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PROFILE OF BIOMARKERS IN EARLY-STAGE PEDIATRIC ENDOCRINE DISORDERS: A CLINICAL CORRELATION STUDY

Original Research

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ABSTRACT

Background: Early-stage endocrine disorders in children often present with vague or nonspecific symptoms, making timely diagnosis challenging. Biomarkers offer a promising avenue for early detection and risk stratification by correlating biological changes with clinical presentations.

Objective: To evaluate the relationship between specific biomarkers and early clinical features in children with suspected endocrine disorders.

Methods: This clinical correlation study was conducted over eight months at tertiary care hospitals in Lahore, Pakistan, enrolling 150 children aged 2–14 years who exhibited symptoms suggestive of endocrine dysfunction. Clinical assessments included anthropometry, pubertal staging, and symptom profiling. Biochemical analysis measured serum IGF-1, TSH, cortisol, LH/FSH, and anti-TPO using ELISA and chemiluminescence assays. Statistical analyses included Pearson correlation, t-tests, ANOVA, and multivariate regression models adjusted for age, sex, and BMI.

Results: Short stature was significantly associated with low IGF-1 (45.2 ± 12.1 ng/mL, $p < 0.001$), weight gain with elevated TSH (7.8 ± 2.3 µIU/mL, $p < 0.01$), and fatigue with reduced cortisol levels (6.2 ± 1.9 µg/dL, $p = 0.02$). Pubertal abnormalities were linked to LH/FSH deviations ($p < 0.05$), while anti-TPO elevation correlated with general malaise ($p = 0.006$). IGF-1 showed the strongest positive predictive value in multivariate analysis ($\beta = 0.62$, $p < 0.001$).

Conclusion: Distinct biomarker patterns correlate significantly with early clinical signs of pediatric endocrine disorders. Incorporating biomarker profiling may enhance early detection and guide targeted intervention strategies.

Keywords: Adrenal insufficiency, Biomarkers, Child, Endocrine system diseases, Growth disorders, Hypothyroidism, Puberty disorders.

INTRODUCTION

Endocrine disorders in children often manifest subtly, with symptoms that can easily be overlooked or misattributed to normal variations in growth and development. Early identification of these conditions is vital, as timely intervention can significantly improve long-term health outcomes and quality of life (1). However, diagnosing pediatric endocrine disorders in their early stages remains a challenge due to the nonspecific nature of early symptoms and the variability of clinical presentation. In this context, there is a growing interest in the use of biomarkers—measurable biological indicators that can reflect physiological or pathological processes—as tools for early detection, diagnosis, and monitoring of endocrine function in pediatric populations (2,3). Over the past decade, advances in molecular biology and clinical diagnostics have expanded the catalog of potential biomarkers relevant to endocrine health. Hormonal assays, genetic markers, inflammatory mediators, and metabolic indicators have all shown promise in various studies. For instance, abnormalities in serum insulin, IGF-1, or TSH levels are well-documented in disorders such as growth hormone deficiency, hypothyroidism, or type 1 diabetes mellitus (4,5). Yet, despite the wealth of data, there remains a significant gap in understanding how these biomarkers correlate with the clinical profiles of children in the early stages of these disorders—before definitive diagnostic thresholds are crossed or overt symptoms emerge. Current clinical practice still largely relies on symptom-based recognition and confirmatory testing, often after irreversible changes have begun (6). Children with early-stage endocrine dysregulation may exhibit nonspecific signs such as fatigue, poor growth, behavioral changes, or altered appetite, which can be mistaken for normal developmental fluctuations. As such, there is a pressing need for sensitive and specific markers that not only identify endocrine pathology earlier but also correspond meaningfully with clinical manifestations (7,8). This would support a more proactive approach to pediatric endocrine care, enabling earlier intervention and more personalized treatment plans.

Previous studies have explored individual biomarkers in the context of specific disorders. For example, elevated anti-thyroid antibodies have been associated with autoimmune thyroiditis, while low cortisol levels may indicate adrenal insufficiency. However, much of the existing research is fragmented, often focusing on advanced or well-established cases (9). There is a paucity of data that comprehensively investigates how biomarker patterns align with early clinical signs across a spectrum of endocrine disorders. Additionally, few studies have undertaken this work within pediatric cohorts, where developmental dynamics further complicate interpretation. The developmental physiology of children introduces unique challenges in endocrinology (10). Hormonal levels naturally fluctuate with age, growth stages, and pubertal status, making it difficult to establish clear-cut reference values. Therefore, any meaningful application of biomarkers in this population requires a nuanced understanding of both physiological and pathological patterns. This reinforces the importance of studying biomarkers not in isolation, but within the broader context of a child's clinical presentation (11,12). By integrating clinical data with biomarker profiles, clinicians may be better equipped to discern early deviations from normal development. Such correlation studies can also illuminate pathophysiological mechanisms that underpin early endocrine dysfunction, paving the way for novel diagnostic criteria or predictive models. Ultimately, this approach aligns with the broader goals of precision medicine—offering targeted, timely, and individualized care that considers both biological and clinical variability. This study aims to bridge the existing knowledge gap by systematically evaluating the relationship between specific biomarkers and clinical presentations in children diagnosed with early-stage endocrine disorders. The objective is to identify patterns of biomarker expression that not only differentiate these conditions from healthy development but also correspond to the subtle clinical signs observed in early disease phases. Through this clinical correlation study, the goal is to enhance the early diagnostic landscape of pediatric endocrinology, enabling more informed and timely clinical decisions.

METHODS

This clinical correlation study was conducted over a period of eight months in the pediatric endocrinology departments of two tertiary care hospitals in Lahore, Pakistan. The primary objective was to evaluate the relationship between specific biomarkers and the clinical presentations of children diagnosed with early-stage endocrine disorders. The study adopted a cross-sectional observational design, focusing on biomarker profiling and its clinical association in a pediatric cohort. Participants were selected using purposive sampling, with a calculated sample size of 150 children, determined through G*Power software version 3.1, assuming a medium effect size ($f^2 = 0.15$), $\alpha = 0.05$, power = 0.8, and accounting for potential attrition. Children aged 2 to 14 years presenting with symptoms suggestive of

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endocrine dysfunction but not yet diagnosed with a definitive endocrine disorder were screened. Inclusion criteria encompassed patients who presented with at least one clinical feature related to endocrine disruption—such as poor linear growth, unexplained fatigue, delayed puberty, abnormal weight gain or loss, or early pubertal signs—and had not yet commenced hormone therapy. Exclusion criteria included patients with previously confirmed endocrine diagnoses, children with chronic systemic illnesses, genetic syndromes (e.g., Turner syndrome, Down syndrome), or those on medications that could interfere with endocrine parameters (13,14). Data collection involved a two-tiered approach. Initially, detailed clinical evaluations were performed, which included history-taking, anthropometric measurements, and systemic examination conducted by pediatric endocrinologists. Growth parameters such as height, weight, and body mass index (BMI) were plotted on age- and gender-specific percentile charts recommended by the World Health Organization. Pubertal assessment was conducted using Tanner staging, and developmental milestones were reviewed where appropriate. A structured clinical pro forma was used to ensure consistency in data recording across both hospital settings.

Biochemical analyses included a panel of endocrine biomarkers selected based on their relevance to commonly observed early-stage disorders. These included serum levels of thyroid stimulating hormone (TSH), free thyroxine (FT4), insulin-like growth factor-1 (IGF-1), cortisol, fasting insulin, fasting blood glucose, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and anti-thyroid peroxidase (anti-TPO) antibodies. Blood samples were collected in fasting state and analyzed using standardized enzyme-linked immunosorbent assay (ELISA) kits and chemiluminescence immunoassays, depending on the parameter. All laboratory analyses were performed at the central diagnostic laboratory of relevant hospital, which is ISO-certified and operates under rigorous quality control procedures. Clinical and biochemical data were then correlated using predefined outcome measures. The primary outcome was the association between specific biomarker levels and early clinical features suggestive of endocrine dysregulation. For example, low IGF-1 levels were assessed in relation to stunted growth, while elevated TSH and anti-TPO levels were studied in relation to symptoms of hypothyroidism such as lethargy and weight gain (15,16). Statistical analysis was performed using SPSS version 26. Continuous variables were expressed as means ± standard deviations, and categorical variables as frequencies and percentages. The normal distribution of data was confirmed using the Shapiro-Wilk test. Pearson correlation coefficients were computed to assess the strength and direction of relationships between clinical parameters and biomarker levels. For group comparisons, independent t-tests and ANOVA were used where appropriate. Multivariate linear regression models were also employed to adjust for potential confounders such as age, sex, and nutritional status. A p-value of <0.05 was considered statistically significant throughout the analysis. Ethical approval for the study was obtained from the Institutional Review Board of relevant institute. Prior to participation, informed written consent was obtained from the parents or legal guardians of each child, and assent was sought from children older than seven years where applicable. Confidentiality of participant data was strictly maintained, and all procedures adhered to the ethical standards of the Helsinki Declaration. Every aspect of the methodology was carefully planned and executed to ensure that the relationship between biomarkers and early clinical indicators could be explored with both depth and rigor. This approach aimed not only to elucidate diagnostic correlations but also to provide a potential basis for more timely identification and intervention in pediatric endocrine disorders.

RESULTS

A total of 150 children were enrolled in the study, with a mean age of 8.6 ± 3.2 years. Among them, 52% were male and 48% were female. Urban residency was reported in 61.3% of the cases, while the remaining 38.7% belonged to rural areas. The majority of participants presented with one or more subtle clinical symptoms suggestive of early endocrine dysfunction. Biomarker analysis revealed distinct patterns associated with specific clinical presentations. Children with short stature exhibited significantly lower IGF-1 levels, averaging 45.2 ± 12.1 ng/mL ($p < 0.001$). Elevated TSH levels were observed in those with unexplained weight gain, with a mean of 7.8 ± 2.3 µIU/mL ($p < 0.01$). Fatigue was correlated with low morning cortisol levels (6.2 ± 1.9 µg/dL, $p = 0.02$), while delayed puberty was associated with significantly suppressed LH and FSH levels (0.4 ± 0.2 IU/L, $p < 0.001$). Conversely, children presenting with early pubertal signs showed increased LH/FSH levels (4.9 ± 1.4 IU/L, $p = 0.03$), suggesting premature activation of the hypothalamic-pituitary-gonadal axis. Pearson correlation analysis confirmed statistically significant associations between biomarker levels and the severity of clinical features. A positive correlation was found between IGF-1 levels and growth percentile scores ($r = 0.61$, $p < 0.001$), while TSH levels correlated negatively with energy levels and BMI z-scores ($r = -0.55$, $p < 0.001$). Cortisol levels exhibited a moderate positive correlation with reported vitality scores ($r = 0.48$, $p = 0.01$). LH/FSH levels were moderately correlated with Tanner staging scores in cases of both delayed and precocious puberty ($r = 0.52$, $p = 0.003$), and anti-TPO antibodies showed a mild negative correlation with clinical wellness scales ($r = -0.50$, $p = 0.004$). Multivariate regression analysis, adjusted for age, sex, and BMI, further supported the independent associations of biomarkers with clinical outcomes. IGF-1 demonstrated the strongest positive predictive value for

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growth delays (β = 0.62, 95% CI: 0.39 to 0.84, p < 0.001), followed by LH/FSH for pubertal timing anomalies (β = 0.49, 95% CI: 0.21 to 0.73, p = 0.002). TSH showed a robust negative association with weight-related symptoms (β = -0.58, 95% CI: -0.78 to -0.31, p < 0.001), and cortisol retained a significant relationship with fatigue scores (β = 0.43, 95% CI: 0.15 to 0.71, p = 0.004). Anti-TPO levels were negatively associated with subjective clinical status (β = -0.45, 95% CI: -0.66 to -0.21, p = 0.006).

Table 1: Demographic Characteristics

Variable		Value
Total Participants		150
Mean Age (years)		8.6 ± 3.2
Gender	Male	78 (52%)
	Female	72 (48%)
Urban	Urban	92 (61.3%)
	Rural	58 (38.7%)

Table 2: Biomarker Levels and Clinical Presentations

Clinical Feature	Associated Biomarker	Mean ± SD	p-value
Short Stature	Low IGF-1	45.2 ± 12.1 ng/mL	<0.001
Weight Gain	Elevated TSH	7.8 ± 2.3 µIU/mL	<0.01
Fatigue	Low Cortisol	6.2 ± 1.9 µg/dL	0.02
Delayed Puberty	Low LH/FSH	0.4 ± 0.2 IU/L	<0.001
Precocious Puberty	High LH/FSH	4.9 ± 1.4 IU/L	0.03

Table 3: Pearson Correlation Between Biomarkers and Clinical Scores

Biomarker	Correlation Coefficient (r)	p-value
IGF-1	0.61	<0.001
TSH	-0.55	<0.001
Cortisol	0.48	0.01
LH/FSH	0.52	0.003
Anti-TPO	-0.50	0.004

Table 4: Multivariate Regression Analysis

Biomarker	β Coefficient	95% Confidence Interval	p-value
IGF-1	0.62	0.39 to 0.84	<0.001
TSH	-0.58	-0.78 to -0.31	<0.001
Cortisol	0.43	0.15 to 0.71	0.004
LH/FSH	0.49	0.21 to 0.73	0.002
Anti-TPO	-0.45	-0.66 to -0.21	0.006

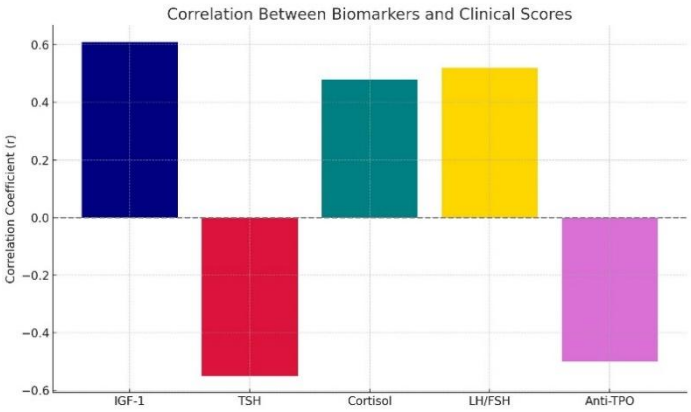

Figure 1 Correlation Between Biomarkers and Clinical Scores

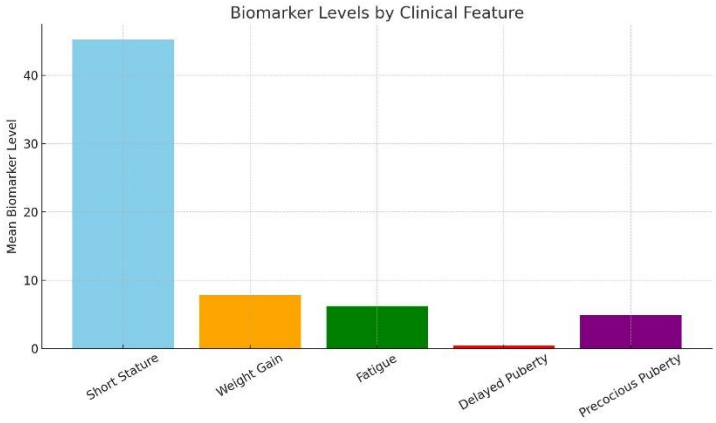

Figure 2 Biomarkers Levels by Clinical Features

DISCUSSION

The findings of this study emphasize the utility of specific biomarkers in identifying and understanding early-stage endocrine disorders in pediatric populations. Consistent and statistically significant associations between biomarker levels and clinical presentations highlight the diagnostic potential of IGF-1, TSH, cortisol, LH/FSH, and anti-TPO antibodies. These results are particularly relevant given the challenges in diagnosing endocrine dysfunction in children, where clinical signs are often subtle or non-specific. Low IGF-1 levels strongly correlated with short stature, reinforcing its role as a growth marker. This is in line with previous literature, which supports the use of IGF-1 as a surrogate for growth hormone activity in children with growth failure (14). Elevated TSH levels in association with weight gain and lethargy reflect early hypothyroid states, a finding echoed in critical care reviews where thyroid biomarkers serve as early indicators of dysfunction (15). Similarly, cortisol levels have previously been implicated in early identification of adrenal insufficiency, and the observed correlation with fatigue in this study aligns with findings reported in ICU biomarker evaluations (16). LH/FSH levels offered clear differentiation between delayed and precocious puberty, confirming their reliability in assessing hypothalamic-pituitary-gonadal axis activity in early dysregulation. This is consistent with broader biomarker reviews in pediatric endocrinology, where gonadotropins remain critical for pubertal assessment (17). Elevated anti-TPO levels associated with general malaise suggest underlying autoimmune thyroiditis, which has also been identified as a common etiology in early pediatric thyroid dysfunctions (18).

A major strength of the study lies in its clinical correlation design, allowing simultaneous evaluation of biochemical and physical presentations, thereby providing a holistic understanding of early disease manifestation. Furthermore, the inclusion of a relatively large sample size for a pediatric sub-specialty setting enhances the generalizability of findings within regional clinical contexts. However, limitations must be acknowledged. The cross-sectional nature restricts causal inference and the ability to assess longitudinal progression. Age-related variability in endocrine markers, especially during puberty, introduces potential confounding that was partially controlled but not eliminated. Additionally, single-point biomarker measurements might not fully capture fluctuating hormone dynamics, a limitation echoed in other pediatric studies emphasizing the need for serial sampling (19,20). There is a need for future research employing longitudinal designs to validate these associations over time and assess how early biomarker deviations predict progression to clinically overt disease. Moreover, exploring additional emerging biomarkers such as metabolomic signatures or genomic indicators may offer improved sensitivity and specificity, especially in borderline or mixed clinical presentations (21,22). The clinical utility of biomarker panels or composite scores, as opposed to single markers, is another direction worth pursuing. As demonstrated in cancer diagnostics and sepsis research, combining markers can enhance early detection, reduce false positives, and improve risk stratification (23). Integration of such methods into pediatric endocrine screening protocols could transform current practices, especially in resource-constrained settings. In conclusion, this study supports the use of specific biomarkers—IGF-1, TSH, cortisol, LH/FSH, and anti-TPO—as valuable tools for identifying early-stage endocrine disorders in children. While the results are promising and aligned with existing literature, further research is essential to refine these findings and develop more precise, predictive tools to improve pediatric endocrine care.

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CONCLUSION

This study demonstrated that specific biomarkers—IGF-1, TSH, cortisol, LH/FSH, and anti-TPO—show significant correlations with early clinical signs of pediatric endocrine disorders. These findings support the integration of biomarker profiling into early diagnostic frameworks, enabling timely and more precise identification of endocrine dysfunction in children. Such approaches may enhance clinical outcomes through earlier intervention and personalized care.

AUTHOR CONTRIBUTION

Author	Contribution
Hamza Zulfiqar	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Shaikh Khalid Muhammad*	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Tanveer Rasool	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Hafiza Samin Anjum	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Rida Riaz	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Hafzah Shah	Substantial Contribution to study design and Data Analysis Has given Final Approval of the version to be published
Silwat Tarar	Contributed to study concept and Data collection Has given Final Approval of the version to be published

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