Sleep Questionnaire: Sleep-Disordered Breathing (SDB) Subscale." A mean score above 0.33 on the 22-item questionnaire was considered indicative of SDB.

Results: This study included 25 patients diagnosed with MPS I (n=8), MPS II (n=1), MPS IIIA (n=2), MPS IIIB (n=2), MPS IVA (n=3), and MPS VI (n=9). Six patients were not receiving ERT. The median score on the Pediatric Sleep Questionnaire: SDB Subscale was 0.27 (range: 0.15-0.56). Eleven patients (44%) had SDB. No significant differences were found in the sleep questionnaire scores based on the patients' MPS subtype ($p>0.05$). There was no correlation between ERT duration, age, and the sleep questionnaire scores. Polysomnography (PSG) was planned for those patients with SDB.

Conclusion: In our study, we found that approximately half of the patients diagnosed with MPS had SDB. MPS patients should be routinely evaluated for sleep-related respiratory problems during follow-up visits, and those with symptoms of SDB should undergo PSG.

Keywords: Mucopolysaccharidosis, sleep disorders, apnea, polysomnography

Introduction

Mucopolysaccharidoses (MPS) are a group of lysosomal storage disorders characterized by deficiencies in the specific enzymes responsible for the degradation of glycosaminoglycans (GAGs). The accumulation of GAGs leads to progressive dysfunction at the cellular, tissue, and organ levels. To date, eleven distinct enzyme deficiencies have been identified, giving rise to seven recognized MPS subtypes (I, II, III, IV, VI, VII, and IX), with additional subtypes described for MPS III and MPS IV (1-4). Except for MPS type

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II (Hunter syndrome), which is inherited in an X-linked recessive manner, all other MPS types follow autosomal recessive inheritance patterns. Most MPS disorders are characterized by multisystem involvement, including short stature, musculoskeletal abnormalities, visual impairment, hearing loss, hepatosplenomegaly, cardiovascular disease, and/or respiratory complications. The specific manifestations and severity vary among the different MPS types. The accumulation of GAGs in tissues, resulting from enzyme deficiency, is primarily responsible for the clinical phenotype (2-4).

The two mainstays of treatment for MPS are enzyme replacement therapy (ERT) and supportive care. ERT is available for patients with MPS types I, II, IVA, VI, and VII. Except for MPS VII, where ERT is given every two weeks, it is usually given by weekly parenteral infusions. Hematopoietic stem cell transplantation, especially if carried out before the age of two, may be an option for certain MPS I patients. Additionally, the development of therapeutic approaches based on genes and enzymes is the focus of current research efforts (5-9).

GAG deposition in the head and neck region and upper airway can lead to airway obstruction through mechanisms such as corneal clouding, periodontal disease, conductive hearing loss, postural abnormalities related to vertebral involvement, and soft tissue enlargement (including macroglossia, adenotonsillar hypertrophy, and tracheomalacia). Additionally, GAG accumulation within the lower respiratory tract may result in both restrictive and obstructive lung diseases. These upper and lower airway abnormalities contribute significantly to the respiratory complications observed in MPS (10,11).

Sleep disturbances are also frequently reported clinical features in patients with MPS (12-15). Sleep disorders represent an important cause of impaired quality of life in this population. Disrupted night-time sleep can interfere with daily functioning, negatively affecting both patients and their families. If not diagnosed and managed early, sleep-related hypoventilation and recurrent hypoxia may lead to irreversible impacts on daytime alertness, fatigue levels, cardiovascular health, and neurocognitive functions (16,17).

The primary aim of this study was to facilitate the early identification of sleep-disordered breathing (SDB) in patients with MPS, a complication known to contribute to impaired quality of life and cognitive decline. By recognizing SDB at an early stage, we seek to prevent potential physical and psychological complications during childhood and to support timely interventions. Ultimately, our goal is to promote a multidisciplinary approach which enables the implementation of appropriate management strategies tailored to the needs of this vulnerable patient population.

Materials and Methods

Study Design and Participants

This descriptive, cross-sectional study was conducted between January and April 2025 in our institution. A total of 25 patients diagnosed with MPS and followed in the pediatric metabolism and pediatric pulmonology outpatient clinics were included. Face-to-face interviews were conducted with the parents of all of the participating patients, and a survey form was completed by the researchers. The sleep quality and respiratory problems of the patients were evaluated through parental reports using the aforementioned questionnaire. Informed consent was obtained from the parents of all of the patients. To detect sleep-related breathing disorders in the patients, the "Pediatric Sleep Questionnaire: Sleep-Related Breathing Disorder Subscale" was administered. Associations between MPS subtypes, patient age, gender, duration of ERT, and the sleep questionnaire scores were analysed. A mean score greater than 0.33 on the 22-item questionnaire indicated the presence of SDB.

The inclusion criteria were: a confirmed diagnosis of MPS by genetic testing, regular follow-up at our clinic, literacy of the parents, and parental consent by signing the voluntary participation form. Those patients who did not meet these criteria were excluded.

Ethical approval for this study was obtained from the University of Health Sciences Türkiye, Van Training and Research Hospital Non-Interventional Clinical Research Ethics Committee (approval number: GOKAEK/2025-05-08, date: 04.07.2025).

Statistical Analysis

All collected data were analysed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics are presented as frequency, percentage, median, and interquartile range. As the assumptions for parametric testing were not met, the Mann-Whitney U test was used for continuous variables, and the chi-square test was applied for nominal variables. Spearman correlation analysis was conducted to evaluate associations between the variables and other parameters. A p value <0.05 was considered statistically significant.

Results

This study included 25 patients with the following MPS subtypes: MPS I (n=8), MPS II (n=1), MPS IIIA (n=2), MPS IIIB (n=2), MPS IVA (n=3), and MPS VI (n=9). Twelve patients (48%) were female. The median age of the patients was 13 years (range: 6-16 years). Six patients were not receiving ERT. The nineteen patients receiving enzyme therapy had been receiving ERT treatment continuously since their diagnosis. Among these 19 patients, four had previously undergone adenotonsillectomy, all of whom had been diagnosed with MPS type I. Four of the eight patients with MPS type I had previously undergone adenotonsillectomy. These four patients had Pediatric Sleep Questionnaire (PSQ) Scores of 0.18, 0.18, 0.22, and 0.59, respectively, with a median score of 0.20 (range: 0.18-0.59). Only one of these patients (25%) had a PSQ score above the diagnostic threshold of 0.33. Although the sample size was small, this result suggests that adenotonsillectomy may be beneficial. The demographic and clinical characteristics of all of the patients are presented in Table I. A classification of the patients based on the median values of their sex, age, duration of ERT and PSQ Scores are presented in Table II.

The median PSQ: Sleep-Related Breathing Disorder Subscale score of the patients was 0.27 (0.15-0.56). A mean score greater than 0.33 on the 22-item questionnaire indicated the presence of SDB. The distribution of PSQ

Table I. Demographic and clinical characteristics of patients with MPS (reordered)

Patient number	Age (years)	Gender	MPS type	Duration of ERT (years)	PSQ score
P1	13	Female	MPS I	8	0.09
P2	6	Male	MPS I	3	0.18
P3	6	Male	MPS I	3	0.18
P4	15	Female	MPS I	10	0.09
P5	7	Male	MPS I	4	0.18
P6	5	Male	MPS I	4	0.63
P7	13	Female	MPS I	12	0.59
P8	14	Female	MPS I	12	0.22
P9	17	Male	MPS II	5	0.59
P10	5	Female	MPS IIIA	None	0.22
P11	4	Male	MPS IIIA	None	0.63
P12	16	Male	MPS IIIB	None	0.22
P13	16	Male	MPS IIIB	None	0.59
P14	6	Male	MPS IVA	3	0.31
P15	4	Male	MPS IVA	None	0.4
P16	23	Male	MPS IV A	9	0.36
P17	5	Male	MPS VI	2	0.0
P18	20	Male	MPS VI	19	0.72
P19	14	Female	MPS VI	12	0.27
P20	9	Male	MPS VI	9	0.0
P21	9	Female	MPS VI	None	0.4
P22	16	Female	MPS VI	12	0.54
P23	14	Female	MPS VI	10	0.04
P24	12	Male	MPS VI	10	0.13
P25	16	Female	MPS VI	12	0.45

ERT: Enzyme replacement therapy, PSQ: Pediatric Sleep Questionnaire Scores, MPS: Mucopolysaccharidoses

Scores according to MPS subtypes are listed in Table III. Eleven patients (44%) had scores above the limit, and that meant that they had sleep-related breathing disorders. Figure 1 illustrates the relationship between MPS subtypes, age, and PSQ scores in the eleven patients with PSQ values above the diagnostic threshold. Elevated PSQ scores were observed across all MPS subtypes, and no clear correlation between age and PSQ scores was evident from the graphical distribution.

Two patients, diagnosed with obstructive sleep apnea (OSA) syndrome by polysomnography (PSG), were receiving positive airway pressure (PAP) therapy. Patient 21 (P21) was a 9-year-old female diagnosed with MPS type VI who was not receiving ERT. This patient exhibited severe respiratory symptoms, prompting further evaluation with PSG and the initiation of PAP treatment. In contrast, Patient 22 (P22) was a 16-year-old female with MPS type VI who had been receiving ERT for 12 years. Despite ongoing ERT, this patient demonstrated clinically significant SDB requiring PAP therapy. No significant differences in sleep questionnaire scores were found based on gender or diagnosis ($p>0.05$ and $p>0.05$, respectively). No correlations were observed between the duration of ERT, age, and the sleep questionnaire scores. The correlation results are presented in Table IV.

Table II. Classification of patients based on the median values of sex, age, duration of enzyme replacement therapy, and Paediatric Sleep Questionnaire scores

Variable	**n (%)**	**Median (interquartile range)**
Gender		
Female	12 (48)	
Male	13 (52)	
Age (years)		13 (6-16)
Patients receiving enzyme replacement therapy (ERT)	19 (76)	
Duration of ERT (years)		5 (1-11)
Pediatric Sleep Questionnaire Score		0.27 (0.15-0.56)

Table III. PSQ scores categorized by MPS subtypes

MPS subtype	**n (Patients)**	**Mean PSQ Score**	**Minimum**	**Maximum**
MPS I	8	0.27	0.09	0.63
MPS II	1	0.59	–	–
MPS IIIA	2	0.42	0.22	0.59
MPS IIIB	2	0.40	0.22	0.59
MPS IVA	3	0.35	0.31	0.40
MPS VI	9	0.36	0.00	0.72

PSQ: Pediatric Sleep Questionnaire Scores, MPS: Mucopolysaccharidoses

Table IV. Correlation results

Variable	**Pediatric Sleep Questionnaire score (r)**	**p value**
Age (years)	0.18	0.326
Duration of ERT (years)	0.23	0.912

ERT: Enzyme replacement therapy

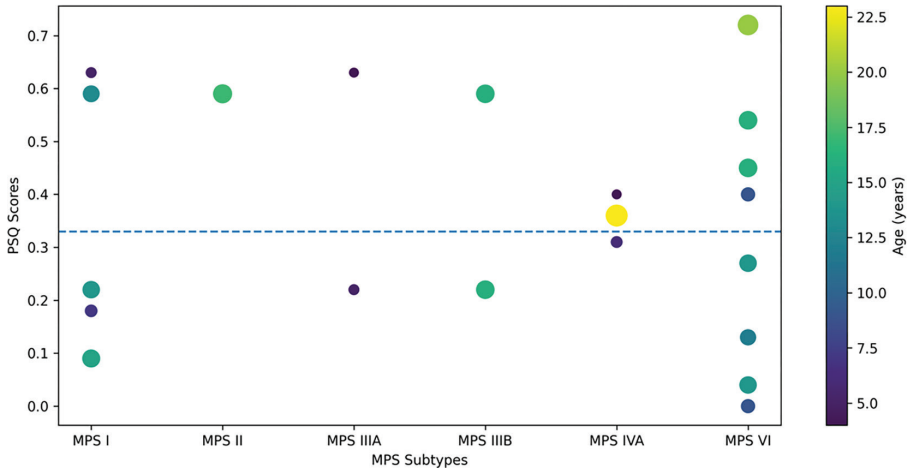

Figure 1. Stratified distribution of sleep-disordered breathing risk in patients with MPS (corrected)
MPS: Mucopolysaccharidoses, PSQ: Pediatric Sleep Questionnaire Scores

Discussion

This study investigated sleep-related breathing disturbances in a diverse cohort of pediatric patients with various subtypes of MPS. Using the PSQ, we identified that nearly half of the patients (44%) exhibited symptoms suggestive of SDB, despite the absence of significant associations with age, gender, MPS subtype, or duration of ERT. These findings underscore the high prevalence of SDB in MPS patients and highlight the importance of systematic screening, regardless of clinical classification or treatment status, in order to facilitate early detection and intervention.

Upper airway obstructions and associated complications are commonly seen in MPS patients. The accumulation of GAGs in tissues, resulting from enzyme deficiency, is primarily responsible for the clinical phenotype (2-4). Supraglottic manifestations are common in MPS and develop due to cranial and spinal abnormalities (e.g., flattened nasal bridge, short neck, high epiglottis, mandibular abnormalities, abnormal cervical vertebrae) and GAG deposition in the mouth, nose, and throat (18). Oral manifestations include gingival hyperplasia, mucosal edema, mucoid secretions, and impaired opening of the mouth. Tonsillar hypertrophy is one of the clinical manifestations, and tonsillectomy may be required for the treatment of OSA. A systematic meta-analysis conducted in 2024 identified MPS I and II as the most frequently operated on MPS subtypes. That study reported improvements in polysomnographic parameters during the postoperative period (2). Postoperatively, these patients demonstrated low PSQ scores, suggesting a potential benefit of surgical intervention in alleviating SDB symptoms in this subgroup.

Among the19 patients receiving ERT in our study, four had previously undergone adenotonsillectomy, all of whom had been diagnosed with MPS type I. These four patients had PSQ scores of 0.18, 0.18, 0.22, and 0.59, respectively, with a median score of 0.20 (range: 0.18-0.59). When evaluated on an individual patient basis, two patients (P2 and P3), both aged 6 years and diagnosed with MPS type I, demonstrated low PSQ scores of 0.18 following adenotonsillectomy, suggesting minimal parent-reported symptoms of SDB. Another patient (P8), a 14-year-old female with MPS type I, also showed a low PSQ score of 0.22, indicating a favourable sleep-related symptom profile after surgical intervention. In contrast, patient P7, a 13-year-old female with the same MPS subtype, exhibited a markedly higher PSQ Score of 0.59 despite a history of adenotonsillectomy, reflecting persistent sleep-related breathing symptoms. Clinically, this patient had a markedly short neck as an anatomical disadvantage and presented with prominent nocturnal symptoms, including loud snoring and habitual mouth breathing during sleep. In comparison, the remaining three patients did not exhibit apparent anatomical airway disadvantages. This anatomical and clinical disparity may partially explain the observed differences in PSQ scores among patients with the same MPS subtype. Collectively, these patient-level observations highlight the heterogeneous nature of airway involvement in MPS type I SDB -disordered breathing when additional anatomical risk factors are present. These findings underscore the importance of individualized airway assessment and continued follow-up in patients with MPS type I.

Respiration physiologically requires the coordinated activity of the diaphragm, chest wall, and upper airway

muscles, all of which are controlled by the brain. Feedback from blood gases (pCO_2 and pO_2) and mechanical reflexes from the chest wall, airways, and lungs regulate and balance this system. In patients with MPS, impaired central ventilation responses may occur due to central nervous system involvement, but the most common respiratory abnormalities are upper and lower airway obstructions and changes in respiratory mechanics, leading to restrictive lung disease. Progressive upper airway compromise is extremely frequent in MPS I, II, and VI, but it is least pronounced in MPS III (5,19). Most patients with severe MPS I develop snoring and obstructive upper airway disease by 2 or 3 years of age. OSA typically occurs first during rapid eye movement sleep and can be diagnosed via sleep studies (20). Our findings are consistent with previous studies demonstrating a high prevalence of SDB and abnormal sleep architecture in patients with mucopolysaccharidosis. Wooten et al. (21) investigated sleep and pulmonary characteristics in a cohort of 30 enzyme-naive MPS II patients, revealing OSA in 90% of cases, reduced rapid eye movement and slow-wave sleep, and frequent episodes of oxygen desaturation and hypoventilation. Importantly, their study identified a significant inverse correlation between pulmonary function, measured by FEV_1, and the severity of sleep-related respiratory abnormalities, including apnea-hypopnea index and elevated end-tidal CO_2 levels (21). Although our cohort included patients with MPS types I, II, and III, and we primarily relied on parent-reported outcomes, the elevated PSQ scores observed in certain individuals may reflect similar underlying disturbances. The overlap between poor sleep quality and impaired respiratory status in both studies highlights the importance of incorporating comprehensive respiratory assessments, including PSG and pulmonary function testing, into the routine clinical care for MPS patients. These findings underscore that even in the absence of overt clinical symptoms, subclinical SDB may be present and clinically significant. Pal et al. (22) conducted a study on children with MPS type I and reported that PSQ-SDB scores showed strong concordance with PSG findings. Elevated scores were significantly associated with moderate-to-severe OSA, supporting the PSQ's validity as a screening tool in this population. It should be emphasised that early recognition of sleep-related breathing problems using PSQ can allow for timely therapeutic interventions such as continuous PAP (CPAP) or adenotonsillectomy. In our study, the median PSQ-SDB scores of those patients with MPS type I were within the normal range, and all patients were receiving ERT. Notably, half of the patients with MPS type I had a history of adenotonsillectomy, suggesting that the favourable sleep-related outcomes in this group may be partially attributable to their prior surgical interventions. The questionnaire used in this study can offer guidance in assessing SDB in those patients who have challenges in accessing or adhering to PSG due to the scarcity of clinics in our country and prolonged appointment waiting times.

Upper-airway obstruction and decreased pulmonary reserve often lead to OSA. Clinical features include mouth-breathing, snoring, apnea, and/or restless sleep. Less frequently, daytime somnolence, failure to thrive, pulmonary hypertension, and cor pulmonale may be noticed. Behavioural and learning problems may also occur secondary to disrupted sleep (23). In a study by Ademhan Tural et al. (15), which investigated sleep-related breathing disorders and associated respiratory problems and exercise capacity in patients diagnosed with MPS IVA and MPS VI, the prevalence of OSA was found to be high in these patients. Due to the high prevalence of OSA in MPS IVA and MPS IV patients, they emphasized the importance of PSG screening for sleep disorders in these individuals (15). Similarly, in our study, we planned to perform PSG for those patients diagnosed with sleep-related breathing disorders.

Sleep disturbances are also frequently reported clinical features in patients with MPS (12-15). Sleep disorders represent an important cause of impaired quality of life in this population. Nashed et al. (24) reported a similarly high prevalence of OSA and gas exchange abnormalities in a pediatric cohort with multiple types of mucopolysaccharidosis, using full overnight PSG. Their findings of frequent oxygen desaturation and CO_2 retention, as well as the anatomical factors contributing to upper airway obstruction, mirror the sleep disturbances observed in our study, especially among those patients with elevated PSQ Scores (24). The success of treatment strategies, including CPAP and adenotonsillectomy in Nashed's cohort, further suggests that early and targeted intervention may ameliorate sleep-related respiratory complications.

Together with Wooten et al. (21), who demonstrated that pulmonary function decline correlates with SDB severity, Nashed's data reinforce the need for a dual approach in MPS patient management. Specifically, our results highlight the potential value of integrating objective sleep studies and anatomical airway assessments into routine clinical monitoring, particularly when subjective questionnaires suggest moderate or severe sleep-related symptoms (21,24). This study also emphasized the importance of identifying sleep disturbances in MPS patients and the role of PSG in guiding appropriate therapeutic strategies.

Study Limitations

The primary limitation of this study was its relatively small sample size, which is an inherent challenge in research involving rare diseases such as mucopolysaccharidosis. The limited number of participants may reduce the generalizability of our findings and restrict the statistical power to detect more subtle associations. The small number of patients within each MPS subtype limited the statistical power of subtype-based correlation analyses, and therefore these results should be interpreted cautiously. Our work aimed to contribute to the growing body of evidence by drawing attention to the need for the early recognition and systematic evaluation of sleep-related symptoms in this vulnerable population.

Conclusion

In our study, we found that approximately half of those patients diagnosed with MPS had SDB. We emphasize the need for routine follow-up evaluation of MPS patients for sleep-related breathing problems and the need for PSG in those with symptoms of SDB.

Ethics

Ethics Committee Approval: Approval for this study was obtained from the University of Health Sciences Türkiye, Van Training and Research Hospital Non-Interventional Clinical Research Ethics Committee (approval number: GOKAEK/2025-05-08, date: 04.07.2025) according to the guidelines of the Helsinki Declaration of Human Rights.

Informed Consent: Informed consent was provided by all of the patients.

Footnotes

Authorship Contributions

Surgical and Medical Practices: G.U., F.E.K., Concept: F.E.K., Design: G.U., Data Collection or Processing: G.U., F.E.K., N.G., Analysis or Interpretation: N.G., T.R.G., Literature Search: G.U., T.R.G., Writing: G.U., T.R.G.

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Original Article

Safety and Efficacy of Early versus Conventional Enteral Feeding after Colostomy Closure in Children with High Anorectal Malformation

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ABSTRACT

Aim: The restoration of intestinal continuity after colostomy closure is a critical step and postoperative recovery is influenced by nutritional strategies. This study aimed to evaluate the safety and efficacy of early versus conventional feeding in children undergoing sigmoid colostomy closure on postoperative recovery parameters.

Materials and Methods: A prospective randomized observational study was carried out at a tertiary care hospital between January 2022 and October 2025. Fifty children (<16 years) undergoing stoma closure were randomized into two groups: Group A (early feeding within 48 hours postoperatively) and Group B (conventional feeding after return of bowel function or on postoperative day 5). Demographic data, perioperative parameters, and postoperative outcomes including time to initiation of feeding, time to full feeds, bowel function recovery, complications, and hospital stay were analyzed using SPSS v24.0.

Results: Of the 50 patients (39 males, 11 females; mean age 1.1 years), 25 were allocated to each group. Feeding was initiated significantly earlier in Group A (mean 18.7 hours) compared with Group B (52.6 hours; $p<0.001$). Time to achieve full feeds was shorter in Group A (median 42.5 hours) versus Group B (72.5 hours; $p<0.001$). First bowel movement occurred earlier in Group A (mean 4.1 days) than Group B (5.9 days; $p<0.01$). Median hospital stay was reduced in Group A (4.5 days) compared with Group B (6 days; $p<0.01$). No anastomotic leaks or wound dehiscence were observed. Minor complications included transient vomiting and urinary tract infections, with no significant differences between the groups.

Conclusion: Early enteral feeding after stoma closure in children with high anorectal malformation is safe, well tolerated, and associated with faster recovery and shorter hospital stays compared with conventional feeding.

Keywords: Early enteral feeding, colostomy closure, high anorectal malformation, ERAS, postoperative recovery

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Introduction

Anorectal malformation (ARM) is a spectrum of congenital anomalies which affect the distal anus and rectum, occurring in approximately 1 in 5,000 live births (1,2). Management of high ARM often requires staged surgical management, beginning with a high divided sigmoid diverting colostomy followed by definitive repair and later stoma closure. The creation of a temporary diverting colostomy allows for the safe passage of the stool while the definitive posterior sagittal anorectoplasty is performed and the area heals. The subsequent procedure, colostomy closure, marks the final stage of reconstruction and is a common operation in pediatric surgery (2,3). Restoration of intestinal continuity after colostomy closure is a critical step in the overall treatment pathway, and postoperative recovery is influenced by nutritional strategies.

Despite the routine nature of stoma closure, the postoperative period is often complicated by paralytic ileus, pain, and feeding intolerance, which can prolong hospital stay and impact recovery (4). Historically, conventional postoperative management has dictated a policy of delayed enteral feeding, often requiring patients to remain nil per oral (NPO) until there is clear evidence of returning bowel function (e.g., passage of flatus or stool), typically spanning four to five days. This approach is primarily rooted in the concern that early mechanical stimulation or increased intra-luminal pressure might compromise the integrity of the freshly created bowel anastomosis, potentially leading to a catastrophic anastomotic leak. However, this period of mandatory starvation, which is increasingly recognized as detrimental, leads to a catabolic state, malnutrition, weight loss, and reduced immunity (5-7).

However, modern pediatric surgical practices are increasingly challenging this traditional paradigm. Mounting evidence from adult and pediatric literature, particularly in non-gastrointestinal surgeries, supports the safety and significant benefits of initiating early enteral nutrition (EEN) (6,7). The concept of Enhanced Recovery After Surgery (ERAS) or "Fast-Track" protocols, initially established in adult surgery, advocates for a multimodal approach, with early enteral feeding (EEF) being a cornerstone (8,9). EEF, typically defined as the initiation of nutrition within 24 to 48 hours post-surgery, has a sound physiological basis. EEF is hypothesized to stimulate peristalsis, accelerate the resolution of postoperative ileus, maintain the integrity of the gut mucosal barrier, and prevent the catabolic state associated with prolonged starvation. Furthermore, rapid restoration of oral intake is a cornerstone of enhanced recovery protocols, aiming to reduce hospital morbidity and the overall duration of hospitalization (8,9).

Despite this mounting evidence, institutional protocols for pediatric colostomy closure often vary widely and so require standardization. The present prospective randomized observational study was designed to rigorously compare a protocol of EEF (Group A) initiated within 48 hours versus conventional feeding (Group B) (NPO until day 5 or the return of bowel function) in children undergoing sigmoid colostomy closure for high ARM. The primary objective was to definitively assess the impact of EEF on postoperative recovery parameters, including time to full feeding, first bowel movement, and the duration of hospital stay, while strictly monitoring for complications.

Materials and Methods

This prospective randomized observational study was carried out in a tertiary care hospital between January 2022 and October 2025. The study population consisted of children undergoing stoma closure following a high divided sigmoid colostomy for high ARM. Ethical approval was obtained from the Khaja Bandanawaz University Ethical Committee (no.: IEC/2021/178, date: 06.05.2021), and written informed consent was obtained from the parents/guardians, and assent from children older than 7 years, in accordance with institutional ethical committee guidelines. Children younger than 12 years scheduled for stoma closure after high divided sigmoid colostomy for high ARM were included in this study. Those patients with hemodynamic instability or those with multiple anomalies, syndromes or reanastomosis were excluded from this study.

Data regarding age, sex, weight, and duration of surgery were noted. None of our patients underwent preoperative proximal bowel preparation but, in all patients, distal stoma washes with normal saline (25 mL/kg) were performed the day before surgery. Preoperatively, antibiotics were administered before the induction of anesthesia. Preoperatively, complete blood count, kidney function tests, serum electrolytes, and the body mass index of the patients were recorded. Intestinal continuity was restored using a single-layer interrupted absorbable suture [Vicryl® (Polyglactin 910) 3-0/4-0]. All children were given adequate preoperative, intraoperative, and postoperative fluids and analgesia as per the standard protocol. Patients were randomized by using odd and even enrollment numbers, odd numbers were allotted to early feeding (Group A) and even were allotted to conventional feeding (Group B).

Group A (Early Feeding)

Enteral nutrition was initiated within 48 hours of surgery, either orally or via a nasogastric tube. Feeding began with clear fluids, followed by milk. The initial regimen was 1-2 mL/kg every 2 hours, with increments of 1 mL/kg after tolerance of two consecutive feeds. Oral feeding was introduced once nasogastric feeds were well tolerated. Full feeding was defined as tolerance of at least 80% of daily maintenance fluid requirements. If intolerance occurred (vomiting, abdominal distension, or high gastric aspirates), two feeds were withheld and the process was restarted after 4-6 hours.

Group B (Conventional Feeding)

The patients remained NPO until the fifth postoperative day or until bowel function returned, indicated by the passage of stool/flatus and a reduction in nasogastric aspirates.

All patients were given Ceftriaxone, Amikacin and Metronidazole postoperatively for 5 days as per the institutional protocol. In the postoperative period, the time until the initiation of feeding in hours, the time to achieve full feeding in hours, the requirement of nasogastric tube reinsertion and episodes of feeding intolerance, electrolyte imbalance, the time to the appearance of the first bowel sounds, the time to first bowel movement, the time to discharge, hospital stay, and complications such as surgical site infections (SSI), wound dehiscence, intraabdominal collection, anastomotic leak, vomiting, and abdominal distension were noted. Signs of anastomotic leak (tachycardia, fever, abdominal tenderness, clinical deterioration) were closely monitored. Suspected cases underwent blood investigations, ultrasound, and abdominal X-rays. Patients with confirmed leaks were excluded from this study and treated according to institutional treatment protocols. After discharge, the patients were followed up at 15 days and one month for any complications such as feed-intolerance or wound complications.

Statistical Analysis

Data were collected using a structured proforma, entered into an MS Excel sheet, and analyzed using SPSS 24.0 version IBM USA. Qualitative data are expressed in terms of proportions, while quantitative data are expressed in terms of mean and standard deviation. Associations between two qualitative variables were analyzed using chi-square/Fisher's exact test. A p value of <0.05 was considered statistically significant, while a p value of <0.001 was considered highly significant.

Results

A total of 50 patients were included in this study, 25 in each group were recruited, comprising 39 males (78%) and 11 females (22%) with a male to female ratio of 3.5:1. In the early feeding group (Group A), 20 patients were male, whereas in the conventional feeding group (Group B), 19 were male. The mean age was comparable between both groups (Table I), with an age range of between 6 months to 5 years. In this study, the mean body weight was comparable in both groups (Table I), the mean duration of surgery in Group A was 90 minutes and it was 92 minutes in Group B, which was comparable (Table I).

Postoperative recovery parameters demonstrated significant differences between the two groups. The median time to the initiation of oral feeding was 58 hours in Group A compared with 92 hours in Group B (p=0.001). On average, feeding was initiated at 18.7 (15 to 25) hours in Group A and 52.6 (19 to 95) hours in the Group B (p<0.001). Median full feeding hours were 42.5 and 72.5 hours in Group A and Group B, respectively (p<0.001). The median time to first bowel sound was 40 hours in Group A and 49 hours in Group B, but this difference was not statistically significant (p=0.208). First bowel movement in Group A was recorded at an average of 4.10 postoperative days, compared with 5.90 days in Group B (p<0.01). Reinsertion of the nasogastric tube was not required in either group (Table II).

The median duration of hospital stay was significantly reduced in Group A (4.5 days) compared with Group B (6 days; p<0.01). There were 2 cases of vomiting in the early feeding group (Group A), which were temporary and resolved spontaneously. Septic complications were noted in 5 patients in Group A and 4 patients in Group B (p=0.7).

Table I. Demographic and perioperative characteristics of the study groups

Parameter	Group A (early feeding, n=25)	Group B (conventional feeding, n=25)	p value
Male: female	20:5	19:6	0.74
Mean age (years)	1.18±0.9	1.05±0.8	0.853
Mean body weight (kg)	8.79±2.1	9.29±2.3	0.834
Mean duration of surgery (min)	90±12	92±14	0.62

Table II. Postoperative recovery parameters in the study groups

Parameter	Group A (early feeding, n=25)	Group B (conventional feeding, n=25)	p value
Median time to initiation of oral feeding (hours)	58	92	0.001
Median time to full feeds (hours)	42.5	72.5	0.001
Median time to first bowel sound (hours)	40	49	0.208
Median hospital stay (days)	4.5	6.0	0.01
Vomiting (n)	2 (transient, resolved)	0	0.15
Septic complications (n)	5 (mostly UTI)	4 (mostly UTI)	0.70

UTI: Urinary tract infection

The majority were urinary tract infections managed with antibiotics (Table II). There were no cases of wound infection, wound dehiscence, anastomotic leak, or requirement for relook surgery in either group. The follow-up periods were uneventful in both groups.

Discussion

The closure of a colostomy in the pediatric population, particularly following high ARM, has historically been associated with significant morbidity. Traditional surgical dogma dictated a conservative approach, prolonged nasogastric decompression and a strict NPO regimen to protect the tenuous anastomosis from mechanical stress and potential leakage. The results of this prospective randomized study challenge this paradigm, providing compelling evidence that EEF is not only feasible, but also offers superior postoperative recovery metrics compared to conventional management.

In this study, the early feeding group (Group A) initiated feeds at a mean of 18.7 hours compared to 52.6 hours in the conventional group ($p<0.001$). Despite this aggressive approach, there was no statistically significant increase in complications. We observed no anastomotic leaks or wound dehiscence in the early feeding group. This aligns with recent meta-analyses in pediatric gastrointestinal surgery suggesting that starvation does not protect anastomosis (10). In fact, physiologic evidence suggests that EEN promotes anastomotic healing by increasing collagen deposition and enhancing blood flow to the gut, whereas prolonged fasting may lead to mucosal atrophy and increased bacterial translocation (11-13).

A significant finding in our study was the accelerated return of bowel function in the early feeding group. While the time to the first bowel sound was comparable between the groups ($p=0.208$), the functional endpoint, the first bowel movement, occurred significantly earlier in Group A (4.10 days) compared to Group B (5.90 days) ($p<0.01$). This supports the concept of the gastrocolic reflex; the introduction of intraluminal nutrients triggers the release of gastrointestinal hormones (such as gastrin and cholecystokinin) and stimulates peristalsis (13-15). By withholding feeding in the conventional group, this physiological reboot is delayed, prolonging the duration of postoperative ileus, and may paradoxically increase the risk of bacterial translocation due to the breakdown of the mucosal barrier (13,14). The physiological rationale for early feeding lies in the stimulation of gut motility, maintenance of mucosal integrity, and prevention of bacterial translocation. EEN also supports immune function, reduces catabolism, and promotes faster wound healing (12-15).

A critical yet often overlooked advantage of early feeding is the reduction in intravenous fluid requirements. Patients in the conventional feeding group required intravenous (IV) fluids for nearly 5 days. Prolonged administration of crystalloids is known to cause interstitial edema, including edema of the bowel wall. Bowel wall edema can impair anastomotic healing and inhibit peristalsis, creating a vicious cycle which prolongs ileus (15). By transitioning to oral intake rapidly, the early feeding group relied less on IV hydration, potentially reducing intestinal edema and facilitating the quicker return of bowel sounds as observed in our data. In pediatric surgery, patient comfort is inextricably linked to surgical physiology. Children who are kept NPO for extended periods are prone to hunger, irritability, and prolonged crying. Crying induces significant aerophagia (swallowing of air), which exacerbates gastric dilation and abdominal distension, potentially putting more tension on the anastomosis than a small volume of liquid feed (16,17).

We observed that children in the early feeding group were generally more settled. The low incidence of

vomiting (only 2 cases), which were transient and resolved spontaneously, underscoring the safety of early feeding protocols, suggests that the small intestine recovers motility almost immediately after surgery, and the stomach is capable of handling clear fluids long before colonic function fully returns. The fear that early peristalsis will mechanically disrupt a fresh suture line is the primary barrier to adopting early feeding. However, our study utilized a single-layer interrupted suture technique with Vicryl 3-0/4-0, which provides immediate mechanical stability. Our results showed zero anastomotic leaks in the early feeding group. This aligns with findings from the ERAS Society (18), which suggests that the collagen deposition phase of healing is actually supported by the nutrients provided via enteral feeding (18). The absence of wound dehiscence or significant intra-abdominal collections in our study further corroborates that the metabolic state of the fed child supports better tissue repair than the catabolic state of the starved child. Furthermore, septic complications were comparable between the 2 groups (p=0.7), with the majority being urinary tract infections rather than SSI. This dispels the notion that early feeding increases the risk of abdominal distension leading to wound complications or aspiration pneumonia. From a healthcare systems perspective, the reduction in hospital stay is the most impactful finding. The early feeding group was discharged at a median of 1.5 days earlier than the conventional group (p<0.01). In a tertiary care setting with high patient volume, this accelerated turnover increases bed availability and reduces the direct costs associated with hospitalization (nursing care, IV fluids, and medication) (18). Our study corroborates these findings, specifically in the context of high ARM, where prolonged hospitalization and delayed recovery can impose significant burdens on families and healthcare systems (18).

Several studies in adults and a growing body of evidence in pediatrics have demonstrated the safety and efficacy of EEF after intestinal anastomosis, including stoma closure (19,20).

Study Limitations

This study had limitations such as its single-center design and relatively small sample size. Longer follow-up beyond one month would be valuable in order to assess late complications such as adhesive intestinal obstruction. Additionally, while randomization was performed using odd-even enrollment, more robust randomization methods could further strengthen internal validity. Multicenter trials with larger cohorts would further validate these findings.

Conclusion

EEF initiated within the first 24 hours is safe, well tolerated, and significantly reduces the duration of ileus and hospital stay. It does not increase the risk of anastomotic leakage or wound complications. Instead, it significantly reduces the time to full feeding, accelerates the return of bowel functions, and shortens hospital stay. Based on these findings, the traditional practice of keeping children NPO for 5 days is unnecessary, and an early feeding protocol should be considered as the standard of care for pediatric stoma closure.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Khaja Bandanawaz University Ethical Committee (no.: IEC/2021/178, date: 06.05.2021).

Informed Consent: Written informed consent was obtained from the parents/guardians, and assent from children older than 7 years, in accordance with institutional ethical committee guidelines.

Footnotes

Authorship Contributions

Concept: N.D.S., S.K., A.S., Design: N.D.S., S.K., Data Collection or Processing: N.D.S., S.K., A.S., Analysis or Interpretation: N.D.S., S.K., A.S., Literature Search: N.D.S., A.S., Writing: N.D.S., S.K.

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Original Article

Clinical and Laboratory Findings in Children with Positive Newborn Screening for Cystic Fibrosis: A Multicenter Retrospective Study

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ABSTRACT

Aim: In some settings, the diagnostic evaluation of cystic fibrosis (CF) may be delayed due to limited access to sweat chloride tests. This study aimed to describe the clinical and laboratory findings observed during the evaluation of children with positive newborn screening (NBS) results for CF.

Materials and Methods: We retrospectively reviewed the data of children referred after positive NBS for CF who were evaluated at three pediatric pulmonology centers between 2015 and 2021. NBS was used as a referral tool, and the diagnosis of CF was established according to standard diagnostic criteria, including the sweat chloride test and/or genetic analysis. Demographic characteristics, clinical features, and laboratory findings were compared between those children diagnosed with CF after NBS and those not diagnosed with CF.

Results: A total of 1,469 children were included, of whom 76 (5.2%) were diagnosed with CF. CF was more frequently observed in those children with parental consanguinity, a history of meconium ileus, steatorrhea, doll-like facial appearance, metabolic alkalosis, hyponatremia, hypokalemia, hypochloremia, and having a sibling with CF (all $p<0.05$).

Conclusion: This large multicenter cohort study presents real-life data on the clinical and laboratory findings observed in those children with positive NBS for CF. This study does not propose an alternative diagnostic strategy to the sweat chloride test, but highlights supportive clinical features which may raise clinical suspicion and emphasizes the importance of timely referral and follow-up, particularly in settings where access to confirmatory testing may be delayed.

Keywords: Cystic fibrosis, immunoreactive trypsinogen, newborn screening, sweat chloride

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Introduction

Cystic fibrosis (CF) is an autosomal recessive disorder caused by pathogenic variants in the gene encoding the CF transmembrane regulator (CFTR) protein, resulting in defective chloride transport across epithelial cells. This defect leads to the production of thick, viscous secretions, impaired mucociliary clearance, and progressive multisystem involvement, particularly affecting the respiratory and gastrointestinal systems (1,2).

Newborn screening (NBS) programs for CF aim to detect affected infants before the onset of clinical symptoms, thereby enabling the early initiation of treatment and improved long-term outcomes (3). Most NBS strategies are based on biochemical screening and begin with the measurement of immunoreactive trypsinogen (IRT) from dried blood spots (1). Elevated IRT levels indicate pancreatic duct obstruction and leakage of pancreatic enzymes into the circulation (4). Infants with persistently increased IRT levels are subsequently referred to specialized CF centers for confirmatory diagnostic evaluation, primarily using the sweat chloride test (5,6).

Early diagnosis through NBS enables the timely initiation of essential interventions, including pancreatic enzyme replacement therapy, salt and fat-soluble vitamin supplementation, and structured pulmonary care, which together reduce CF-related morbidity and mortality (7,8). The sweat chloride test remains the cornerstone and gold standard for the diagnosis of CF (9,10). However, access to sweat chloride tests may be limited due to the need for specialized equipment, standardized procedures, and experienced personnel (11,12).

The limited availability of sweat chloride tests has been recognized as a challenge in developing countries and increasing concerns have also been reported in parts of Europe (11,12). In our country, nationwide access to the sweat chloride test was interrupted between 2018 and 2019 due to a licensing issue related to pilocarpine. During such periods, diagnostic confirmation may be delayed, and reliance on genetic testing alone may not be feasible because of prolonged turnaround times and the high genetic heterogeneity observed in the population. Under these circumstances, clinicians may face uncertainty regarding early clinical decision-making for infants with suspected CF.

In situations where the sweat chloride test is delayed or unavailable, careful clinical evaluation and supportive laboratory findings may help raise clinical suspicion and guide interim management while awaiting confirmatory diagnosis. This study does not advocate for the replacement of the sweat chloride test as the diagnostic standard, but rather to describe the clinical and laboratory findings observed during the evaluation of children with positive NBS results for CF in real-life settings. By presenting data from a multicenter cohort, we aimed to highlight supportive features which may assist clinicians in identifying those infants who require close follow-up and timely referral during periods of limited access to confirmatory testing.

Materials and Methods

This multicenter retrospective study was conducted in three pediatric pulmonology centers between 2015 and 2021. Children who were referred to these centers following positive NBS results for CF were evaluated. Children without follow-up data or lacking sufficient core clinical information to ascertain their CF diagnostic status were excluded. Analyses for individual variables were performed using the available data.

Since January 1st, 2015, the Ministry of Health in Türkiye has implemented a nationwide NBS program for CF using the IRT/IRT protocol. Dried heel blood samples are analyzed for IRT levels. If the first IRT (at approximately 72 hours of life) is ≥90 μg/L and the second IRT (at 7-14 days of life) is ≥70 μg/L, the NBS result is considered positive. Infants with positive NBS results are referred by primary care physicians to specialized CF centers for further diagnostic evaluation (13).

NBS was used as a referral tool only and not as a diagnostic method. According to the European Cystic Fibrosis Society (ECFS), the diagnosis of CF is established by a sweat chloride concentration >59 mmol/L and/or the identification of two disease-causing CFTR variants in the presence of suggestive clinical findings, such as positive NBS, bronchiectasis, CF-related respiratory pathogens, salt loss syndrome, or exocrine pancreatic insufficiency (14). Only those children referred after positive NBS have been included in this study. Those children diagnosed with CF independently of NBS have not been included.

The following data were recorded for all of the children: age at first admission following NBS positivity, gender, gestational age (preterm or term), first and second IRT levels, duration of follow-up, age at diagnosis of CF (if applicable), parental consanguinity, a history of meconium ileus, the presence of steatorrhea (based on fecal fat excretion testing), daily weight gain, the presence of a doll-like facial appearance, having a sibling with CF, pancreatic elastase levels (if available), blood pH and bicarbonate (HCO_3) levels, and serum sodium, potassium, chloride,

and albumin levels measured at admission, regardless of presenting symptoms.

Although the sweat chloride test is routinely performed at participating centers, access was temporarily restricted for part of the study period due to a nationwide licensing problem with pilocarpine. When performed, the sweat chloride test results, obtained by either conductivity measurement or chloride titration, were recorded. All of the collected variables were analyzed in order to assess their associations with a confirmed diagnosis of CF.

The definitions used are as follows:

- Meconium ileus: intestinal obstruction caused by thickened meconium in the ileum (15).

- Doll-like facial appearance: a round facial appearance with puffy cheeks, small nose, and small chin; typically observed in infancy and associated with hypoalbuminemia and malnutrition; also seen in other malabsorptive conditions (16).

- Hyponatremia: serum sodium <135 mmol/L.

- Hypokalemia: serum potassium <3.5 mEq/L.

- Hypochloremia: serum chloride <96 mmol/L.

- Hypoalbuminemia: serum albumin <3.5 g/dL (17-22).

- Pseudo-Bartter syndrome: defined according to ECFS registry guidelines as metabolic alkalosis with blood pH >7.45, serum sodium <130 mmol/L, and serum chloride <90 mmol/L (23).

Ethical approval was obtained from the Clinical Research Ethics Committee of Gazi University (approval number: 11, date: 04.01.2021), and this study was conducted in accordance with the principles of the Declaration of Helsinki. Due to the retrospective design of this study, informed consent was not requested by the ethics committee.

Statistical Analysis

IBM SPSS Statistics version 22.0 (IBM, Armonk, NY, USA) and IBM SPSS Amos-24 were used for the statistical analyses. The conformity of the variables to the normal distribution was examined using visual (histogram and probability graphs) and analytical methods (the Kolmogorov-Smirnov test). Categorical variables are presented as numbers and percentages, while continuous variables are expressed as mean ± standard deviation or medians with interquartile range (IQR) as appropriate.

Binary logistic regression and multivariate logistic regression analyses were used in order to evaluate associations between clinical and laboratory variables and the diagnosis of CF. Variables with a p value<0.10 in univariate analysis and those considered clinically relevant were included in the multivariate model. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Sensitivity, specificity, positive predictive values, and negative predictive values were determined using 2 by 2 tables. A p value<0.05 was considered statistically significant.

Results

During the study period, 1,484 children had a positive NBS result for CF. Fifteen children were excluded due to a lack of follow-up or insufficient core clinical information, leaving 1,469 children for analysis. The demographic and clinical characteristics of the children with positive NBS for CF are presented in Table I.

The median first IRT level was 99 (IQR: 90-121.5) µg/L and the median second IRT level was 74 (IQR: 70-90) µg/L. The median daily weight gain was 30 (IQR: 23-38) g/day. Pancreatic elastase levels were available in 45 (3.1%) children; among these, 10 (22.2%) children had pancreatic insufficiency, and the median pancreatic elastase level was 369 (IQR: 204.5-476) µg/mL.

Following NBS positivity, 390 (26.5%) children were unable to undergo a sweat chloride test, while 1,079 (73.5%) children underwent at least one sweat chloride test. Among those tested, 204 (18.9%) had a sweat conductivity test, 948 (87.9%) had a sweat chloride titration test, and 73 (6.8%) children underwent both tests. The median of the sweat conductivity test results was 30.4 (10.8-120.0) mmol/L, and

Table I. Demographic and clinical characteristics of children with positive newborn screening for cystic fibrosis (n=1,469)

Gender Female (n/%) Male (n/%)	 818/55.7 651/44.3
Age at admission (days) [median (IQR)]	27 (21-37)
Gestational age at birth (n=1,330) Premature (n/%) Mature/Term (n/%)	 146/11.0 1,184/89.0
Parental consanguinity (n/%) (n=1,407)	249/17.0
History of meconium ileus (n/%) (n=921)	6/0.7
Doll-like facial appearance (n/%) (n=1,469)	29/2.0
Metabolic alkalosis (n/%) (n=858)	78/9.1
Hyponatremia (n/%) (n=902)	64/7.1
Hypokalemia (n/%) (n=839)	16/1.9
Hypochloremia (n/%) (n=880)	29/3.3
Hypoalbuminemia (n/%) (n=687)	95/13.8
Steatorrhea (n/%) (n=423)	94/22.2

IQR: Interquartile range

the median sweat chloride concentration was 26.2 (10.0-121.0) mmol/L.

Overall, 76 (5.2%) children were diagnosed with CF. The median age at diagnosis of CF was 40 (IQR: 30-73) days. Among the children diagnosed with CF, 60 (78.9%) underwent a sweat chloride test, while 16 (21.1%) children were diagnosed based on genetic testing in the absence of a sweat chloride test. Of all of those children with a sibling, seven (1.0%) had a sibling with CF.

The association between the clinical and laboratory variables and CF diagnosis in univariate analyses are presented in Table II. First and second IRT levels were higher in those children diagnosed with CF compared with those not diagnosed (Table II). Pseudo-Bartter syndrome was identified in 7 (9%) among the 78 children with metabolic alkalosis. When combinations of laboratory abnormalities were examined, CF was diagnosed in 12 (66.7%) of the 18 children with concurrent hyponatremia and hypochloremia [OR (95% CI): 26.9 (9.76-74.11), p=0.001]. Among the children with hyponatremia, hypochloremia, and hypoalbuminemia, 5 (83.3%) of the 6 children were diagnosed with CF [OR (95% CI): 60.8 (7.00-527.71), p=0.001]. CF was diagnosed in 6 (54.5%) of 11 children with hyponatremia, hypochloremia, and hypokalemia [OR (95% CI): 14.7 (4.38-49.52), p=0.001]. Additionally, 3 (75%) of 4 children with the combination of hyponatremia, hypochloremia, hypoalbuminemia, and hypokalemia were diagnosed with CF [OR (95% CI): 35.4 (3.64-345.24), p=0.002].

Albumin levels were measured in 23 (79.3%) of 29 children with doll-like facial appearance, with a median albumin level of 2.6 (IQR: 2.2-3.2) g/dL. Hypoalbuminemia was found in 18 (62.1%) of the children with a doll-like facial appearance.

The multivariate logistic regression analysis results are shown in Table III. The model explained 37.6% of the variance in CF diagnosis. When hypochloremia, doll-like facial appearance, and having a sibling with CF were included in the model, all three variables were significantly associated with a diagnosis of CF ($p<0.05$). The standardized beta coefficients were 0.117 for hypochloremia, 0.391 for doll-like facial appearance and 0.290 for having a sibling with CF.

The sensitivity and specificity of individual clinical and laboratory features are summarized in Table IV. The sensitivity and specificity values were as follows: parental consanguinity (27.4% and 82.8%), sibling with CF (20.0% and 99.8%), meconium ileus at birth (6.3% and 99.6%), doll-like facial appearance (32.4% and 99.6%), metabolic alkalosis (30.9% and 92.8%), hyponatremia (29.2% and 94.8%), hypochloremia (22.8% and 99.1%), hypokalemia (15.7% and 99.3%), hypoalbuminemia (40.8% and 89.3%), and steatorrhea (70.6% and 79.8%).

Table II. Univariate analysis of clinical and laboratory variables associated with cystic fibrosis

Variables	Diagnosed with CF (n=76)	Not diagnosed with CF (n=1,393)	Odds ratio (95% CI[a])	p*
First IRT level (µg/L) [median (min-max)]	136 (90-360)	98 (90-500)	1.01 (1.01–1.02)	**0.001**
Second IRT level (µg/L) [median (min-max)]	108 (70-275)	73 (70-285)	1.02 (1.02–1.03)	**0.001**
Prematurity [n/N (%)]	7/57 (12.3)	139/1,273 (10.9)	1.1 (0.50-2.56)	0.668
Parental consanguinity [n/N (%)]	20/73 (27.4)	229/1,334 (17.2)	1.8 (1.07-3.10)	**0.039**
Metabolic alkalosis [n/N (%)]	21/68 (30.9)	57/790 (7.2)	5.7 (3.21-10.27)	**0.001**
Hypoalbuminemia [n/N (%)]	29/71 (40.8)	66/616 (10.7)	5.8 (3.36-9.85)	**0.001**
Hyponatremia [n/N (%)]	21/72 (29.2)	43/830 (5.2)	7.5 (4.16-13.64)	**0.001**
Steatorrhea [n/N (%)]	12/17 (70.6)	82/406 (20.2)	9.4 (3.24-27.67)	**0.001**
Meconium ileus at birth [n/N (%)]	2/32 (6.3)	4/889 (0.4)	14.8 (2.59-83.69)	**0.016**
Hypokalemia [n/N (%)]	11/70 (15.7)	5/769 (0.7)	28.5 (9.58-84.71)	**0.001**
Hypochloremia [n/N (%)]	16/70 (22.9)	7/810 (0.9)	33.9 (13.41-86.14)	**0.001**
Doll-like facial appearance [n/N (%)]	23/76 (30.3)	6/1,393 (0.4)	110.3 (42.93-283.30)	**0.001**
Sibling with CF [n/N (%)]	6/30 (20.0)	1/645 (0.2)	161.0 (18.64-1,390.28)	**0.001**

*p<0.05 is significant
[a]CI: Confidence interval
[Odds ratios and 95% confidence intervals were calculated using binary logistic regression to evaluate associations with cystic fibrosis]
[Odds ratios for continuous variables represent the change in odds per unit increase]
CF: Cystic fibrosis, IRT: Immunoreactive trypsinogen

Table III. Multivariate logistic regression analysis of variables associated with cystic fibrosis

	Variables	B	S.E.	β (Beta)	p*
Cystic fibrosis	**Hypoalbuminemia**	0.025	0.022	0.038	0.256
	Hyponatremia	0.027	0.027	0.030	0.329
	Hypochloremia	0.166	0.047	0.117	0.001
	Parental consanguinity	0.009	0.013	0.016	0.475
	Doll-like facial appearance	0.614	0.040	0.391	0.001
	Sibling with CF	0.621	0.069	0.290	0.001

[Variance ratio: R^2=0.376]
*p<0.05 is significant
B: Unstandardized coefficient, S.E.: Standard error, β (Beta): Standardized coefficient, CF: Cystic fibrosis

Table IV. Sensitivity and specificity of clinical and laboratory features in children with cystic fibrosis

Variables	Sensitivity (%)	Specificity (%)	PPV[α] (%)	NPV[β] (%)
Sibling with CF (n=7)	20.0	99.8	85.7	96.4
Doll-like facial appearance (n=29)	32.4	99.6	79.3	96.6
Hypochloremia (n=23)	22.8	99.1	69.6	93.7
Hypokalemia (n=16)	15.7	99.3	68.7	92.8
Meconium ileus at birth (n=6)	6.3	99.6	33.3	96.7
Hyponatremia (n=64)	29.2	94.8	32.8	93.9
Hypoalbuminemia (n=95)	40.8	89.3	30.5	92.9
Metabolic alkalosis (n=78)	30.9	92.8	26.9	93.9
Steatorrhea (n=94)	70.6	79.8	12.8	98.5
Parental consanguinity (n=249)	27.4	82.8	8.0	95.4

[α]Positive predictive value, [β]Negative predictive value, CF: Cystic fibrosis

Discussion

This multicenter retrospective study aimed to evaluate the clinical and laboratory findings observed during the evaluation of children with positive NBS results for CF, particularly in situations where access to sweat chloride tests was limited or delayed. The findings highlight that having a sibling with CF and the presence of a doll-like facial appearance were the most prominent supportive clinical features associated with a diagnosis of CF among NBS-positive children.

In addition, a history of meconium ileus, steatorrhea, metabolic alkalosis, hyponatremia, hypokalemia, hypochloremia, and hypoalbuminemia were also associated with an increased likelihood of CF. Although CF is an autosomal recessive disorder and parental consanguinity is a well-known risk factor, it was less predictive than the other clinical and laboratory features in our cohort. This observation may be related to the high CF carrier frequency and marked genetic heterogeneity in our population. In populations where carrier rates are high, the presence of consanguinity alone may not be distinguishing; however, the coexistence of characteristic clinical findings may be more informative in raising clinical suspicion.

The doll-like facial appearance has historically been an underrecognized clinical feature in CF (16). Kose et al. (16) described this appearance in edematous, malnourished children with hypoalbuminemia. In the present study, doll-like facial appearance emerged as a strong clinical indicator of CF, even in some cases without documented hypoalbuminemia, supporting its value as a readily recognizable physical finding. Although this facial phenotype is not specific to CF and may also be observed in other malabsorptive or metabolic conditions, its presence in children with positive NBS should prompt careful evaluation and close follow-up, particularly when access to confirmatory diagnostic testing is limited (24).

Family history plays an important role in the early recognition of CF. In our study, having a sibling with CF

was the most strongly associated factor, emphasizing the importance of heightened clinical awareness and early evaluation in the siblings of affected individuals. While parental consanguinity was relatively common in our population, it did not emerge as a dominant distinguishing feature. This may reflect the widespread CF carrier status in Türkiye, where CF can occur even in the absence of consanguinity. In populations with lower carrier frequencies, however, consanguinity may retain greater clinical relevance as a supportive clue (25-28).

Meconium ileus is one of the earliest and most specific manifestations of CF and has been reported in 10-20% of affected newborns (25,29,30). Although the frequency of meconium ileus in our cohort was lower, its presence remained strongly associated with a CF diagnosis and should be considered an important early warning sign in those infants with positive NBS results.

Several laboratory abnormalities may support clinical suspicion of CF, particularly electrolyte disturbances such as hyponatremia, hypochloremia, and metabolic alkalosis, either alone or in combination as pseudo-Bartter syndrome, which have been reported as early manifestations of CF especially in younger infants (25,31). In our cohort, hypochloremia was the most frequently observed electrolyte abnormality among those children with CF. Additional findings, including hypokalemia and hypoalbuminemia, were also commonly encountered and may further strengthen clinical suspicion when present in combination (32).

Several studies have demonstrated regional variability in sodium and electrolyte imbalances among children with CF, influenced by climatic conditions, nutritional status and CFTR mutation distribution. Hyponatremia, hypochloremia, and metabolic alkalosis have been reported as early manifestations of CF, particularly in infants and in warmer climates or resource-limited settings. A narrative review synthesizing data from multiple geographic regions emphasized that salt loss and related electrolyte abnormalities remain clinically relevant across different age groups and health-care systems (33). In this context, supportive laboratory findings may provide valuable guidance for clinicians when confirmatory diagnostic testing is delayed or temporarily unavailable.

Previous studies evaluating laboratory findings in NBS-positive infants have emphasized that, while such markers do not replace the sweat chloride test, they may support clinical decision-making during the diagnostic process, particularly when confirmatory testing is delayed or unavailable (11). Our findings highlight the importance of a comprehensive clinical assessment and the integration of multiple supportive features, rather than relying on a single parameter.

Study Limitations

This study had several limitations. Its retrospective design and the absence of nationwide data may limit its generalizability. Some clinical findings, such as doll-like facial appearance, are subjective and may vary between observers. In addition, not all laboratory parameters were available for every child, and some abnormalities may have been transient and therefore not captured at the time of initial evaluation.

Conclusion

In children with positive NBS for CF, having a sibling with CF and the presence of a doll-like facial appearance were the most prominent supportive clinical features observed in those ultimately diagnosed with CF. While parental consanguinity remains clinically relevant, particularly in populations with lower CF carrier frequencies, it was not a distinguishing feature in our cohort. Careful anamnesis, physical examination, and basic laboratory evaluation remain essential components of the clinical assessment of NBS-positive children, especially in settings where access to sweat chloride tests is limited or delayed. In the presence of findings suggestive of CF, early referral and close follow-up may be considered while awaiting confirmatory diagnostic testing in order to minimize disease-related complications.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Clinical Research Ethics Committee of Gazi University (approval number: 11, date: 04.01.2021).

Informed Consent: Due to the retrospective design of this study, informed consent was not requested by the ethics committee.

Footnotes

Authorship Contributions

Surgical and Medical Practices: P.A., A.T.A., T.R.G., G.Ü., A.İ.Y., B.S.K., S.P., M.H., M.K., T.Ş.E., Concept: P.A., A.T.A., T.R.G., S.P., M.K., T.Ş.E., Design: P.A., A.T.A., T.Ş.E., Data Collection or Processing: P.A., T.R.G., G.Ü., A.İ.Y., B.S.K., M.H., Analysis or Interpretation: P.A., A.T.A., T.R.G., S.P., M.K., T.Ş.E., Literature Search: P.A., Writing: P.A., A.T.A., T.R.G., S.P., M.K., T.Ş.E.

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Original Article

Copeptin Response to Clonidine Stimulation in Healthy Children

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ABSTRACT

Aim: The aim of this study was to evaluate whether clonidine, a centrally acting alpha-2-adrenergic agonist widely used in pediatric endocrinology for growth hormone (GH) stimulation testing, also induces copeptin release in children. Since copeptin is a stable, easily measurable marker of vasopressin, its stimulation could offer a practical diagnostic approach for distinguishing diabetes insipidus (DI) from primary polydipsia.

Materials and Methods: We conducted a prospective diagnostic pilot study including ten otherwise healthy children (age 3-14 years) undergoing standardized clonidine stimulation testing for suspected GH deficiency. Following oral administration of clonidine, serial blood samples were collected at predefined intervals in order to measure plasma GH and copeptin concentrations. Additionally, blood pressure and heart rate were continuously monitored in order to assess hemodynamic effects and overall tolerability. Adverse events and subjective tolerability were documented systematically.

Results: Administration of clonidine led to a significant reduction in systolic and diastolic blood pressure in all participants. However, contrary to expectations, copeptin levels decreased significantly in all subjects (p=0.013). No serious adverse events occurred, and overall tolerability of the test was rated as high, in line with clinical experience.

Conclusion: Contrary to the initial hypothesis, clonidine does not stimulate copeptin secretion in children and is unsuitable as a diagnostic tool for DI. Nevertheless, its high tolerability and consistent copeptin suppression warrant further exploration of its neuroendocrine effects.

Keywords: Copeptin, clonidine, diabetes insipidus, vasopressin, children

Introduction

Diabetes insipidus (DI) is a rare endocrine disorder characterized by excessive urine output (polyuria) and increased thirst (polydipsia), resulting from either insufficient production of or an inadequate response to vasopressin (1). Central DI is due to deficient vasopressin secretion, while nephrogenic DI arises from renal insensitivity to vasopressin (1,2). Primary polydipsia, on the other hand, is characterized by excessive fluid intake and, consequently, excessive diuresis (3). Discriminating between these subcategories is crucial as treatment for each condition differs considerably (3). Until recently, the indirect water deprivation test was the accepted diagnostic gold standard for differentiating between polyuric states, even though its diagnostic criteria were based on data from only 36 patients (4,5) and yielded a poor overall diagnostic accuracy of 70% (3). Additional measurements of plasma

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vasopressin concentrations to enhance the sensitivity of the water deprivation test did not overcome the test's limitations, mainly due to technical restrictions of the vasopressin assay (6). Copeptin, on the other hand, the C-terminal part of the vasopressin precursor, is released in equal amounts with vasopressin and provides a stable and easily measurable alternative (7). Several alternative tests for diagnosing DI based on copeptin measurements have been proposed (7,8). Measuring plasma copeptin after hypertonic saline infusion has been suggested as the most reliable method; however, it may lead to side effects such as thirst, nausea, dizziness, and headaches (6,9) due to the hypernatremia it causes. It also requires careful monitoring of plasma sodium concentrations (6).

Recently, the arginine stimulation test was developed (6). This test is based on the fact that arginine, as an alpha-receptor agonist, stimulates various anterior pituitary hormones, such as prolactin and growth hormone, and it is widely used as a simple and well-tolerated method for diagnosing growth hormone (GH) deficiency (6,10). Arginine-stimulated copeptin measurements are an accurate test for DI and are recommended as the first choice for distinguishing DI from other causes of polydipsia and/or polyuria (6). It is a simple and safe test which rarely causes side effects (6). Similar to arginine, glucagon, also an alpha-receptor agonist, can stimulate the secretion of GH and affect the neurohypophysis (10,11). Glucagon-induced increases in plasma copeptin have the potential to be used as a safe and precise test for the differential diagnosis of polyuria–polydipsia syndromes (11).

Clonidine is a centrally acting medication which functions as an agonist on alpha-adrenergic and imidazoline receptors (12). By stimulating alpha-receptors in the depressor area of the vasomotor center in the medulla oblongata and hypothalamus, clonidine lowers blood pressure, heart rate, total peripheral resistance, plasma renin activity, and the excretion of aldosterone and catecholamines in urine, with minimal effect on resting cardiac output, exercise response, or changes in kidney function (13). Furthermore, clonidine is used to treat a range of conditions, including attention deficit hyperactivity disorder, tics, cancer pain, neonatal opioid withdrawal, and symptoms linked to sympathetic overactivity, such as hot flashes, migraines, and restless leg (13,14). It is also used off-label for managing withdrawal, anxiety, insomnia, and post-traumatic stress disorder (14), as well as in the diagnosis of pheochromocytoma through a suppression test based on measuring catecholamine levels before and after clonidine administration (15). Additionally, clonidine is recognized as a stimulant of pituitary hormone secretion and it is used as a well-tolerated, straightforward tool for diagnosing GH deficiency. Clonidine affects GH secretion through selective activation of alpha-2-adrenergic receptors in the hypothalamus (10).

Alpha-adrenergic activation in the hypothalamus stimulates the secretion of GH-releasing hormone, leading to an increase in GH levels in plasma (10). At the same time, clonidine is believed to inhibit the endogenous release of somatostatin, which also contributes to increased GH release (10). However, the effect of clonidine on vasopressin secretion is poorly investigated.

The purpose of this study was to investigate whether clonidine, as a pituitary-stimulating agent, can also affect the release of vasopressin/copeptin. This investigation aimed to clarify whether the clonidine test can serve as a diagnostic method for DI and potentially for other conditions where copeptin may function as a diagnostic marker.

Materials and Methods

Study Design and Participants

This prospective diagnostic pilot study was conducted at the Pediatric Department of Sørlandet Hospital in Arendal, Norway, from August 2024 to April 2025. Ten children (5 males, 5 females) aged 3-14 years [mean 7.9 years, standard deviation (SD) 3.84] undergoing routine evaluation for short stature were enrolled. Table I presents the participants' age, gender, weight, and height data. Inclusion criteria included general good health and no history of DI, polyuria, or polydipsia. Exclusion criteria included acute illness, known endocrine disorders, and medications which affect vasopressin levels.

Ethical Considerations

This study was approved by the Norwegian Regional Committee for Medical and Health Research Ethics (approval number: 602201, date: 15.11.2023) and the Institutional Board at Sørlandet Hospital HF, Norway. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Informed consent was obtained from both parents of each participant. The children received age-appropriate information and provided assent where applicable.

Procedures

Participants fasted overnight and arrived at the clinic at 08:00. Baseline measurements included height, weight, blood pressure, and urine osmolality. A peripheral venous catheter (PVC) was inserted for serial blood sampling.

Clonidine was administered orally at a dose of 0.10 mg/m² body surface area.

Blood samples were collected at baseline, as well as at 30, 60, 90, and 120 minutes after clonidine administration for the analysis of copeptin and GH. Blood pressure was measured at each time point. Subjective tolerability was assessed using a Visual Analog Scale (VAS) for symptoms such as nausea, dizziness, and fatigue.

Laboratory Analysis

GH was measured using an immunoluminometric assay (Immulite 2000xpi, Siemens Healthineers). Copeptin levels were measured via TRACE technology (Time Resolved Amplified Cryptate Emission) with the BRAHMS KRYPTOR system. The samples were analyzed at the Hormone Laboratory, Oslo University Hospital.

Statistical Analysis

Descriptive statistics were calculated. Changes in blood pressure, GH, and copeptin levels were analyzed using Friedman's test and the Wilcoxon signed-rank test. A p value of less than 0.05 was considered statistically significant. IBM SPSS Statistics version 21.0 was utilized.

Results

Blood Pressure Effects

Clonidine significantly reduced both systolic and diastolic blood pressure across all time points (p=0.006 and p=0.019, respectively) (Figure 1A and 1B).

Copeptin Response

The participants' copeptin levels are shown in Table II. Data were missing (N/A) for the baseline copeptin value for one participant (no. 4) due to technical issues. Significant differences were observed between the baseline copeptin values. The lowest measured value was 5.1 pmol/L, while the highest value was 37 pmol/L (M=13.03; SD=10.43).

Table I. Demographic characteristics of the study population: age, gender, weight, and height of participants

Participant no.	Age (years)	Gender	Weight (kg)	Height (cm)
1	11	M	26.0	135.5
2	3	M	11.4	89.5
3	10	F	31.3	135.4
4	8	F	20.6	120.1
5	8	F	18.2	116.0
6	3	F	12.2	90.6
7	3	F	14.4	96.0
8	8	M	23.2	124.5
9	11	M	23.7	135.0
10	14	M	42.7	148.6

Table II. Participants' copeptin levels at baseline and at 30, 60, 90, and 120 minutes during the clonidine test. Values in pmol/L

Participant no.	0 min	30 min	60 min	90 min	120 min
1	5.2	11.0	7.6	5.7	4.6
2	9.7	7.5	7.4	30.0	19.0
3	5.1	4.0	3.6	4.3	3.8
4	N/A	5.8	5.2	4.8	5.1
5	5.5	4.9	4.8	4.7	4.9
6	5.8	5.0	5.0	4.8	4.1
7	19.0	16.0	15.0	14.0	16.0
8	17.0	13.0	13.0	13.0	14.0
9	13.0	12.0	8.0	8.0	6.0
10	37.0	21.0	14.0	10.0	9.8

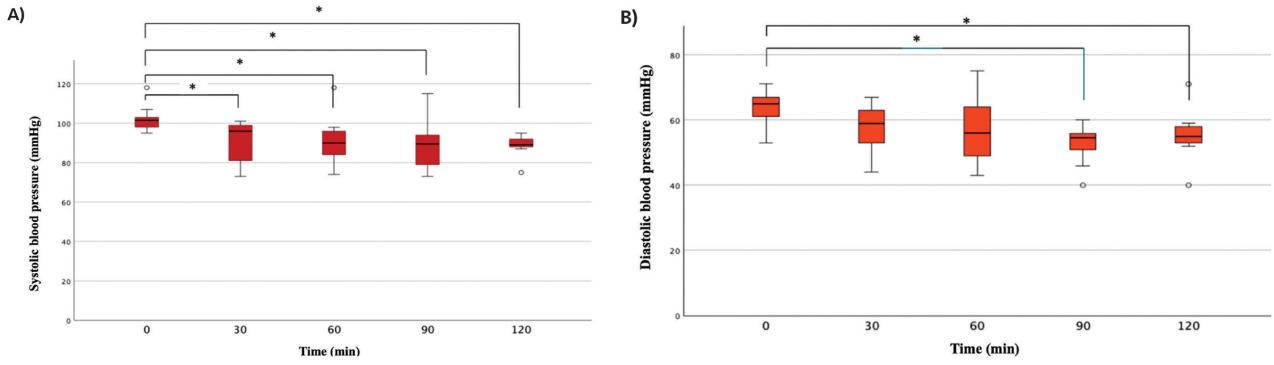

Figure 1. Blood pressure during the clonidine test. **A)** Changes in systolic blood pressure during the clonidine test. The median (Q2) is shown as a black horizontal line within each box. The first quartile (Q1) is the lower edge of the box, while the third quartile (Q3) is the upper edge. The minimum and maximum values are illustrated by the lower and upper horizontal lines extending from the box, respectively. Outlier values are marked with "°". The symbol "*" indicates statistically significant changes from time 0 ($p<0.05$) in systolic blood pressure values. **B)** Changes in diastolic blood pressure during the clonidine test. The median (Q2) is shown as a black horizontal line within each box. The first quartile (Q1) is the lower edge of the box, while the third quartile (Q3) is the upper edge. The minimum and maximum values are illustrated by the lower and upper horizontal lines extending from the box, respectively. Outlier values are marked with "°". The symbol "*" indicates the instances of diastolic blood pressure, between 0 minutes and 90 or 120 minutes, respectively, where the lowest level of statistical significance was achieved

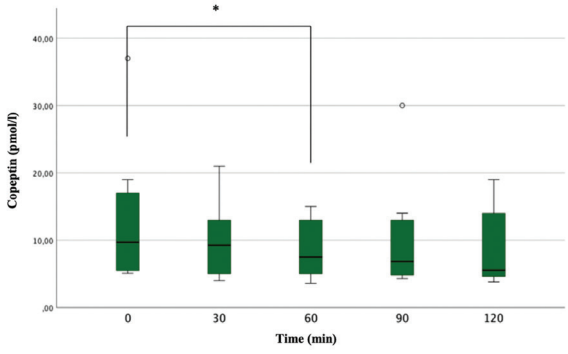

Figure 2. Distribution of copeptin values over time during the clonidine test. The vertical axis represents copeptin value (pmol/L), while the horizontal axis indicates time (minutes). The median (Q2) is shown as a black horizontal line within each box. The first quartile (Q1) is the lower edge of the box, while the third quartile (Q3) is the upper edge. The minimum and maximum values are illustrated by the lower and upper horizontal lines extending from the box, respectively. Outlier values are marked with "°". The symbol "*" indicates a statistically significant decrease in copeptin value between 0 and 60 minutes ($p=0.038$; Wilcoxon signed-rank test)

The distribution of the copeptin values over time for all participants combined is presented in Figure 2. Contrary to the initial hypothesis, all participants showed a statistically significant decrease in plasma copeptin levels after clonidine administration ($p=0.013$; Friedman's test) (Figure 2). No increases were seen at any time point.

Growth Hormone Response

GH levels increased significantly in four participants, confirming the expected stimulation. GH deficiency was indicated in six participants, consistent with their clinical evaluation (GH<10 µg/L) (10).

Test Tolerability

VAS scores showed high tolerability. The most common symptoms were mild fatigue and dizziness, which resolved spontaneously. No participant withdrew from the test.

Discussion

The aim of this study was to investigate whether clonidine, acting as a pituitary-stimulating agent, influenced the release of vasopressin/copeptin. This study involved children aged 3-14 years who underwent a clonidine stimulation test as part of the diagnostic evaluation for GH deficiency.

Copeptin, a stable byproduct of vasopressin synthesis, can be reliably measured in plasma and serves as a surrogate marker for vasopressin release (17). Copeptin levels respond rapidly to changes in osmolality, non-specific stress, and reductions in blood pressure (8). In our study, high baseline copeptin levels were observed, which may potentially be attributable to elevated osmolality or stress-related factors. Osmolality changes are known to significantly affect copeptin concentrations, which rise during dehydration and decline rapidly following fluid intake (18). In this context, we found that participants 4, 7,

8, and 9 had urine osmolality values exceeding the reference range, which may explain the higher baseline copeptin levels observed in participants 7, 8, and 9. Data were missing for the baseline copeptin value for participant no. 4 due to technical issues. These elevated urine osmolality values may be due to the fluid restriction for at least eight hours prior to testing, as per the study protocol. Furthermore, in the GH stimulation test, since the patient is kept fasting and without fluids overnight, elevated baseline copeptin levels should be expected. In this test, ten hours of dehydration have already occurred, and increased copeptin secretion is likely. However, in the hypertonic saline infusion test, the patient is not yet dehydrated because fluid intake has not been stopped. Therefore, the baseline copeptin measurements may have lost their diagnostic significance in the current study. Performing the clonidine-stimulated copeptin test without dehydration may yield different results. Additionally, psychological and procedural stress may have contributed to high copeptin levels. Stress activates the hypothalamic-pituitary-adrenal (HPA) axis, leading to the secretion of adrenocorticotropic hormone, cortisol, and vasopressin (17). This could explain the elevated copeptin values in participants 2, 8, and 10, who also exhibited the highest cortisol levels. Participant 10 had both the highest cortisol and baseline copeptin levels. It is likely that PVC insertion and general hospital procedures induce stress, especially in young children. Furthermore, participants with higher baseline copeptin levels showed a more significant decrease over time. This decline, observed between baseline and the end of the test, was statistically significant, particularly between baseline and 60 minutes after clonidine administration. A further decline was noted at 120 minutes, though this was not statistically significant. Given the small sample size, these findings should be interpreted cautiously, as the observed copeptin changes may have been coincidental.

It is well established that a drop in blood pressure triggers the release of vasopressin (and thus copeptin), helping to maintain circulatory homeostasis through several mechanisms: vasoconstriction (via V1a and V1b receptors), water reabsorption (via V2 receptor activation), and sodium retention (through the activation of the renin-angiotensin system) (19,20). Clonidine, a centrally acting agent, stimulates alpha-adrenergic and imidazoline receptors (13). This suppresses sympathetic nervous system activity, resulting in reduced blood pressure (13). In our study, a statistically significant decrease in both systolic and diastolic pressure was observed in all participants. The most significant change was recorded at 90 minutes post-administration, confirming clonidine's hypotensive effect. This drop in blood pressure would typically be expected to stimulate the release of vasopressin/copeptin (19,20). Moreover, clonidine activates alpha-2-adrenergic receptors in the hypothalamus, promoting the release of GH from the pituitary gland (10). This is the rationale behind its use in GH stimulation testing, reflecting its similar impact on other pituitary hormones, as observed with arginine and glucagon (10). Based on this physiological background, we hypothesized that clonidine-induced hypotension and pituitary stimulation would result in increased vasopressin/copeptin secretion. However, our observations revealed a paradoxical outcome: while clonidine effectively reduced blood pressure, copeptin levels decreased instead of increasing. This result may be explained by clonidine's central inhibition of sympathetic tone. By reducing adrenaline and noradrenaline levels, clonidine lowers stress responses and decreases HPA signaling (14). The reduced sympathetic drive likely suppresses vasopressin/copeptin secretion, even in the presence of hypotension. The interplay between fluid balance systems and baroreceptor feedback may involve biphasic regulation of vasopressin, depending on physiological needs (14). In this case, central sympathetic suppression appears to dominate, overriding baroreceptor-induced vasopressin release. As a result, copeptin levels fell during clonidine administration. This finding is in concordance with two reported studies (20,21) which also reported a decrease in copeptin levels during clonidine stimulation, consistent with our findings.

Furthermore, the test was well tolerated with the participants reporting minimal discomfort, and all of the participants completing the test. Toward the end of the procedure, most participants became tired or fell asleep, which is a common side effect of clonidine. Mild reactions, such as fatigue, hypotension, and gastrointestinal symptoms, were observed, consistent with the existing literature (10,20,21).

Study Limitations

This study's small sample size limits its generalizability. Furthermore, the absence of a comparator group, such as participants undergoing arginine or hypertonic saline stimulation, represents a limitation. As this was designed as a pilot study, the primary objective was to explore clonidine's potential as a copeptin stimulant. However, this objective was not achieved, and further investigation in this direction will not be pursued.

Conclusion

This study confirms clonidine's established effects on GH stimulation and blood pressure reduction in children. However, contrary to expectations, clonidine did not stimulate copeptin release. Instead, it caused a paradoxical decrease in copeptin levels, likely due to its central suppression of sympathetic tone. These findings suggest that clonidine's inhibitory effects on the sympathetic nervous system may override vasopressinergic activation, despite hypotensive conditions. While clonidine remains a valuable and well-tolerated agent for GH stimulation testing, it cannot be recommended as a diagnostic stimulant for copeptin-based evaluation in DI or similar conditions.

Ethics

Ethics Committee Approval: This study was approved by the Norwegian Regional Committee for Medical and Health Research Ethics (approval number: 602201, date: 15.11.2023) and the Institutional Board at Sørlandet Hospital HF, Norway.

Informed Consent: They were included in the study after obtaining informed consent from their legal guardians.

Footnotes

Authorship Contributions

Surgical and Medical Practices: N.R.P., K.H., Concept: N.R.P., Design: N.R.P., Data Collection or Processing: N.R.P., J.K., K.H., Analysis or Interpretation: N.R.P., J.K., Literature Search: N.R.P., J.K., Writing: N.R.P., J.K.

Conflict of Interest: The authors have no conflicts of interest to declare.

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Erratum

J Pediatr Res 2021;8(4):408-13

DOI: 10.4274/jpr.galenos.2021.67689

In the article entitled "The Risk Factors of Precocious Puberty in Girls: Is the Condition Related to Polychlorinated Biphenyls?", which was published in the Journal of Pediatric Research in 2021 (J Pediatr Res 2021;8(4):408–413; DOI: 10.4274/jpr.galenos.2021.67689), the authors have recently noticed that the Informed Consent statement and Financial Disclosure were inadvertently reported incorrectly in the published version. In addition, the Funding Statement and Acknowledgments sections were unintentionally omitted.

The correct statements are provided below. We apologize for this error.

We sincerely apologize for this oversight and for any inconvenience it may have caused. The original published statements and the corrected versions are presented below.

Published on page 413:

Ethics

Ethics Committee Approval: The study was conducted after approval of the Ethics comittee of Ege University Faculty of Medicine (approval date: 29.12.2015; approval no: 15-11/4).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Design: Ş.D., Data Collection or Processing: R.B.G.B., S.Ö., Ö.K., Ş.D., Writing: R.B.G.B., R.D.G.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

Corrected statements on page 413:

(The corrected parts are given in bold)

Ethics

Ethics Committee Approval: The study was conducted after approval of the Ethics comittee of Ege University Faculty of Medicine (approval date: 29.12.2015; approval no: 15-11/4).

Informed Consent: Written informed consent was obtained from the parents or legal guardians of the participants prior to participation. In addition, written informed consent was obtained from the parents or legal guardians for the publication of this paper.

Peer-review: Externally peer-reviewed.

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Authorship Contributions

Design: Ş.D., Data Collection or Processing: R.B.G.B., S.Ö., Ö.K., Ş.D., Writing: R.B.G.B., R.D.G.

Conflict of Interest: No conflict of interest was declared by the authors.

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