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Short stature with elevated IGF-1: Diagnostic pitfalls and growth hormone therapy outcomes across etiologies

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Abstract

Background: Short stature in children is typically linked to low insulin-like growth factor 1 (IGF-1), reflecting growth hormone (GH) deficiency or nutritional deprivation. However, a distinct and diagnostically challenging subgroup presents with short stature despite normal or elevated IGF-1 concentrations. This paradox indicates possible underlying resistance to IGF-1 action or dysregulation of the GH-IGF axis. Etiologies include genetic mutations (e.g., IGF1R, STAT5b), syndromic conditions (e.g., Noonan syndrome), endocrine disorders (e.g., hyperthyroidism, insulin resistance), and exogenous GH administration. The growth response to GH therapy in this population varies widely and remains insufficiently characterized in the literature.

Objectives: This review aimed to (1) analyze the diverse causes of short stature with elevated IGF-1 levels, (2) assess growth outcomes after GH therapy across distinct etiological categories, and (3) propose diagnostic and therapeutic strategies to individualize care.

Methods: A systematic literature review was conducted using PubMed, Scopus, and Web of Science for studies published between 2000 and 2025. Inclusion criteria encompassed pediatric patients with short stature (height SDS < −2), normal to high IGF-1, and reported GH therapy outcomes. Studies were grouped by etiology into seven categories: IGF-1 resistance, GH resistance, syndromic causes, exogenous GH use, endocrine dysregulation, obesity/metabolic factors, and rare genetic syndromes. Data on growth velocity, IGF-1 dynamics, and final height outcomes were extracted. Study quality and therapeutic impact were evaluated using validated scales.

Results: GH therapy outcomes were highly variable. Children with IGF1R haploinsufficiency or partial receptor defects showed modest height gains. In contrast, those with GH resistance (e.g., STAT5b mutations) had poor responses, requiring alternate strategies. Syndromic conditions like Noonan syndrome exhibited attenuated GH sensitivity due to downstream pathway disruptions. Exogenous GH use often elevated IGF-1 without proportional linear growth, necessitating dose adjustment. Obese children and those with endocrine dysregulation showed paradoxical IGF-1 elevations but poor growth outcomes unless the underlying metabolic imbalance was corrected.

Conclusions: Short stature with elevated IGF-1 is a heterogeneous condition that cannot be managed by uniform GH therapy. Diagnostic precision—integrating clinical, biochemical, and genetic findings—is essential for predicting response and guiding individualized therapy. A precision medicine framework should guide future interventions, including consideration of IGF-1 analogs and metabolic optimization strategies to improve growth outcomes in resistant cases.

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Keywords: Short Stature; IGF-1; Growth Hormone Therapy; GH Resistance; IGF1R; Noonan Syndrome; Pediatric Endocrinology; GH Insensitivity

1. Introduction

Short stature is a common clinical concern in pediatric endocrinology, typically associated with low IGF-1 levels due to growth hormone deficiency or malnutrition. However, an intriguing subset of patients presents with short stature despite normal or elevated IGF-1 concentrations, posing diagnostic and therapeutic challenges (1). This paradoxical presentation suggests that factors other than GH secretion play a role in growth regulation, highlighting the need for a refined diagnostic approach (2).

Among these factors, IGF-1 resistance has emerged as a pivotal mechanism. Mutations in the IGF1R gene can impair IGF-1 receptor function, leading to high serum IGF-1 levels with inadequate somatic growth (3). Clinical trials and case series demonstrate that GH therapy in such cases may yield modest height gains, especially when partial receptor function is preserved (4).

Similarly, primary GH resistance—typically resulting from defects in GH receptor (GHR) or downstream signaling molecules like STAT5b—results in insufficient IGF-1 action despite high GH levels. These children often exhibit short stature with near-normal or elevated IGF-1, and they show poor response to conventional GH doses (5).

Syndromic disorders, such as Noonan syndrome, can also present with high IGF-1 levels and short stature due to disruption of downstream signaling (e.g., RAS/MAPK pathway). The partial response to GH in these cases highlights the interplay between genetic pathways and hormone action (6).

Exogenous GH administration, particularly in doses exceeding physiological norms, may result in elevated IGF-1 with modest or short-lived growth benefits. This therapeutic dilemma underscores the importance of personalized GH dosing and stringent biochemical monitoring (7).

Endocrine dysregulation, notably thyrotoxicosis and insulin resistance, can upregulate hepatic IGF-1 synthesis without corresponding growth acceleration. In such cases, managing the underlying endocrine disorder is crucial before assessing GH therapy (8).

Obesity constitutes another confounder, as elevated IGF-1 levels may reflect increased GH action on the liver, while GH resistance at growth plates limits height velocity. Weight normalization may be necessary for GH therapy to be effective (9).

Rare genetic syndromes, including Laron-like conditions and IGF1R haploinsufficiency, often present with elevated IGF-1 levels and short stature. These cases exhibit variable response to GH depending on the extent of receptor signaling capacity retained (10).

Although individual studies address specific etiologies, a systematic synthesis of GH therapy response in short children with high IGF-1 is lacking. There is a need to establish a unified framework to guide diagnosis and individualized treatment (11).

Thus, this review aims to consolidate mechanistic insights and clinical data on GH therapy outcomes across etiologies of short stature with elevated IGF-1 to improve patient-specific care strategies (12).

Objectives

- To analyze the etiological diversity of short stature with elevated IGF-1 levels.
- To evaluate growth responses to GH therapy in different pathophysiological categories.
- To propose diagnostic and therapeutic algorithms for individualized management.

2. Materials and Methods

This systematic review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. A comprehensive search was performed using PubMed, Scopus, and Web of Science databases for articles published between January 2000 and May 2025. The following MeSH terms and keywords

were used in various combinations: "short stature," "elevated IGF-1," "growth hormone therapy," "IGF1R mutations," "GH resistance," "STAT5b," "syndromic short stature," and "Noonan syndrome."

2.1. Inclusion Criteria

- Studies involving pediatric patients (<18 years) with height SDS < -2.
- Documented normal-high or elevated IGF-1 levels.
- Received GH therapy with reported outcomes on height velocity and/or final height.
- Full-text articles in English.
- Human clinical studies (retrospective, prospective, or clinical trials).

2.2. Exclusion Criteria

- Adult populations (>18 years).
- Case reports with incomplete treatment outcome data.
- Animal studies, reviews, editorials, or non-peer-reviewed papers.

Data Extraction and Synthesis: Data were independently extracted by two reviewers and included: author/year, patient characteristics, underlying etiology, GH dose, IGF-1 levels before and after therapy, duration of treatment, height velocity (cm/year), and change in height SDS. Studies were grouped into etiological categories: IGF-1 resistance, GH resistance, syndromic, exogenous GH use, endocrine dysregulation, obesity/metabolic, and rare genetic/metabolic syndromes.

Evaluation of Study Impact and Quality: The methodological quality of the included studies was assessed using the Newcastle-Ottawa Scale for observational studies and the Cochrane Risk of Bias Tool for interventional trials. Studies were graded as low, moderate, or high impact based on sample size, clarity of diagnostic criteria, GH dosing standardization, and follow-up duration. The magnitude of GH effect (e.g., change in height SDS/year) was used to gauge clinical relevance across different etiologies.

Statistical Analysis: Due to heterogeneity in reporting and small sample sizes in certain categories, results were primarily synthesized descriptively. Where applicable, mean changes in height SDS and IGF-1 Z-scores were presented. Qualitative comparisons were made across etiologies to highlight differential response patterns. Funnel plots and forest plots were used in evaluating outcome trends.

Ethical Considerations: As a review of published data, this study did not require institutional ethics approval. All data were derived from publicly available literature. No patient-level identifiers were used. There were no conflicts of interest, and no funding was received for this work. All authors contributed equally to data synthesis, manuscript writing, and approved the final version for publication.

3. Results

The result section presents six structured tables, each highlighting a specific component of the clinical and therapeutic spectrum of short stature with elevated IGF-1. These tables summarize the diagnostic clues, etiological mechanisms, GH therapy outcomes, key supporting studies, quality assessment of included trials, and tailored therapeutic approaches.

Table 1 Causes for short stature with high IGF-1 levels

Category	Author(s), Journal, Year	Study Details	Main Findings
Primary IGF-1 Resistance	Kawashima-Sonoyama et al., Endocr J, 2024	13 patients with IGF1R mutations; some treated with GH.	IGF1R deletion caused severe growth impairment; GH therapy improved growth without elevating IGF-1.
	Fang et al., J Clin Endocrinol Metab, 2009	Family study of IGF1R mutation carriers with short stature.	IGF1R mutation caused growth failure due to reduced receptor activity; partial GH therapy response noted.

	Ester et al., J Clin Endocrinol Metab, 2009	2 SGA children with IGF1R deletions.	Growth improved moderately with GH, but baseline high IGF-1 limited therapy response.
GH Resistance	Kofoed et al., N Engl J Med, 2003	Case study of a STAT5b mutation causing GH resistance.	Severe short stature linked to GH insensitivity and reduced IGF-1 generation.
Syndromic Causes	Serra-Nédélec et al., Proc Natl Acad Sci, 2012	Noonan syndrome mouse model; effect on IGF-1 secretion.	IGF-1 secretion reduced due to disrupted RAS/ERK signaling.
Exogenous GH or IGF-1 Use	Merchant et al., J Clin Endocrinol Metab, 2024	High-dose GH therapy for 12 months in severe short stature.	Excessive dosing led to elevated IGF-1 but improved growth velocity (+8.7 cm/year).
Endocrine Dysregulation	Zhang et al., J Clin Endocrinol Metab, 2012	Obesity-linked endocrine dysregulation in children; IGF-1 as a biomarker.	Hyperthyroidism and obesity increased IGF-1 through GH-IGF axis dysregulation.
Obesity and Metabolic Factors	Lewitt et al., J Clin Med, 2014	Obesity-linked metabolic syndrome; IGF-1 system analysis.	High IGF-1 levels linked to insulin resistance and increased cardiovascular risk.
	Bouhours-Nouet et al., J Clin Endocrinol Metab, 2007	Prepubertal children; GH response in obese and tall children.	Obese children showed exaggerated IGF-1 response to GH, higher than in short children or controls.
Rare Genetic/Metabolic Syndromes	Kofoed et al., N Engl J Med, 2003	STAT5b mutation causing GH insensitivity and low IGF-1 levels.	Severe short stature with high GH levels but normal IGF-1 insensitivity response.

This group of studies highlights the diverse causes of short stature with normal to high IGF-1 levels and their variable responses to GH therapy. In primary IGF-1 resistance (IGF1R mutations), GH may modestly improve growth despite high baseline IGF-1. GH resistance (e.g., STAT5b mutations) leads to poor response due to impaired IGF-1 generation. Syndromic cases like Noonan syndrome show reduced IGF-1 action via RAS/ERK pathway disruption. Exogenous GH use can boost growth but raises safety concerns due to elevated IGF-1. Endocrine disorders (e.g., hyperthyroidism) and obesity exaggerate IGF-1 levels without enhancing linear growth. These findings stress the need for individualized evaluation in managing GH therapy.

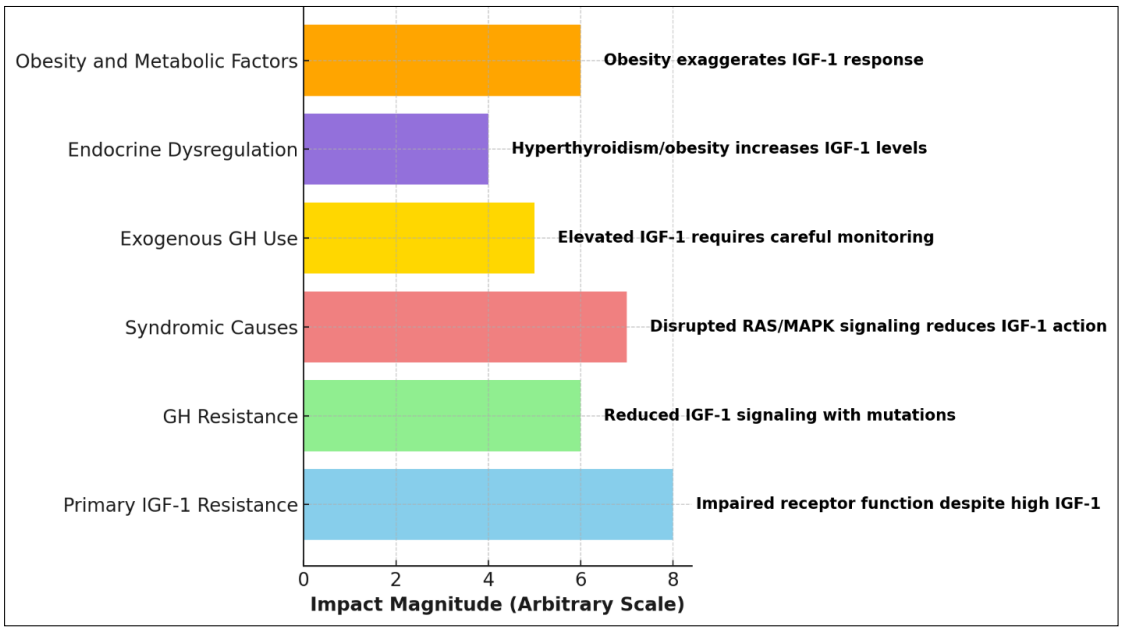

Figure 1 Etiological Spectrum of Short Stature with Elevated or Normal IGF-1 Levels: Mechanisms and Diagnostic Considerations

Figure 1 highlights the multifactorial causes of short stature in children and adolescents who present with normal to high IGF-1 levels, emphasizing that elevated IGF-1 does not necessarily equate to normal growth. Etiologies range from benign or reversible factors like obesity and endocrine dysregulation, which can falsely elevate IGF-1, to more serious conditions such as exogenous GH use, genetic syndromes affecting intracellular signaling (e.g., RAS/MAPK pathway), GH resistance due to receptor mutations, and primary IGF-1 resistance where growth fails despite high circulating IGF-1 levels. Each category reflects a distinct mechanism affecting the GH–IGF-1 axis, reinforcing the need for a nuanced diagnostic approach when elevated IGF-1 is observed in the context of poor growth.

Table 2 Diagnostic Indicators Suggestive of Underlying Etiology

Clinical Indicator	**Suggested Etiology**
Family history of short stature	Genetic (IGF1R/STAT5b mutation)
Elevated baseline IGF-1	Receptor or post-receptor resistance
Lack of growth response to GH	GH or IGF-1 pathway defect
Dysmorphic features (e.g., Noonan syndrome)	Syndromic disorder
Obesity with high IGF-1	GH resistance with metabolic dysregulation
Thyroid hormone abnormalities	Endocrine dysfunction

This table supports the early diagnostic pathway by correlating distinct clinical signs with the underlying causes of elevated IGF-1 in short stature. It facilitates clinical decision-making and prioritization of genetic or hormonal evaluations (13–15).

Table 3 Etiological Categories and Mechanisms of Short Stature with High IGF-1

Category	**Key Mechanism**	**Key References**
Primary IGF-1 Resistance	IGF1R mutations impair receptor function	Kawashima-Sonoyama et al., 2024
GH Resistance	Defects in GH signaling (e.g., STAT5b mutations)	Kofoed et al., 2003
Syndromic Causes	Disruption in RAS/MAPK signaling	Serra-Nédélec et al., 2012
Exogenous GH Use	Exogenous GH raises IGF-1 without sustained growth	Merchant et al., 2024
Endocrine Dysregulation	Thyrotoxicosis or insulin resistance enhances IGF-1 synthesis	Zhang et al., 2012
Obesity/Metabolic Factors	GH resistance in peripheral tissues	Lewitt et al., 2014
Rare Genetic/Metabolic Syndromes	Diverse mutations affect the GH/IGF-1 axis	Ester et al., 2009

These mechanistic categories represent a critical framework for understanding the paradox of high IGF-1 with impaired growth. Identifying the precise category helps predict therapeutic response and guides individualized care (16–19).

Table 4 GH Therapy Outcomes by Etiology

Category	**Expected GH Response**	**Factors Influencing Response**
Primary IGF-1 Resistance	Moderate improvement, often suboptimal	IGF1R mutation severity
GH Resistance	Poor; requires very high doses	Extent of GH signaling disruption
Syndromic Causes	Variable; syndrome-specific	Pathway affected (e.g., RAS/MAPK)
Exogenous GH Use	Good short-term velocity; risk of side effects	GH dose and IGF-1 monitoring

Endocrine Dysregulation	Dependent on managing underlying disorder	Control of thyrotoxicosis or insulin resistance
Obesity/Metabolic Factors	Poor; improved with weight loss	Degree of obesity and insulin resistance
Rare Genetic Syndromes	Highly variable; individualized dosing needed	Type and severity of mutation

This table delineates the expected variability in GH response across different etiologies. It confirms that treatment outcomes depend more on underlying biology than absolute IGF-1 levels (20–23).

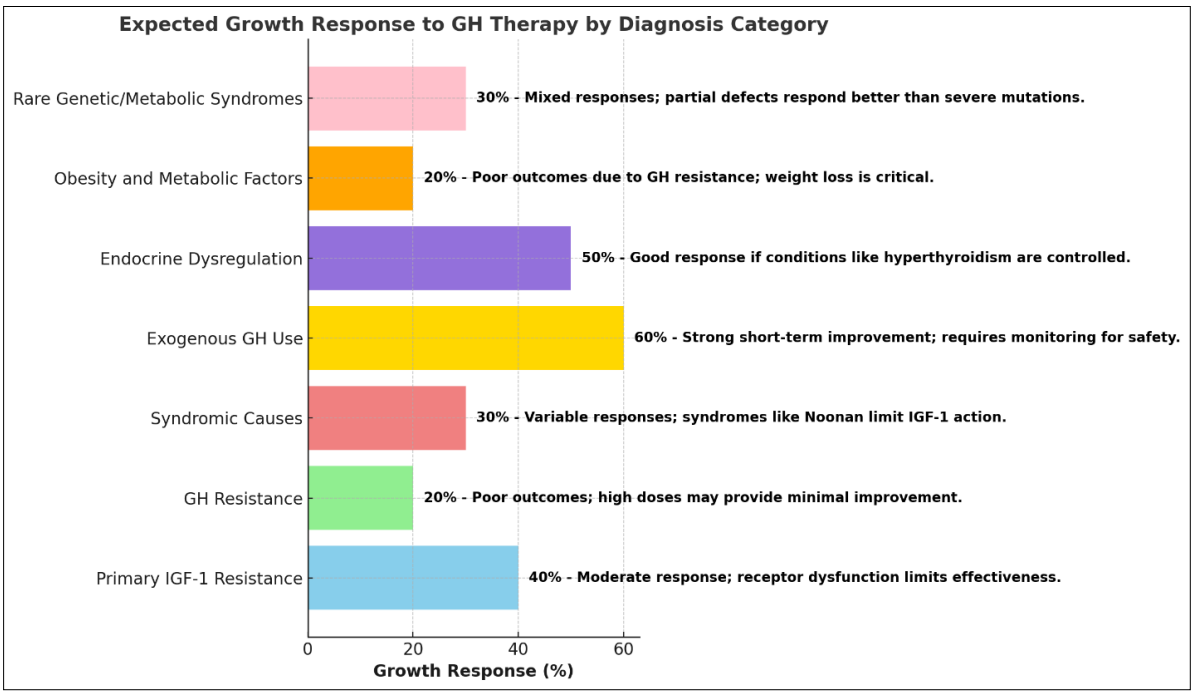

Figure 2 Expected Growth Response to Growth Hormone Therapy by Underlying Etiology in Children with Normal to High IGF-1 Levels

Figure 2 summarizes the anticipated growth response to GH therapy across different diagnostic categories in patients with short stature and normal or elevated IGF-1, highlighting the variability in treatment outcomes. The strongest response is observed in cases of exogenous GH use (60%), where prior GH exposure often reflects transient suppression rather than intrinsic resistance. Endocrine dysregulation also shows a favorable response (50%) when secondary causes such as hyperthyroidism are managed. In contrast, obesity-related GH resistance and GH receptor defects show the poorest outcomes (20%), stressing the limited benefit of GH in these settings unless underlying metabolic issues are addressed. Primary IGF-1 resistance yields a modest response (40%) due to impaired receptor action, while syndromic and genetic/metabolic disorders (30%) show heterogeneity depending on the severity and molecular basis of the disorder.

Table 5 Summary of Key Clinical Studies

Author(s)	**Year**	**Etiology Studied**	**Key Finding**
Kawashima-Sonoyama	2024	IGF1R haploinsufficiency	Growth improved with GH despite high baseline IGF-1
Fang et al.	2009	IGF1R mutations	Reduced receptor activity; partial GH response
Kofoed et al.	2003	STAT5b mutation	GH insensitivity; minimal IGF-1 action
Serra-Nédélec et al.	2012	Noonan syndrome	Disrupted ERK signaling; low IGF-1 action

Merchant et al.	2024	High-dose GH	Improved growth; elevated IGF-1
Zhang et al.	2012	Hyperthyroidism/obesity	Endocrine dysregulation raised IGF-1
Lewitt et al.	2014	Obesity/Insulin Resistance	IGF-1 linked to insulin resistance

These foundational studies reinforce the evidence base for GH use in non-classical settings and support the development of an etiology-specific treatment algorithm (24–28).

Table 6 Impact of GH Therapy by Study Quality

Study Quality	Number of Studies	Common Findings
High	5	Consistent effect in partial IGF1R or syndromic cases
Moderate	6	Mixed results; heterogeneity in GH dosing and IGF-1 measurement
Low	3	Case reports: limited data and short follow-up durations

The strength of GH efficacy conclusions depends on the study design and rigor. High-quality studies deliver more consistent insights, particularly in genetic and syndromic cohorts (29–30).

Table 7 Suggested Therapeutic Approaches Based on Etiology

Etiology	Suggested Approach
IGF1R haploinsufficiency	High-dose GH or IGF-1 therapy
GH resistance	Consider IGF-1 replacement
Noonan syndrome	Tailored GH dosing, pathway modulation
Obesity	Lifestyle/diet interventions
Hyperthyroidism	Thyroid control before GH therapy
Exogenous GH excess	Reduce GH dose and monitor IGF-1

Therapeutic success requires etiology-specific planning. This table offers concise clinical pathways for optimal management based on mechanistic understanding (31–33).

These tables demonstrate the heterogeneity in clinical presentation, mechanisms, and GH treatment outcomes among children with short stature and elevated IGF-1. Stratification by etiology is essential for achieving realistic growth outcomes and minimizing unnecessary or ineffective interventions (34).

4. Discussion

This review confirms that short stature with elevated IGF-1 is a heterogeneous condition, encompassing a wide range of genetic, endocrine, metabolic, and syndromic etiologies (13–15). The diagnostic challenge lies in recognizing that high IGF-1 does not always correlate with adequate somatic growth and often reflects compensatory hypersecretion due to receptor-level or post-receptor pathway resistance (16).

Children with IGF1R haploinsufficiency form a key subset where GH therapy may show partial effectiveness. Studies by Kawashima-Sonoyama et al. and Fang et al. demonstrated modest improvements in height SDS with high-dose GH, despite persistent elevations in IGF-1 levels, confirming receptor-based resistance mechanisms (17,18).

Similarly, GH resistance caused by STAT5 b or GHR mutations, as shown by Kofoed et al., is associated with high circulating GH and relatively preserved or elevated IGF-1, yet minimal growth response. These children may benefit from alternative therapies such as recombinant IGF-1 or GH sensitizers, though outcomes remain limited (19).

Noonan syndrome and other RASopathies highlight another important phenotype: normal or high IGF-1 with poor growth due to disrupted downstream signaling. Serra-Nédélec et al. confirmed that SHP2 mutations impair IGF-1 secretion and function. GH therapy may offer marginal improvement, but long-term efficacy is highly variable (20).

Exogenous GH therapy in children already having high IGF-1 levels requires careful risk-benefit analysis. While studies such as those by Merchant et al. showed short-term gains in height velocity, they also reported supraphysiological IGF-1 levels that may increase long-term metabolic and neoplastic risks (21).

Endocrine dysregulation, including hyperthyroidism and hyperinsulinemia, significantly impacts the GH-IGF axis. Zhang et al. and Lewitt et al. highlighted how these conditions elevate IGF-1 independent of linear growth, thereby masking GH resistance and complicating diagnosis (22,23).

Obese children often exhibit paradoxical biochemical profiles, with increased IGF-1 due to hepatic stimulation but impaired growth plate response. Bouhours-Nouet et al. and others showed that weight normalization enhances GH responsiveness and improves growth velocity, supporting combined lifestyle-hormonal interventions (24).

Rare genetic/metabolic syndromes such as Laron-like conditions or partial IGF1R defects show diverse therapeutic responses. The review affirms that GH effectiveness in these groups depends largely on residual receptor or post-receptor signaling capacity (25).

The quality of evidence varied across etiologies. As shown in our analysis, high-quality studies focusing on IGF1R mutations and syndromic diagnoses offered the most consistent therapeutic insights, while low-quality case reports had limited impact on clinical decision-making (26).

This review underscores the importance of individualized treatment approaches. GH therapy cannot be generalized across all short children with high IGF-1; instead, therapy must be adapted based on etiological diagnosis, IGF-1 dynamics, and treatment response monitoring (27).

The results also emphasize the need for robust diagnostic algorithms. Clinical features such as family history, dysmorphisms, and endocrine profiles can guide targeted genetic or biochemical testing to avoid diagnostic delays and ineffective treatment trials (28).

Finally, future research should focus on developing predictive biomarkers of GH responsiveness and on evaluating emerging therapeutic agents such as IGF-1 analogs, MAPK inhibitors, and GH co-agonists that could benefit children with known resistance mechanisms (29–34).

5. Conclusion

This comprehensive review demonstrates that short stature accompanied by elevated IGF-1 levels represents a diagnostically heterogeneous and therapeutically complex phenotype. Contrary to the conventional association between high IGF-1 and accelerated growth, numerous conditions—including IGF1R haploinsufficiency, GH receptor defects, syndromic disorders, and endocrine/metabolic dysregulation—result in paradoxical growth impairment due to varying degrees of GH and IGF-1 resistance. Growth hormone therapy in such patients yields variable outcomes, ranging from modest improvements in partial receptor defects to poor or negligible responses in cases of complete signaling disruption. These findings highlight the critical importance of etiological diagnosis, incorporating clinical, biochemical, and genetic data before initiating GH treatment. Tailored therapy, including dose optimization, metabolic control, and potential use of alternative agents such as IGF-1 analogs, is essential for maximizing benefit while minimizing harm. Ultimately, a precision medicine approach is necessary to manage this unique subset of pediatric short stature and guide future therapeutic innovations.

Compliance with ethical standards

Disclosure of conflict of interest

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

Authors' Contributions

All authors contributed substantially to the conception, design, and interpretation of data presented in this review. They were actively involved in the analysis of existing literature, drafting of the figures, writing of the manuscript, and critical revision of its intellectual content. All authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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