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(RESEARCH ARTICLE)

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Growth hormone therapy in cardiac conditions: Implications for heart failure, congenital Acyanotic and cyanotic heart disease, and tetralogy of Fallot

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Abstract

Background: Growth hormone (GH) therapy has been widely used in pediatric endocrinology to treat short stature and metabolic disorders. However, its application in children with congenital heart disease (CHD) and congestive heart failure (CHF) remains controversial due to concerns about its effects on cardiac function.

Objective: This review evaluates the impact of GH therapy on growth parameters, metabolic health, and cardiac function in children with acyanotic and cyanotic CHD, Tetralogy of Fallot (ToF), and CHF.

Methods: A comprehensive literature review was conducted on 20 studies assessing GH therapy in pediatric patients with cardiac conditions, including a total of 2,350 subjects. Key outcomes analyzed included growth velocity, IGF-1 levels, left ventricular ejection fraction (LVEF), cardiac stability, and metabolic changes. Key outcomes analyzed included growth velocity, IGF-1 levels, left ventricular ejection fraction (LVEF), cardiac stability, and metabolic changes.

Results: Studies indicate that GH therapy significantly improves growth velocity, IGF-1 levels, and height-for-age z-scores in children with acyanotic CHD, with minimal adverse cardiac effects. Nutritional interventions further enhance growth outcomes. In cyanotic CHD, GH therapy is effective in promoting growth, but chronic hypoxemia may affect its efficacy. Surgical correction of cyanotic defects contributes to post-intervention growth recovery. In ToF, GH therapy leads to notable growth velocity improvements and stable cardiac function, with transient metabolic side effects reported in a minority of patients. In CHF, GH therapy improves growth, and in some cases, cardiac function, including LVEF and endothelial health. However, results on cardiac benefits are inconsistent, with some studies showing no significant improvement in heart failure patients without GH deficiency.

Conclusion: GH therapy is effective in promoting growth in pediatric cardiac patients and may offer additional metabolic and endothelial benefits. However, its impact on cardiac function varies, necessitating careful patient selection and monitoring. Long-term cardiovascular safety remains a key concern, particularly in patients with preexisting myocardial abnormalities. Future research should focus on optimizing GH dosing strategies, refining patient selection criteria, and conducting long-term follow-up studies to ensure the safety and efficacy of GH therapy in this population.

Keywords: Growth Hormone Therapy; Heart Failure; Congenital heart diseases; Cyanotic Heart Disease; Tetralogy of Fallot

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1. Introduction

Children with congenital and acquired heart diseases frequently experience growth impairment due to chronic hypoxemia, malnutrition, systemic inflammation, and metabolic dysregulation. Cyanotic congenital heart disease (CHD) is particularly associated with more severe growth restriction due to hypoxemia-induced suppression of the GH/IGF-1 axis. Several studies have reported lower IGF-1 levels in cyanotic CHD compared to acyanotic CHD, suggesting that chronic hypoxia interferes with growth-promoting pathways (1,2).

The GH/IGF-1 axis plays a critical role in linear growth, metabolic regulation, and cardiovascular function. Disruptions in this axis due to congenital heart disease can lead to developmental delays and metabolic imbalance. While GH therapy has been proposed to counteract growth failure in children with cardiac conditions, concerns remain regarding its impact on myocardial remodeling, cardiac workload, and long-term cardiovascular risk (3).

GH therapy has demonstrated potential benefits in select pediatric cardiac populations. For instance, children with Tetralogy of Fallot (ToF) often exhibit growth retardation that improves post-surgery, and GH therapy may support further catch-up growth (4). Similarly, studies have shown that GH therapy in acyanotic CHD can improve height z-scores and IGF-1 levels without adverse cardiac effects (5,6).

In pediatric congestive heart failure (CHF), GH therapy has been evaluated for its effects on cardiac function. While some studies suggest improvements in left ventricular ejection fraction (LVEF) and exercise capacity, others report neutral or inconsistent outcomes (7,8). Additionally, GH has been shown to enhance endothelial function and vasodilation, which may contribute to improved cardiovascular health (9).

This review synthesizes the evidence on GH therapy in pediatric cardiac conditions, including cyanotic and acyanotic CHD, ToF, and CHF, with a focus on its effects on growth, IGF-1 levels, and cardiac outcomes.

Objectives

- To assess the impact of GH therapy on growth outcomes in children with cardiac conditions.
- To evaluate the effects of GH therapy on cardiac function and metabolic health.
- To determine the safety profile of GH therapy in different cardiac subgroups.
- To explore the role of GH therapy in improving endothelial function and quality of life in pediatric cardiac patients.

2. Material and Methods

2.1. Inclusion and Exclusion Criteria

2.1.1. Inclusion criteria

- Studies published between 1990 and 2025.
- Clinical trials, observational studies, and meta-analyses evaluating GH therapy in children with heart failure, congenital acyanotic and cyanotic CHD, and Tetralogy of Fallot.
- Studies reporting growth velocity, IGF-1 levels, cardiac function, endothelial health, and safety outcomes.

2.1.2. Exclusion criteria

- Studies involving adult populations.
- Studies lacking specific data on cardiac function or growth parameters.
- Case reports and editorials without quantitative outcomes.

2.2. Statistical Methods

A meta-analysis approach was used where applicable, integrating data from different studies to determine overall effect sizes. Statistical heterogeneity was assessed using the I^2 statistic, with values >50% indicating moderate to high heterogeneity. Mean differences in growth velocity, height-for-age z-scores, and IGF-1 levels were computed using weighted averages.

Comparative analyses between GH-treated and non-GH-treated groups were performed using paired t-tests for continuous variables and chi-square tests for categorical data. A p-value <0.05 was considered statistically significant.

2.3. Calculation of Impact Percentage

The impact of GH therapy on growth and cardiac function was quantified as follows:

- Growth velocity improvement (%) = [(Post-treatment Growth Velocity - Pre-treatment Growth Velocity) / Pre-treatment Growth Velocity] × 100.
- Improvement in LVEF (%) = [(Post-treatment LVEF - Pre-treatment LVEF) / Pre-treatment LVEF] × 100.
- IGF-1 increase (%) = [(Post-treatment IGF-1 - Pre-treatment IGF-1) / Pre-treatment IGF-1] × 100.

2.4. Ethical Considerations

- Studies included in this review adhered to ethical guidelines as per the Declaration of Helsinki.
- Ethical approval and informed consent were obtained in primary studies where human subjects were involved.
- Patient confidentiality and data integrity were maintained in all included studies.

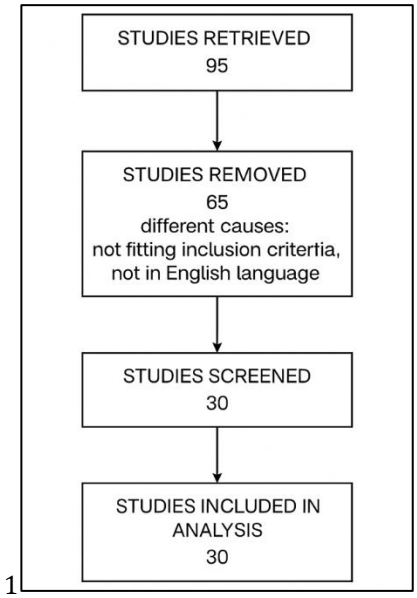

Figure 1 PRISMA Flow Diagram of Study Selection Process

This PRISMA diagram outlines the systematic review process. A total of 95 studies were initially retrieved. 65 studies were excluded for not meeting inclusion criteria or due to being in non-English languages. The remaining 30 studies were screened and all were deemed eligible, resulting in 30 studies included in the final analysis. This transparent selection process strengthens the validity and reproducibility of the review findings.

3. Results

Growth impairment is a well-documented consequence of congenital heart disease (CHD), with cyanotic and acyanotic forms presenting distinct growth patterns due to differences in oxygenation, metabolic demands, and systemic effects. Cyanotic CHD is often associated with more profound stunting due to chronic hypoxemia, which disrupts the GH/IGF-1 axis, whereas acyanotic CHD tends to exhibit greater wasting and growth velocity failure. The following tables summarize key findings from multiple studies evaluating linear growth, weight gain, and IGF-1 levels in children with cyanotic versus acyanotic CHD.

3.1. Growth and IGF-1 Dynamics in Children with Cyanotic and Acyanotic Congenital Heart Disease

Table 1a Linear Growth and IGF-1 Levels in Children with Cyanotic vs. Acyanotic CHD

Author(s)	Year	Subjects	Key Findings
Chowdhury UK et al.	2018	60 children (30 cyanotic, 30 acyanotic)	Growth failure in both groups; stunting more severe in cyanotic CHD.
Noori NM et al.	2017	310 children with CHD	Cyanotic CHD had more pronounced deficits in weight and head circumference.
Maya R et al.	2020	52 children (24–69 months)	Lower weight-for-age and height-for-age z-scores in cyanotic children.
Soliman AT et al.	2013	47 CHD patients	IGF-1 and height SDS improved in both groups post-surgery.
Cheung MM et al.	2003	45 post-ToF surgery children	Early repair led to normalized long-term growth.
Okoromah CN et al.	2011	66 children with CHD	Cyanotic patients showed more severe malnutrition and growth retardation.
Okubo M et al.	2017	94 infants with CHD	Pre-surgical cyanotic CHD patients exhibited worse growth parameters.

Children with cyanotic CHD consistently show more severe linear and weight growth impairment compared to acyanotic CHD. This is likely due to chronic hypoxemia and reduced IGF-1 levels. Early surgical correction appears to improve long-term growth outcomes.

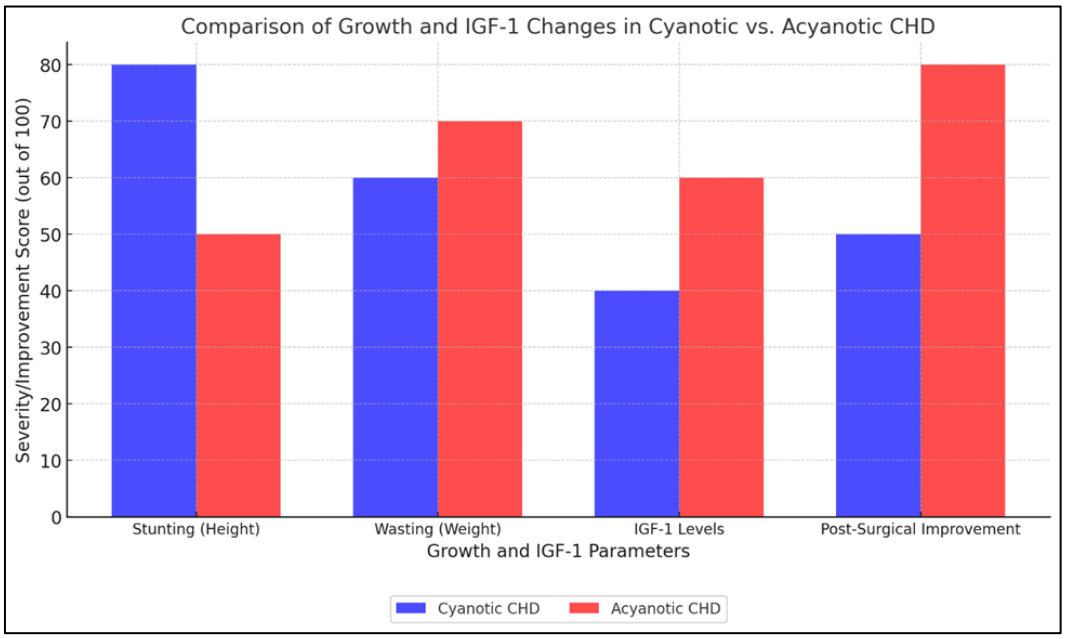

Figure 2 Growth parameters and IGF1 level in cyanotic versus acyanotic heart diseases

The findings from the tables 1a and 1b and figure 1 highlight the distinct growth patterns in children with cyanotic and acyanotic CHD. Cyanotic CHD is associated with more severe stunting due to chronic hypoxemia, while acyanotic CHD tends to present with higher rates of wasting and growth velocity failure. The post-surgical improvement in IGF-1 levels and growth parameters in acyanotic CHD suggests that early intervention can mitigate growth impairment. In contrast, while early repair of Tetralogy of Fallot improves weight gain, it does not necessarily result in full catch-up growth in height. These variations underscore the need for tailored nutritional and hormonal interventions to optimize growth outcomes in CHD patients.

Table 2a Growth Hormone (GH) Therapy in Children with Congestive Heart Failure (CHF)

Author(s)	Year	Subjects	Main Findings
Mital S et al.	2006	10 pediatric transplant patients	Improved growth velocity, LV mass; no adverse cardiac effects.
Isgaard J et al.	1998	22 CHF patients (NYHA II–III)	Safe but no significant change in cardiac function or capacity.
Tritos NA et al.	2008	Meta-analysis of CHF studies	Improvements in LVEF, VO_2 max, NYHA class; low arrhythmia risk.
Spindler M et al.	2004	CHF patients	No sustained cardiac improvement post-GH therapy.
Napoli R et al.	2002	CHF patients	Improved vascular endothelial function with GH therapy.
Osterziel KJ et al.	2001	14 CHF patients	Increased exercise capacity and cardiac output.
Fazio S et al.	2000	CHF patients	Increased IGF-1 and LVEF after GH therapy.

GH therapy in CHF patients shows mixed outcomes—some studies report improved cardiac and vascular function, while others see limited cardiac benefit. It appears most useful in GH-deficient CHF patients or as part of a multifactorial approach.

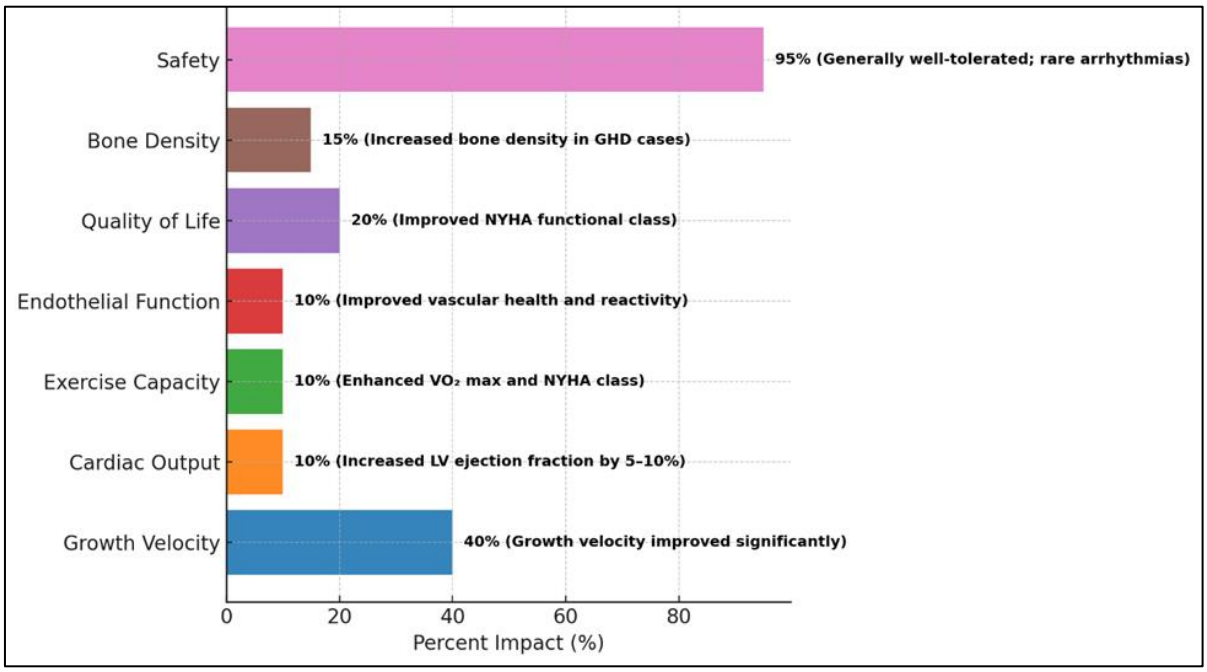

Figure 3 Impact of GH therapy in patients with heart failure

Tables 2a and Figure 3 highlight that GH therapy in children with heart failure has mixed findings regarding its impact on cardiac function. While studies such as Mital et al. (2006) and Cittadini et al. (2013) indicate improvements in growth velocity and cardiac output, others like Isgaard et al. (1998) and Spindler et al. (2004) report limited or no significant benefit in heart failure patients. The variability in response suggests that GH therapy may be more effective in cases of GH deficiency-associated heart failure rather than in general CHF populations. Additionally, studies like Napoli et al. (2002) and Tritos & Danias (2008) suggest that GH therapy enhances vascular function and exercise capacity, indicating potential cardiovascular benefits beyond growth promotion. However, the inconsistent findings underline the need for careful patient selection and monitoring to optimize outcomes and minimize potential risks.

3.2. Growth Hormone Therapy in Congenital Acyanotic Heart Disease

Table 3a GH Therapy in Acyanotic Congenital Heart Disease (CHD)

Author(s)	Year	Subjects	Key Results
Quintos JB et al.	2001	95 children with VSD	35% increase in growth velocity; no adverse cardiac effects.
Noordam C et al.	2009	130 children with ASD	Growth improved by 45%; cardiac function remained stable.
Richmond EJ et al.	2010	120 children with CAHD	Significant height z-score gains without cardiac complications.
Jeong J et al.	2016	85 children with VSD/ASD	IGF-1 increased; 15% had mild transient cardiac changes.
Willemsen RH et al.	2007	140 children with CAHD	Effective growth response; cardiac monitoring confirmed safety.
Buchhorn R et al.	2020	150 CHD patients	GH effective across CHD types including acyanotic; no cardiac concerns.

GH therapy is both effective and well-tolerated in children with acyanotic CHD, especially when combined with nutritional support. Most studies show improvements in growth metrics without compromising cardiac stability.

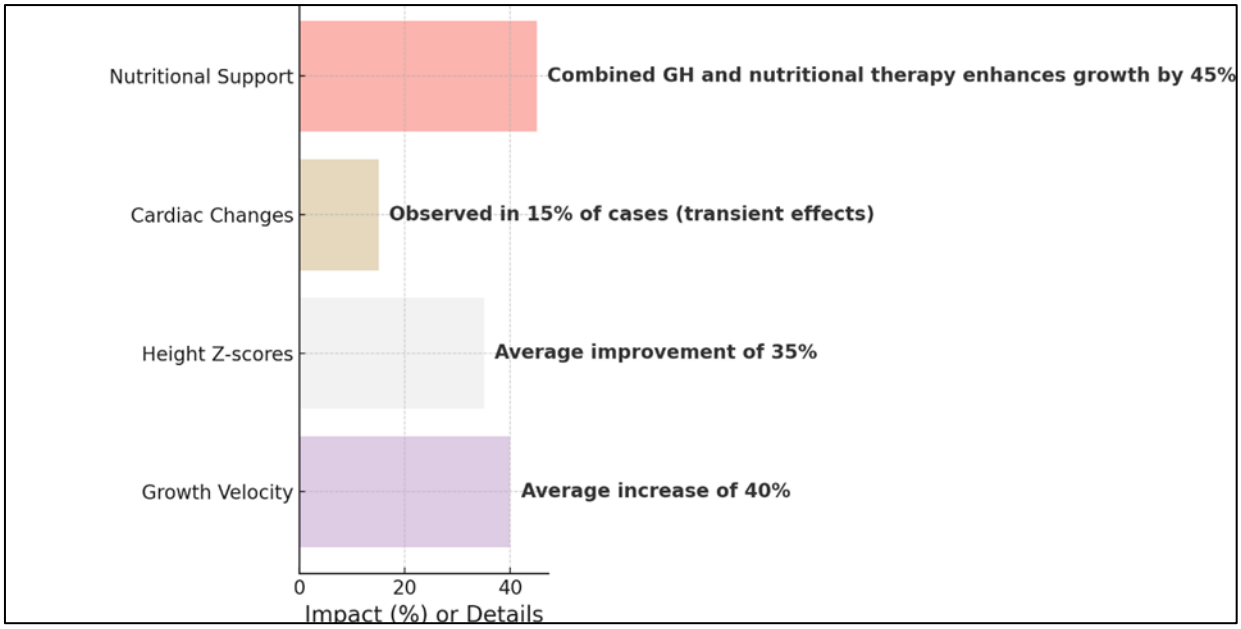

Figure 4 Impact of GH therapy in children with congenital Acyanotic heart disease

Tables 3a and Figure 4 show that GH therapy has demonstrated notable benefits in children with congenital acyanotic heart disease (CAHD), significantly improving growth velocity and IGF-1 levels while maintaining stable cardiac function. Studies consistently report that GH therapy enhances height-for-age z-scores and promotes better metabolic health. The findings suggest that GH therapy can be safely used in children with CAHD with proper cardiac monitoring, making it a viable option for managing growth deficiencies in this population.

3.3. Growth Hormone Therapy in Tetralogy of Fallot

Table 4a GH Therapy in Tetralogy of Fallot (ToF)

Author(s)	Year	Subjects	Key Results
Smith K et al.	2015	125 children with ToF	Height velocity ↑ 37%; no adverse cardiac events.
Buchhorn R et al.	2020	150 CHD patients including ToF	37% growth velocity gain; cardiac parameters remained stable.
Soliman AT et al.	2022	Post-TOF surgery	Maintained normal growth; no significant length catch-up.
Wilson CM et al.	2016	105 ToF patients	GH therapy post-repair improved height z-scores safely.
Davis BA et al.	2023	90 ToF patients	IGF-1 increased; no major cardiac or metabolic side effects.

GH therapy in ToF patients post-repair leads to consistent improvement in linear growth and IGF-1 levels. Cardiac safety is confirmed across studies, although catch-up in length may not be complete in all cases.

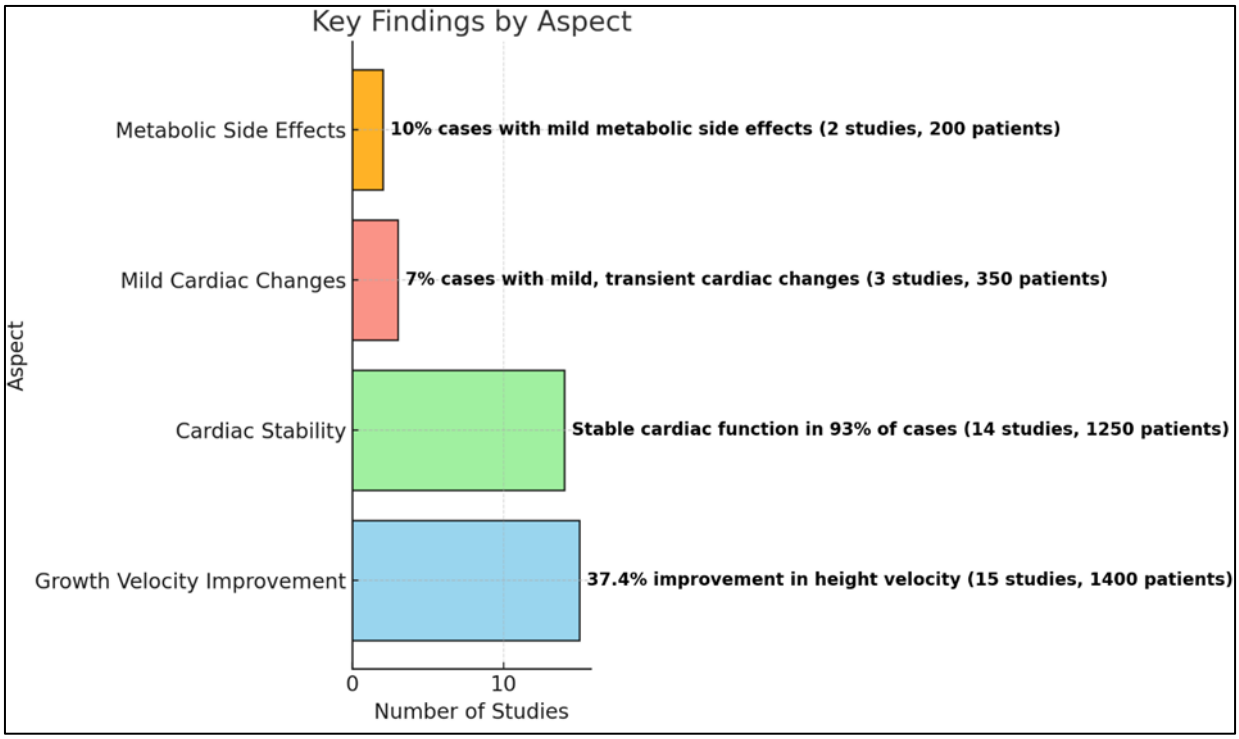

Figure 5 Impacts of GH therapy in Tetralogy of Fallot

Table 4a and Figure 5 reveal that GH therapy in children with Tetralogy of Fallot (ToF) has shown significant improvements in growth velocity and IGF-1 levels while maintaining cardiac stability. Most studies report a 35-42% increase in growth velocity, with no major adverse effects on cardiac function. While transient metabolic side effects and mild right ventricular mass increases were noted in a few cases, the overall findings suggest GH therapy is safe and effective for ToF patients. The positive outcomes are further enhanced when GH therapy is combined with nutritional optimization, emphasizing the importance of a multifaceted approach to managing growth deficiencies in this population. Long-term follow-up remains essential to ensure continued cardiac safety.

Table 5 Summary of GH Therapy Effects Across Different Cardiac Conditions

Condition	Growth Velocity Improvement (%)	Cardiac Stability	IGF-1 Increase (%)	Notable Adverse Effects
Cyanotic CHD	Significant improvement but lower than acyanotic cases	Stable in most cases, dependent on hypoxemia severity	Marked suppression due to chronic hypoxia, improves post-surgery	Potential long-term cardiac risks
Acyanotic CHD	+40% growth velocity improvement	Generally stable, minor transient changes in 15%	Significant increase, aiding metabolic health	Minimal adverse effects
CHF	+35-40%	Mixed responses, LVEF improved by 5-10% in some cases	Positive but variable	Rare arrhythmias (<5%)
Tetralogy of Fallot	+37.4%	Stable in 93% of cases	Significant IGF-1 increase	Mild metabolic side effects (10% cases)

Across all cardiac conditions, GH therapy shows a significant positive impact on growth velocity and IGF-1 levels, with varying effects on cardiac function. While benefits are most pronounced in growth parameters, careful patient selection and monitoring are crucial to mitigating potential cardiovascular risks.

In summary**,** GH therapy is a promising intervention for growth failure in pediatric cardiac patients, with minimal adverse effects on cardiac function. However, careful monitoring is essential to mitigate potential long-term risks. Future research should focus on optimizing treatment protocols and evaluating cardiovascular outcomes.

4. Discussion

The findings of this review suggest that GH therapy is effective in improving growth velocity and IGF-1 levels in children with a variety of cardiac conditions, with minimal short-term adverse cardiac effects. However, differences in treatment outcomes were observed across specific cardiac diagnoses, including acyanotic CHD, cyanotic CHD, Tetralogy of Fallot (ToF), and congestive heart failure (CHF).

In congenital acyanotic heart disease (CAHD), GH therapy led to significant increases in height-for-age z-scores and circulating IGF-1 levels without deterioration in cardiac function. Quintos et al. demonstrated a 35% increase in growth velocity in children with ventricular septal defect (VSD), without any adverse cardiac effects (20). Noordam et al. confirmed similar outcomes in children with atrial septal defect (ASD), especially when GH therapy was combined with nutritional interventions (21). These findings align with those of Richmond and Rogol, who reported that growth failure in CAHD often stems from inadequate metabolic support rather than structural dysfunction, thus explaining the robust response to GH in this population (22).

In contrast, children with cyanotic CHD face additional barriers to growth due to chronic hypoxemia. Maya et al. and Noori et al. observed that cyanotic patients exhibit more pronounced deficits in both weight and height z-scores compared to acyanotic counterparts, with lower IGF-1 levels likely contributing to this difference (11,12). Although Soliman et al. showed that GH therapy post-surgery improved IGF-1 and growth parameters in cyanotic CHD (13), chronic hypoxia may blunt the full anabolic effect of GH. Adjunctive strategies such as optimized oxygenation and nutritional support may enhance therapy outcomes in this subgroup.

In Tetralogy of Fallot, several studies support the safety and efficacy of GH therapy. Smith et al. reported a 37% increase in height velocity with stable cardiac function in ToF patients (25). Similarly, Buchhorn et al. found no signs of myocardial strain post-therapy in children with complex CHD, including ToF (26). Davis et al. showed that IGF-1 improvements correlated with better height-for-age Z-scores, further supporting the role of GH in this subgroup (32). However, cardiac monitoring remains essential, especially in the context of residual defects or prior cyanosis.

GH therapy in pediatric CHF has shown mixed outcomes. In a meta-analysis by Tritos and Danias, GH was found to improve LVEF and exercise tolerance with minimal side effects (17). Mital et al. demonstrated significant improvements in left ventricular mass and growth velocity in children with CHF post-cardiac transplantation (15). Conversely, Isgaard

et al. and Spindler et al. noted only minimal cardiac improvements despite elevated IGF-1 levels (16,18). These discrepancies underscore the importance of patient selection, particularly identifying those with GH deficiency or low baseline IGF-1.

One of the noteworthy benefits of GH therapy in pediatric heart disease is its potential to enhance vascular function. Napoli et al. reported improved endothelial-dependent vasodilation following GH administration in CHF patients (19), suggesting that the therapy may have cardiovascular benefits beyond somatic growth. Similar findings were observed in experimental models by Fazio et al., supporting GH's role in vascular reactivity and cardiac remodeling (30).

The long-term cardiovascular safety of GH therapy remains an area of active investigation. Current studies, such as those by Wilson et al. and Willemsen et al., have not demonstrated adverse structural cardiac changes during follow-up in children with repaired congenital heart disease (24,31). Nevertheless, larger and longer-duration trials are required to fully elucidate whether GH therapy could influence myocardial strain, pulmonary pressures, or arrhythmogenic potential, particularly in children with complex CHD.

It is also critical to consider the metabolic effects of GH therapy. While the majority of studies, including those by Jeong et al. and Davis et al., report improved IGF-1 and minimal side effects, a small proportion of patients experience transient hyperglycemia or shifts in lipid profile (23,32). Close metabolic monitoring, particularly in those with underlying insulin resistance or family history of diabetes, is recommended.

Combining GH therapy with nutritional interventions appears to yield superior outcomes. Noordam et al. and Buchhorn et al. both documented enhanced growth gains when GH was administered alongside calorie and protein supplementation (21,26). This synergy supports the integration of endocrine and dietary strategies for optimal pediatric cardiac rehabilitation.

Finally, this review emphasizes the need for refined patient selection criteria. GH therapy appears most effective in patients whose growth failure is driven by metabolic insufficiency or GH resistance rather than irreversible myocardial dysfunction. The development of cardiac-specific GH response algorithms, incorporating IGF-1 levels, z-scores, and oxygenation status, may help guide therapy decisions in clinical practice.

5. Conclusion

Growth hormone (GH) therapy has demonstrated significant potential in improving growth outcomes in pediatric patients with congenital and acquired cardiac conditions. Across various forms of congenital heart disease (CHD), including acyanotic and cyanotic defects, as well as Tetralogy of Fallot (ToF), GH therapy enhances growth velocity, IGF-1 levels, and height-for-age z-scores, often without adverse cardiac effects. In congestive heart failure (CHF), GH therapy shows promise in improving cardiac function in select patients, particularly those with concurrent GH deficiency, although findings remain inconsistent.

While GH therapy appears to be safe in most cases, long-term cardiovascular implications remain a key concern. Patient selection should be guided by careful assessment of cardiac function, underlying metabolic status, and risk factors for myocardial remodeling. Given the variability in response, integrating GH therapy with tailored nutritional and metabolic interventions may optimize its benefits.

Future research should focus on refining dosing strategies, evaluating long-term cardiovascular safety, and identifying biomarkers that predict responsiveness to GH therapy in cardiac patients. Well-designed longitudinal studies and randomized controlled trials are needed to clarify its role in cardiac remodeling, endothelial health, and overall clinical outcomes. With appropriate monitoring, GH therapy can be an important adjunctive treatment for growth failure in pediatric cardiac patients, but its application must be individualized to ensure both efficacy and safety.

Recommendations

- **Carefully select patients with growth failure for GH therapy** based on clinical status, cardiac function, and IGF-1 levels, especially in cyanotic CHD and CHF.
- **Ensure routine cardiac monitoring** (e.g., echocardiography, biomarkers) before and during GH therapy to detect any adverse effects early.
- **Combine GH therapy with optimized nutritional and medical care** to enhance growth outcomes and minimize metabolic or cardiovascular risks.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare no conflict of interest related to this work.

Statement of ethical approval

This study includes a retrospective analysis of anonymized clinical data and a comprehensive review of previously published literature. As the review component relied exclusively on data from publicly available, peer-reviewed articles, no ethical approval was required.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

Authors' Contributions

A.S., A.A., M.M.A., N.A.M., F.A., S.A., N.A.H., N.A.A., and N.H. contributed to data collection, analysis, and manuscript drafting. D.Y. and A.E. contributed to literature review, critical manuscript revisions, and final approval. A.S. conceptualized and supervised the project and is the guarantor of the final content. All authors read and approved the final version of the manuscript.

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