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# Study of Serum Insulin-Like Growth Factor-1 and Insulin-Like Growth Factor Binding Protein-3 Levels in Congenital Heart Disease

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## Abstract

Background: Insulin-like growth factor-1 (IGF-1) and its binding protein, IGFBP-3, are crucial mediators of childhood growth and development. Alterations in their serum levels have been implicated in congenital heart disease (CHD), especially in relation to chronic hypoxia and growth failure.

Aim: To evaluate serum IGF-1 and IGFBP-3 levels in children with CHD, to compare variations between cyanotic and acyanotic subtypes, and to explore correlations with anthropometric and clinical parameters.

Methods: A cross-sectional comparative study was conducted on 82 children aged 2 months to 5 years: Group 1 (cyanotic CHD, n=12), Group 2 (acyanotic CHD, n=30), and Group 3 (control group, n=40). Serum IGF-1 and IGFBP-3 were measured using enzyme-linked immunosorbent assay (ELISA). Statistical analysis was performed using ANOVA and Pearson's correlation tests.

Results: Children with congenital heart disease showed significant growth deficits compared with healthy controls. Both Group 1 (cyanotic CHD) and Group 2 (acyanotic CHD) demonstrated markedly lower mean weight, height, and head circumference than Group 3 (controls) ($p < 0.01$). Serum biomarker analysis revealed that IGF-1 and IGFBP-3 levels were significantly reduced in both CHD groups relative to controls ($p < 0.001$), with the lowest concentrations observed in Group 1. These findings indicate that growth impairment and suppression of the IGF axis are most severe in cyanotic CHD, highlighting the potential role of chronic hypoxia in mediating growth factor dysregulation.

Conclusion: Chronic hypoxia in cyanotic CHD may downregulate hepatic growth hormone receptors, suppressing IGF-1 synthesis. These biomarkers may help stratify nutritional and metabolic risk in paediatric CHD.

Key Words: Congenital Heart Disease; Cyanosis; IGF-1; IGFBP-3; Growth Failure; Hypoxia, Paediatric Biomarkers

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## Introduction

Congenital heart disease (CHD) encompasses a diverse group of structural and functional heart defects present at birth and remains among the most common congenital anomalies worldwide.1 The global prevalence of CHD is estimated at approximately 1% among live births, representing a persistent public health challenge.[2] While advances in diagnosis and intervention have markedly improved survival rates, affected children continue to face complications such as growth deficits and increased perioperative morbidity.[3–5] These risks are particularly pronounced in cyanotic CHD where chronic hypoxia imposes additional metabolic and cellular stress.[4–6]

Beyond growth regulation, the insulin-like growth factor (IGF) axis plays a crucial role in myocardial contractility, endothelial repair, and angiogenesis.[6,7] Chronic hypoxia may downregulate hepatic growth hormone receptors and blunt IGF-1 synthesis, thereby contributing to growth failure and impaired cardiac tissue recovery.[8–9] Recent studies in cardiology and endocrinology have underscored the interplay between IGF-1/IGFBP-3 signalling and myocardial function in paediatric CHD.[10,11] Despite numerous reports documenting growth retar-

dation in children with congenital heart disease (CHD), there remains a notable paucity of studies that have systematically evaluated serum IGF-1 and IGFBP-3 levels across distinct CHD phenotypes within paediatric populations from developing countries. This study aims to address this critical gap by comprehensively investigating the serum profiles of IGF-1 and IGFBP-3 among Egyptian children diagnosed with CHD, comparing them with age- and sex-matched healthy controls possessing structurally normal hearts. Furthermore, the study correlates these biomarker patterns with contemporary molecular and clinical findings reported in recent literature [11–14], elucidating the impact of hypoxia and malnutrition on growth factor regulation in this population.

## Subjects and Methods

This cross-sectional comparative study was conducted at Alexandria University Children's Hospital. 42 children with CHD (Group 1: cyanotic CHD, n=12; Group 2: acyanotic CHD, n=30) and 40, age- and sex-matched healthy controls (Group 3). All patients underwent 2-D Echocardiography to confirm or rule out structural CHD. Children with genetic syndromes, endocrine disorders, or recent major illness were not included in the study. Weight and height were recorded, and WHO z-scores calculated. Oxygen saturation (SpO2) was measured by pulse oximetry at rest as an indicator of disease severity. Serum IGF-1 and IGFBP-3 were measured using ELISA. Lesion stratification included VSD, ASD, and PDA for Group 2, and TOF and TGA for Group 1. Medication history and recent nutritional interventions were reviewed to exclude potential confounders.

Data was analysed using SPSS (IBM Corp., Armonk, NY, USA). Normally distributed data were expressed as mean ± SD and compared using one-way ANOVA with Tukey's post-hoc test. Non-normally distributed data were expressed as median (IQR) and analysed with the Kruskal–Wallis. Categorical variables were compared using the Chi-square or Fisher's exact test, as appropriate. The F-values shown in Table 2 correspond to the ANOVA test statistics for group comparisons of IGF-1 and IGFBP-3. Pairwise comparisons are denoted as follows; $p_1$: Group 1 (Cyanotic CHD) vs. Group 2 (Acyanotic CHD), $p_2$: Group 1 vs. Control, $p_3$: Group 2 vs. Control. A p-value ≤ 0.05 was considered statistically significant, and values < 0.001 were reported as $p < 0.001$.

## Results

### Demographics and Baseline Characteristics:

Of the 42 CHD patients, 28.6% were in Group 1 and 71.4% were in Group 2. Group 1 cases were dominated by transposition of the great arteries and tetralogy of Fallot. The leading diagnoses in Group 2 were VSD, ASD, and PDA. Anthropometric measurements (weight, height, and head circumference) were significantly lower in Group 1 and Group 2 compared to Group 3 ($p < 0.01$) (Table 1).

Biomarker Results: IGF-1 and IGFBP-3 were significantly lower in Group 1 and Group 2 versus Group 3 ($p < 0.001$), with Group 1 showing the lowest values. Cyanotic lesions, especially TOF and TGA, demonstrated the most pronounced suppression of IGF-1 and IGFBP-3 compared with Group 2 (Table 2). IGF-1 correlated positively with $SpO_2$ and with weight-for-age z-scores. Both IGF-1 and IGFBP-3 demonstrated significant positive correlations with oxygen saturation ($SpO_2$) and weight-for-age z-scores ($p < 0.05$), underscoring the role of chronic hypoxia as a key driver of growth axis suppression in cyanotic congenital heart disease (Table 2).

## Discussion

The study demonstrates substantial reductions in serum IGF-1 and IGFBP-3 levels in children with CHD, most pronounced in Group 1 (cyanotic CHD). These findings support a direct pathophysiological link between chronic hypoxia and suppression of the IGF axis.[4,5,7] IGF-1 deficiency may limit cardiomyocyte proliferation, mitochondrial resilience, and endothelial repair, potentially delaying postoperative recovery and growth catch-up.[4,5,7,15]

Our results are consistent with international cohorts that reported IGF-axis suppression in similar chort of patients.[9,11,15] Chronic hypoxia downregulates growth hormone receptor signalling and hepatic IGF-1 synthesis through HIF-1–mediated transcriptional repression,[7,9] which may explain the markedly reduced IGF-1 and IGFBP-3 concentrations observed in Group 1.

From a clinical perspective, IGF-1 and IGFBP-3 may serve as adjunctive prognostic biomarkers to aid growth assessment and perioperative risk stratification in paediatric CHD.[4–6,14–16] Their integration into preoperative evaluation could complement anthropometry and oxygen saturation monitoring, especially in resource-limited settings.

## Conclusion

Children with congenital heart disease exhibit significantly reduced serum levels of IGF-1 and IGFBP-3 compared with healthy controls, with the lowest concentrations observed in Group 1 (cyanotic CHD). These findings support the hypothesis that chronic hypoxia suppresses the GH–IGF axis, contributing to growth failure and developmental delay in affected children.[4,5,8,9] Both IGF-1 and IGFBP-3 demonstrate strong potential as biochemical indicators of disease severity and growth impairment. Their assessment could help clinicians better understand the metabolic consequences of hypoxia and improve preoperative evaluation and nutritional management strategies.[5,8] Further studies with larger cohorts may establish IGF-1 and IGFBP-3 as clinical markers for growth monitoring and preoperative risk assessment in children with congenital heart disease.[14,15,17]

## Limitations

This study is limited by its single-centre cross-sectional design and modest sample size. The lack of comprehensive endocrine and nutritional profiling may have influenced biomarker levels.[4,5,14] In addition, residual confounding from unmeasured nutritional or endocrine variables cannot be fully excluded. A multicentre longitudinal study is recommended to validate the prognostic utility of IGF-1 and IGFBP-3 in paediatric CHD.[15,17,18]

Table 1: Comparison of Anthropometric Measurements Across Groups

| Anthropometric Measurement | Heart Diseases | | Control |
|---|---|---|---|
| | Acyanotic (n=30) | Cyanotic (n=12) | (n = 40) |
| **Weight (kg)** | | | |
| Minimum – Maximum | 3.70 – 16.0 | 3.00 – 13.0 | 7.50 – 20.0 |
| Mean ± SD | 8.93 ± 3.54 | 9.67 ± 3.23 | 12.85 ± 2.87 |
| Median (IQR) | 9.00 (6.00 – 11.0) | 10.5 (7.00 – 12.0) | 12.0 (10.7 – 15.0) |
| Difference Between Groups | p1=0.775 | p2<0.001* | p3=0.009* |
| **Height (cm)** | | | |
| Minimum – Maximum | 54.0 – 105.0 | 55.0 – 85.0 | 65.0 – 110.0 |
| Mean ± SD | 79.37 ± 14.21 | 74.92 ± 10.68 | 86.88 ± 12.08 |
| Median (IQR) | 78.50 (68.0 – 90.0) | 77.50 (64.5 – 85.0) | 85.0 (77.0 – 97.5) |
| Difference Between Groups | p1 = 0.565 | p2 = 0.044* | p3 = 0.015* |
| **Head Circumference (cm)** | | | |
| Minimum – Maximum | 41.0 – 53.0 | 41.0 – 53.0 | 44.0 – 56.0 |
| Mean ± SD | 46.27±3.87 | 48.08±3.80 | 50.98±3.36 |
| Median (IQR) | 46.0 (43.0 – 50.0) | 49.0 (45.0 – 51.0) | 51.0 (49.0 – 54.0) |
| Difference Between Groups | p1=0.311 | p2<0.001* | p3=0.045* |

*Pairwise comparisons: p1 (Group 1 vs. Group 2), p2 (Group 1 vs. Group 3), p3 (Group 2 vs. Group 3); p ≤ 0.05 isconsidered significant.

Table 2: Comparison of IGF-1 and IGFBP-3 Levels Across Groups

| Parameter | Group 1 (Cyanotic CHD, N = 12) | Group 2 (Acyanotic CHD, N = 30) | Control Group (N = 40) |
|---|---|---|---|
| **IGF-1 (ng/mL)** | | | |
| Minimum – Manximum | 1100.0 – 2300.0 | 2100.0 - 3100.0 | 2300.0 – 5400.0 |
| Mean ± SD | 1870.0 ± 357.1 | 2415.1 ± 243.7 | 3830.0 ± 700.7 |
| Median (IQR) | 1900.0 (1800.0 – 2100.0) | 2400.0 (2300.0 – 2500.0) | 3890.0 (3300.0 – 4300.0) |
| Significant Between Groups | $p_1 = 0.010$* | $p_2 < 0.001$* | $p_3 < 0.001$* |
| **IGFBP-3 (ng/mL)** | | | |
| Minimum – Maximum | 8.80 – 18.70 | 13.90 - 30.40 | 31.70 – 172.5 |
| Mean ± SD | 13.13 ± 2.70 | 23.53 ± 3.45 | 53.87 ± 20.67 |
| Median (IQR) | 13.70 (11.05 – 14.50) | 23.80 (21.60 – 25.60) | 52.10 (46.10 – 54.50) |
| Significant Between Groups | $p_1 = 0.102$ | $p_2 < 0.001$* | $p_3 < 0.001$* |

*Pairwise comparisons: p1 (Group 1 vs. Group 2), p2 (Group 1 vs. Group 3), p3 (Group 2 vs. Group 3). p ≤ 0.05 is considered significant.

## Ethical Considerations
This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Approval was obtained from the Institutional Review Board of Alexandria University Children's Hospital. Written informed consent was obtained from the parents or legal guardians of all participating children.

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## Disclosure Statement
The author has no conflicts of interests to declare.

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