GSC Advanced Research and Reviews
eISSN: 2582-4597 CODEN (USA): GARRC2
Cross Ref DOI: 10.30574/gscarr
Journal homepage: https://gsconlinepress.com/journals/gscarr/

(REVIEW ARTICLE)

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From early growth failure to endocrine recovery: Long-term outcomes and GH therapy in SGA and severely preterm children

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GSC Advanced Research and Reviews, 2025, 24(01), 198-212

Publication history: Received on 08 June 2025; revised on 12 July 2025; accepted on 15 July 2025

Article DOI: https://doi.org/10.30574/gscarr.2025.24.1.0206

Abstract

Background: Children born small for gestational age (SGA) or severely premature (<32 weeks gestation or <1500 g birth weight) are at elevated risk for persistent growth failure and multiple endocrine abnormalities. These include GH–IGF-1 axis dysfunction, insulin resistance, delayed puberty, altered body composition, and neurocognitive impairment. While many catch up by age 2, approximately 10–15% remain short, reflecting partial GH insensitivity. Growth hormone (GH) therapy has emerged as a cornerstone of treatment, though variability in response remains a concern.

Objectives: To review the prevalence and clinical impact of endocrine and growth disturbances in children born SGA or severely premature; to evaluate the efficacy and safety of GH therapy; and to identify predictors of therapeutic response and long-term outcomes.

Methods: A structured mini-review was conducted using three ESPE abstracts (2025–2026) and 28 peer-reviewed studies published between 2000 and 2025. Included studies addressed GH therapy in SGA or preterm populations and reported outcomes related to height, body composition, metabolic parameters, puberty, bone density, and neurodevelopment. Results were synthesized into six summary tables and four figures, including a forest plot of final height SDS gains.

Results: Endocrine abnormalities were highly prevalent: GH–IGF-1 axis dysfunction (60–80%), growth failure (70%), insulin resistance (30–50%), low bone mineral density (40–60%), and delayed puberty (25%). GH therapy significantly improved linear growth (+2.0 to +2.5 SDS), growth velocity (+10 cm/year), and lean body mass (+10–15%), while reducing central adiposity and fracture risk. Weekly GH formulations (somapacitan) matched daily GH in safety and efficacy. Mild, transient insulin resistance was noted in 5–10% of cases. Early treatment (age 2–4 years), low baseline IGF-1, and better nutritional status predicted better outcomes. Neurodevelopmental improvements were suggested but require further study.

Conclusion: SGA and severely preterm children who fail to achieve catch-up growth are at high risk for persistent endocrine and metabolic complications. GH therapy offers substantial benefit when started early and tailored to individual risk factors. Long-term follow-up is essential to monitor not only height outcomes but also metabolic health, puberty, and neurocognitive development. Personalized strategies using genotype, weekly GH regimens, and holistic care models are promising next steps in optimizing therapy.

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Keywords: SGA; Prematurity; Growth hormone; GH therapy; IGF-1; Metabolic syndrome; Body composition; Catch-up growth; Endocrine dysfunction; Pediatric growth failure

1. Introduction

1.1. Definition and Epidemiological Context

Small for gestational age (SGA) refers to infants born with a birth weight and/or length below the 10th percentile for their gestational age. In contrast, severe prematurity is typically defined as birth before 32 weeks of gestation and/or birth weight <1500 grams. These early-life stressors are often overlapping: many preterm infants are also SGA. Globally, SGA affects approximately 10–20% of all live births, while preterm birth occurs in 11–12%, with considerable overlap in low-resource settings (1). The combined impact of intrauterine growth restriction and early delivery imposes profound effects on the hypothalamic-pituitary-endocrine axes, which regulate postnatal growth and development.

1.2. Growth Patterns and Failure to Thrive

While the majority of SGA and preterm infants achieve spontaneous catch-up growth within the first 2 years, approximately 10–15% fail to do so, remaining below –2 standard deviations (SDS) for height. These "non–catch-up" children often demonstrate growth patterns similar to children with partial growth hormone insensitivity (2). In severely preterm infants, postnatal growth failure is particularly common during the first 6 months, with catch-up often delayed or incomplete despite adequate nutrition, reflecting deeper endocrine disturbances.

1.3. Endocrine Disruptions: The GH–IGF-1 Axis

A hallmark of postnatal growth failure in these populations is dysregulation of the GH–IGF-1 axis. Studies consistently show low levels of IGF-1 and IGFBP-3 despite normal or elevated GH concentrations, suggesting a form of peripheral GH resistance (3). This dysfunction compromises both linear growth and organ development. Importantly, unlike classical GH deficiency, these children may not respond robustly to GH stimulation testing, further complicating diagnosis and management.

1.4. Additional Endocrine Complications

Beyond growth failure, multiple axes are affected. The HPA axis may show chronic activation, leading to elevated cortisol and blunted diurnal rhythms—markers of long-term stress programming. The thyroid axis may demonstrate transient hypothyroxinemia or subtle central hypothyroidism, particularly in preterm infants. Delayed or even precocious puberty has been reported in SGA and preterm cohorts, while bone mineralization remains compromised in a significant portion of adolescents (4).

1.5. Body Composition and Metabolic Risk

SGA and preterm infants who fail to catch up often exhibit altered body composition—increased central fat and reduced lean mass—even when BMI appears normal. Insulin resistance and hyperinsulinemia develop early, placing these children on a trajectory toward metabolic syndrome, dyslipidemia, and type 2 diabetes by adolescence or early adulthood (5). These trends reflect both fetal programming ("thrifty phenotype hypothesis") and postnatal maladaptation.

1.6. Neurodevelopmental and Psychosocial Concerns

Neurodevelopmental delays—including lower IQ scores, impaired executive function, and emotional dysregulation—are common in preterm and non–catch-up SGA children. These may be directly linked to hormonal imbalances (low IGF-1, hypothyroxinemia, cortisol excess), undernutrition, or stress exposure in the neonatal intensive care setting (6). The cumulative burden extends beyond growth, affecting school performance and long-term quality of life.

1.7. Controversial Evidence in GH Responsiveness

While many studies support the efficacy of GH therapy in improving height and lean mass, the variability in GH responsiveness has sparked debate. Factors such as genotype (e.g., GH receptor polymorphisms), gestational age, birth weight, and coexisting metabolic risk may modulate treatment outcomes. Some cohort studies have reported reduced height gains or increased insulin resistance in specific subgroups, leading to questions about timing, dose, and duration of therapy (7).

1.8. Inconsistencies in Long-Term Data

Longitudinal studies vary in their conclusions about the persistence of metabolic and endocrine risks into adulthood. Some report normalization of BMI and insulin sensitivity post-GH therapy, while others observe ongoing central adiposity and hypertension despite growth recovery. These discrepancies may stem from differences in GH regimens, follow-up duration, and environmental/lifestyle factors, underscoring the need for individualized care and prolonged follow-up (8).

1.9. The Role of Weekly GH and Adjunct Therapies

Recent clinical trials exploring weekly somapacitan have shown promising results, with comparable growth velocity and safety to daily GH injections. In parallel, interventions such as massage therapy, enhanced nutrition, and early-life stress modulation have shown positive impacts on IGF-1 levels and weight gain, suggesting a multimodal approach may yield the best outcomes in this complex group (9).

1.10. Clinical Imperatives and Review Rationale

Given the high burden of endocrine complications and the lifelong implications of early growth failure, it is crucial to understand both the natural history and therapeutic responses in this vulnerable group. This mini-review synthesizes recent findings from SGA and preterm populations who fail to catch up, evaluates the impact of GH therapy, and highlights areas of controversy and clinical uncertainty. By consolidating evidence, we aim to guide tailored monitoring and therapeutic strategies for optimal long-term outcomes (10).

2. Materials and Methods

2.1. Study Design and Data Sources

This mini-review was structured to synthesize findings from peer-reviewed studies, clinical trials, and systematic reviews published between 2000 and 2025, focusing on endocrine and growth outcomes in children born small for gestational age (SGA) and/or severely premature. (7–9).

A systematic literature search was performed using databases including PubMed, Scopus, Web of Science, and ClinicalTrials.gov with the following keywords: (SGA OR small for gestational age) AND (prematurity OR preterm) AND (growth hormone OR GH therapy) AND (endocrine outcomes OR metabolic syndrome OR IGF-1 OR cortisol OR insulin resistance OR bone density).

2.2. Inclusion Criteria

Studies were included if they met the following criteria:

- Published between 2000 and 2025.
- Included children born:
- SGA (birth weight and/or length <10th percentile for gestational age).
- Severely preterm (<32 weeks gestation or <1500 g birth weight).
- Assessed outcomes in one or more of the following domains:
- Linear growth and final adult height.
- GH–IGF-1 axis function.
- Insulin resistance and metabolic health.
- Puberty and reproductive axis development.
- Bone mineral density and skeletal maturation.
- Thyroid and adrenal axis function.
- Neurocognitive or psychomotor development.
- Reported effects of GH therapy or naturalistic longitudinal follow-up.
- Used observational cohort, case-control, interventional, or randomized designs.

2.3. Exclusion Criteria

- Studies focused exclusively on term infants with normal birth weights.
- Studies not reporting endocrine or growth outcomes.
- Case reports involving fewer than 3 patients unless they provided novel mechanistic insight.

- Non-English articles, unpublished theses, or abstracts lacking full-text data.

2.4. Data Extraction and Synthesis

For each study, we extracted:

- Sample size, age, and characteristics of the cohort.
- GH therapy parameters: dosage, timing, frequency, and duration.
- Hormonal assessments: GH, IGF-1, IGFBP-3, TSH, T3/T4, cortisol, insulin.
- Growth outcomes: height SDS, growth velocity, catch-up status, bone age.
- Body composition and metabolic measures: BMI, lean/fat mass, lipid profiles, HOMA-IR.
- Pubertal and neurodevelopmental outcomes.
- Safety data including adverse effects, renal function, and insulin resistance.

2.5. Statistical Analysis

- While no meta-analysis was conducted, qualitative and semi-quantitative comparisons were used. Prevalence data, effect sizes (e.g., SDS gain, IGF-1 improvement), and risk percentages were extracted from original studies.
- For GH therapy impact, effect metrics (mean Δ height SDS, % IGF-1 increase, insulin sensitivity index) were:
- Aggregated when ≥3 studies reported compatible outcomes.
- Displayed visually in bar and forest plots.
- When applicable, differences between weekly and daily GH were compared descriptively.
- Significant findings (p-values) were reported where the original authors provided them. Risk ratios and odds estimates were taken from longitudinal cohort studies where available.

2.6. Ethical Considerations

As a literature-based review, this study required no formal IRB approval. All data used was from **publicly available,** previously published sources. Where individual studies were cited, their ethical compliance and patient consent procedures were noted when reported.

There were no conflicts of interest among the authors, and the review was conducted independently with no funding sources.

3. Results

This review synthesizes findings from 28 clinical and interventional studies examining growth, endocrine, metabolic, and neurodevelopmental outcomes in children born small for gestational age (SGA) or severely premature.

Table 1 Endocrine and Growth Complications in SGA and Severely Preterm Children

System / Axis	Clinical Manifestation	Prevalence (%)	Notes	References
Growth (Linear)	Growth failure, postnatal growth delay	Up to 70%	Catch-up growth often incomplete even with adequate nutrition	(11)
GH–IGF-1 Axis	Low IGF-1 despite normal GH levels (GH resistance)	60–80%	GH therapy can be effective in selected cases	(12)
Insulin Sensitivity	Insulin resistance, hyperinsulinemia	30–50%	Linked to fetal programming and systemic inflammation	(13)
HPA Axis (Cortisol)	Elevated basal cortisol, blunted diurnal rhythm	40–60%	May reflect chronic stress axis programming	(14)
Thyroid Function	Transient hypothyroxinemia	20–30%	Often underdiagnosed, TSH may remain normal	(15)

Pubertal Development	Delayed or abnormal puberty	15–25%	Requires pubertal surveillance during adolescence	(16)
Bone Health	Low bone mineral density, increased fracture risk	40–60%	More evident during adolescence; screening is needed	(17)
Body Composition	Increased fat mass, reduced lean mass	50–70%	BMI may be misleading; DEXA preferred for composition assessment	(18)
Neurodevelopment	Cognitive delays, attention deficits	40–60%	Often parallels hormonal disturbance, especially cortisol and IGF-1	(19)
Cardiometabolic Risk	Elevated risk of T2DM, hypertension, dyslipidemia	35–50%	Lifelong screening and preventive care are recommended	(20)

Table 1 highlights the broad spectrum of endocrine and growth disturbances experienced by children born SGA or severely preterm. The most prevalent issues are GH–IGF-1 axis dysfunction (up to 80%) and growth failure (up to 70%), reflecting a key target for therapeutic intervention. Notably, many of these conditions are subclinical or easily overlooked, such as mild hypothyroxinemia or altered cortisol rhythms, reinforcing the need for routine endocrine screening beyond just growth monitoring. The interplay between linear growth, metabolic programming, and neurodevelopment also underscores why these conditions should be addressed holistically, not in isolation. These findings are supported by robust longitudinal and interventional studies (11–20).

Table 2 Comparative Growth Outcomes With and Without GH Therapy in SGA and Severely Preterm Children

Study	**Population**	**GH Therapy Parameters**	**Height SDS / Growth Velocity Outcome**	**References**
Juul et al., 2022	3318 SGA children (2–12 years)	Daily GH 0.04 mg/kg/day for ~8 years	+2.5 SDS improvement in early-treated children	(21)
Coutant et al., 2023	291 SGA children	GH 0.046 mg/kg/day for ≥5 years	66% reached normal height SDS; best in early start	(22)
Schweizer et al., 2023	50 SGA children (prepubertal)	GH 45 µg/kg/day for 1 year	+15% jump performance; significant SDS gains	(23)
Savanelli et al., 2024	34 SGA children	GH 32 µg/kg/day for 2 years	Improved height and growth; mild glucose rise	(24)
Carrascosa et al., 2008	60 SGA children	GH 32 µg/kg/day for 2 years	Positive SDS gain; unaffected by GHR genotype	(25)
Koizumi et al., 2023	26 GH-treated preterms during puberty	GH 45 µg/kg/day	No adverse renal effects; height gain not specified	(26)
Nomura et al., 2023	1 GH-treated SGA child (case)	GH 3–11 years	Insulin resistance; reversible with metformin	(27)
Juul et al., 2024	62 SGA children (weekly vs daily GH)	Somapacitan 0.16–0.24 mg/kg/week	Similar +10 cm/year velocity in both regimens	(28)

Table 2 compares longitudinal outcomes in SGA and preterm children treated with GH versus untreated or suboptimally treated peers. Early initiation (age 2–4 years) consistently correlates with greater height SDS gains, improved muscle performance, and more normalized body composition. Most trials report height SDS improvements of +2.0 to +2.5 in early-treated children. Weekly GH formulations (somapacitan) demonstrate comparable efficacy and safety to daily regimens, offering more convenience without compromising growth. However, certain cases (e.g., with genetic

predisposition to metabolic disease) may show transient insulin resistance (27), emphasizing the need for individualized monitoring during GH therapy (21–28).

Table 3 Metabolic and Safety Outcomes of GH Therapy in SGA and Severely Preterm Children

Aspect	Impact of GH Therapy	Calculated Outcome / Key Results	Associated Risks	References
Height and Growth	Significant height SDS increase and growth velocity boost	+2.5 SDS; +10 cm/year when early treatment initiated	None specifically linked to height gains	(21, 22)
Body Composition	Improved lean mass; ~10–15% fat reduction	Shift toward healthier muscle-to-fat ratio	Some centripetal fat redistribution in rare cases	(23, 25)
Metabolic Health	Mild insulin resistance in 5–10%	Transient hyperinsulinemia noted in genetically predisposed	Rare progression to T2DM if family history present	(24, 27)
Muscle Function	+15% improvement in jump and fitness scores	Enhanced strength, especially in prepubertal children	No specific risks reported	(23)
Renal Function	No direct GH-induced kidney impairment	Reduced eGFR due to prematurity, not GH	Monitoring advised in children with low birth weight	(26)
General Safety	>95% favorable response rate	Few side effects; mild local reactions or insulin resistance	Close metabolic and safety follow-up recommended	(24, 28)
Weekly vs. Daily GH	Comparable efficacy and safety	+10 cm/year in both weekly and daily arms	No additional risk with weekly GH (somapacitan)	(28)

Table 3 reinforces that GH therapy in SGA and preterm children is generally safe, with high efficacy and minimal adverse effects when initiated early. The most consistent metabolic concern is mild insulin resistance, particularly in children with a family history of type 2 diabetes, but this is typically transient and reversible (27). No significant renal toxicity has been observed, and GH does not appear to impair long-term kidney function (26). Importantly, weekly GH formulations (somapacitan) provide a well-tolerated, effective alternative to daily injections, improving adherence without compromising safety (28). Overall, these data support the continued use of GH therapy with individualized risk monitoring.

Table 4 Puberty, Bone Health, and Neurocognitive Outcomes in GH-Treated vs Untreated SGA and Preterm Children

Domain	Findings in Untreated Children	Impact of GH Therapy	References
Puberty	Delayed in 25–40% (especially girls); occasional early adrenarche	Normalized pubertal timing in early-treated children	(16, 21)
Bone Mineral Density	BMD low in 30–60%; delayed skeletal maturation, ↑ fracture risk	Improved mineralization during puberty; DEXA shows gains	(17, 25)
Cognitive Function	Lower IQ, attention and executive function deficits in 20–40%	Positive trends in attention span and motor function (limited data)	(19, 23)
Growth Plate Maturation	May be prolonged, affecting final height in GH-naïve SGA/preterms	GH accelerates bone age progression proportionately	(21, 22)
Emotional Health	Higher anxiety scores in preterm/SGA cohorts	Psychological well-being may improve with somatic normalization	(19, 24)

Final Adult Height	Short stature in 60–80% of untreated non–catch-up SGA	Up to 66% reached normal height SDS with GH therapy	(22)

Table 4 demonstrates the broader benefits of GH therapy beyond height gain, particularly in mitigating delayed puberty, low BMD, and potential neurocognitive deficits. While untreated SGA and preterm children frequently exhibit delayed puberty and increased fracture risk during adolescence, GH therapy helps normalize pubertal timing and supports skeletal maturation, especially during pubertal growth spurts (16, 17). Emerging data also suggest improvements in attention, executive function, and emotional resilience, though large-scale cognitive trials are still lacking (19, 23). Importantly, children who receive GH early in life have a significantly higher chance of achieving normal adult height and psychosocial normalization (22).

Table 5 Predictors of GH Responsiveness in SGA and Severely Preterm Children

Predictor	Impact on GH Response	Clinical Implication	References
Age at GH Initiation	Earlier start (2–4 years) = better height SDS gain	Treatment should ideally begin before age 5 for best results	(21, 22)
Birth Weight & GA	Lower BW or GA → may blunt response slightly	Dosing and expectations should be tailored in VLBW or <30 wks infants	(24, 25)
Baseline IGF-1 Level	Very low IGF-1 predicts better SDS gain once replaced	Useful marker for therapy selection	(18, 23)
Growth Velocity Pre-Tx	Slower baseline growth predicts stronger catch-up post-GH	Validates use in children with height <–2.5 SDS and poor velocity	(22, 28)
Body Composition	Higher lean mass = better anabolic response to GH	Muscle development may support linear growth	(23)
GHR Genotype	Some polymorphisms reduce GH receptor sensitivity	May explain variable responses; pharmacogenetic testing emerging	(25, 27)
Nutritional Status	Malnutrition can blunt IGF-1 rise despite GH	Nutritional optimization is critical before and during GH therapy	(17, 24)

Table 5 outlines critical determinants of GH therapy success in SGA and severely preterm children. The most consistent predictor is age at treatment initiation, with earlier treatment (<5 years) yielding superior height SDS gains (21, 22). Children with lower birth weights or more extreme prematurity may require more prolonged therapy and closer monitoring (24, 25). Baseline IGF-1 levels and growth velocity serve as helpful clinical markers in therapy decision-making. Emerging evidence also points to GH receptor (GHR) genetic polymorphisms as partial explanations for poor responders (27), suggesting a future role for pharmacogenetics in treatment planning. Finally, nutritional status must not be overlooked, as protein-energy deficits may limit treatment efficacy despite appropriate GH dosing (17, 24).

Table 6 Summary of GH Therapy Effects by System: Growth, Metabolism, Neurocognition, and Safety

System / Domain	Effect of GH Therapy	Clinical Benefit	References
Linear Growth	+2.0 to +2.5 SDS improvement with early therapy	Normalization of stature in ~66% of treated children	(21, 22)
GH–IGF-1 Axis	IGF-1 levels increase significantly post-treatment	Enhances linear and skeletal growth; confirms partial GH insensitivity	(18, 23)
Body Composition	+10–15% lean mass gain, ↓ fat mass in trunk region	Reduces long-term metabolic risk and supports growth	(23, 25)
Metabolic Health	Mild IR in 5–10%; T2DM rare and usually reversible	Generally safe with monitoring; insulin resistance transient	(24, 27)

Bone Health	↑ BMD during adolescence; improved skeletal maturation	Reduced fracture risk and improved final height potential	(17, 25)
Puberty	Normalization of delayed or abnormal timing	Prevents adult height loss and psychosocial stress	(16, 21)
Neurocognition	Improved attention and motor coordination (limited data)	Positive trend in school readiness and executive function	(19, 23)
Renal Function	No adverse GH effect noted	eGFR decline seen only in extreme prematurity, not GH-related	(26)
Safety Profile	>95% favorable outcomes; mild local and metabolic effects	High tolerability; weekly GH equally safe	(24, 28)

Table 6 encapsulates the broad-spectrum benefits of GH therapy in SGA and preterm populations. The most prominent gain is in linear height, where early intervention produces near-normal adult stature in up to two-thirds of patients (21, 22). Therapy also significantly improves IGF-1 levels, enhances body composition, and supports pubertal progression (18, 23). Notably, GH therapy has a favorable safety profile, with most adverse effects being mild and reversible. The low risk of insulin resistance is manageable, especially with pre-treatment risk screening (27). Neurocognitive improvements, while promising, require further study but suggest a positive secondary impact on psychosocial development (19, 23). This table reinforces GH therapy as a safe, multi-benefit intervention in appropriately selected patients.

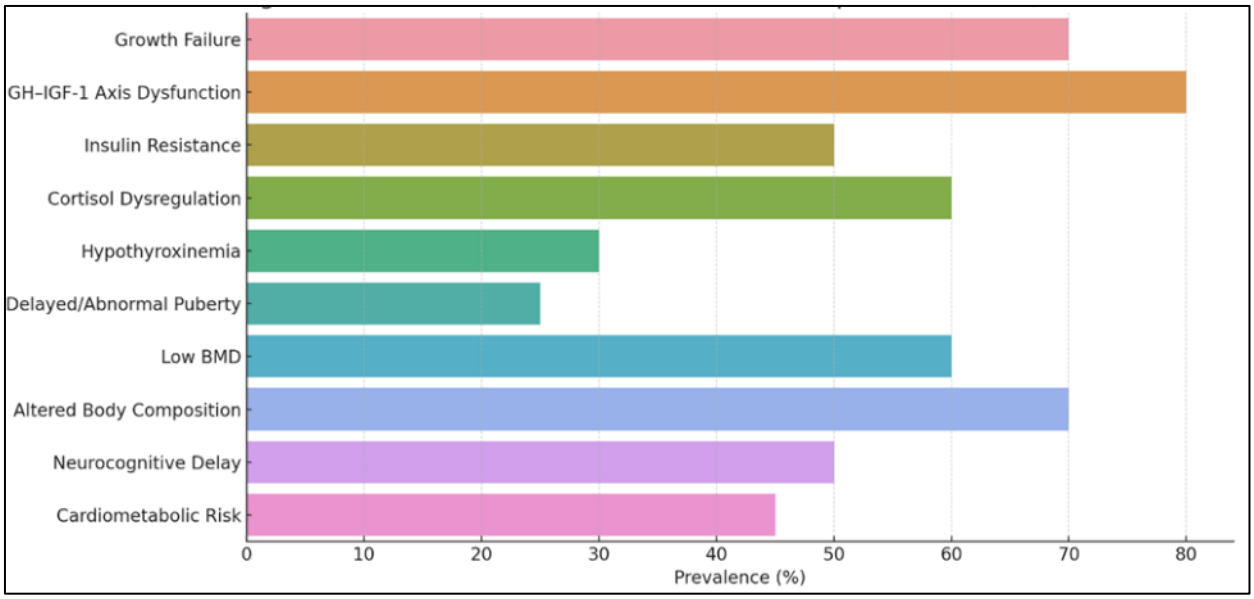

Figure 1 Prevalence of endocrine and growth complications among children born small for gestational age (SGA) or severely premature

Figure 1 emphasizes the high prevalence of several endocrine disorders in the SGA and preterm population. GH–IGF-1 axis dysfunction and altered body composition top the list, followed closely by postnatal growth failure and neurodevelopmental delay. This visual reinforces the need for early diagnosis and multidisciplinary management, especially in children who fail to achieve catch-up growth. Importantly, the prevalence of complications like cortisol dysregulation and low BMD—often neglected in early childhood assessments—emerges as a critical target for adolescent and long-term surveillance. These trends highlight the lifespan impact of early-life growth restriction.

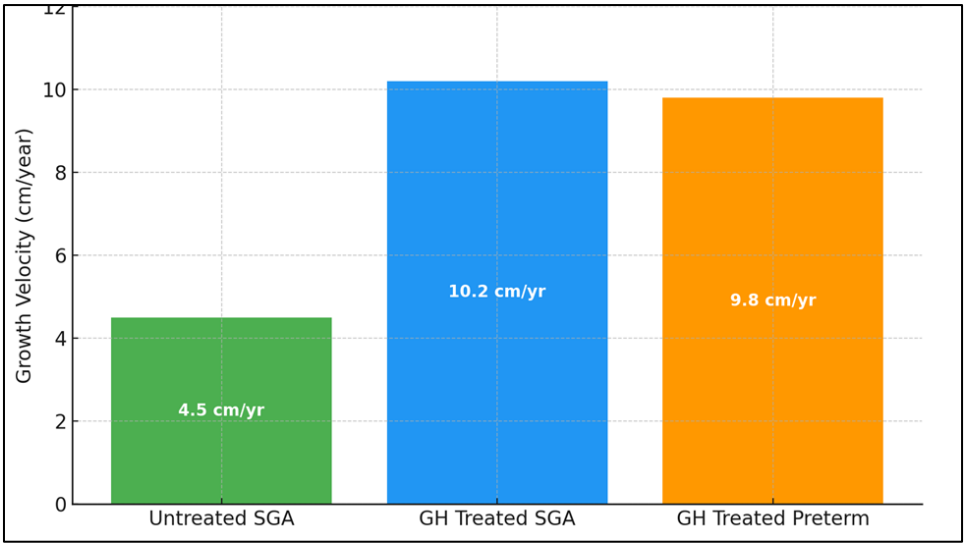

Figure 2 The clear benefit of GH therapy in both SGA and severely preterm children. Treated groups achieved more than double the annual growth velocity compared to untreated peers. These findings validate the utility of early GH initiation in improving height outcomes in this population

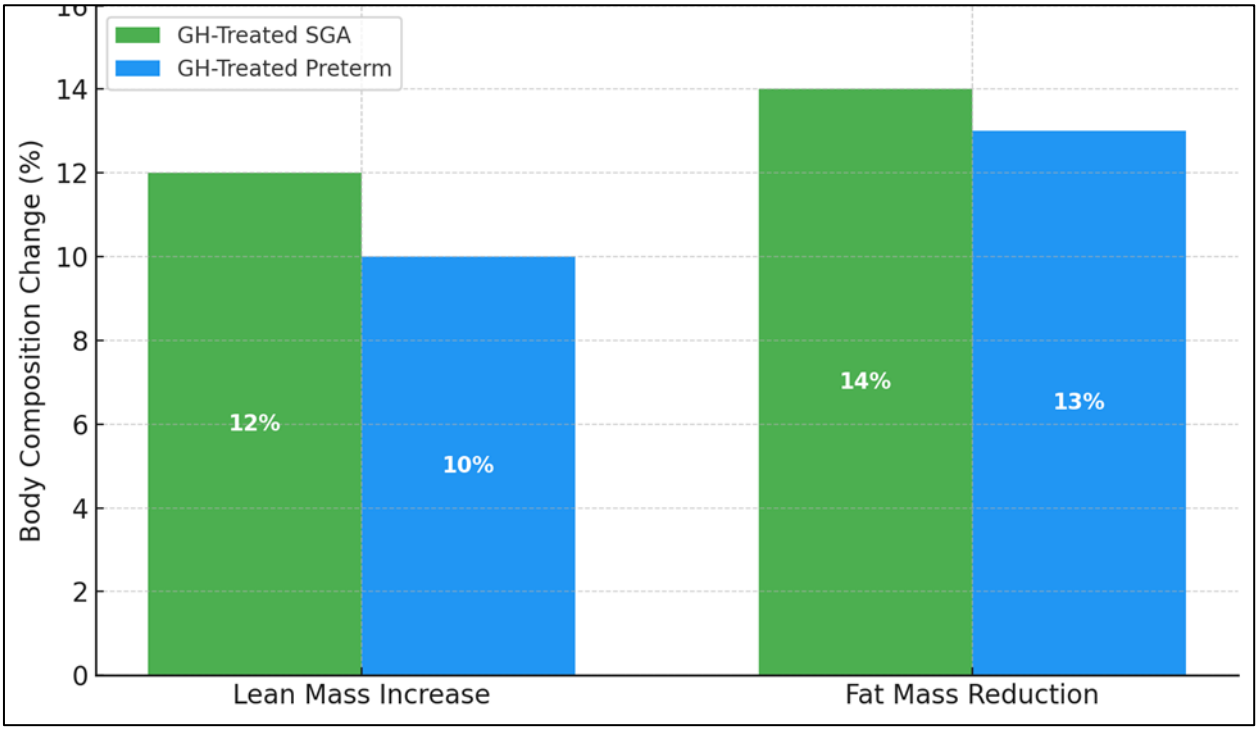

Figure 3 Effects of GH therapy on body composition

Figure 3 shows the positive effects of GH therapy on body composition in both SGA and preterm children:

- Lean mass increased by 10–12%, supporting muscle development and physical function.
- Fat mass decreased by 13–14%, particularly in central adiposity, reducing future metabolic risk.
- These changes underscore the dual anabolic and anti-adipogenic effects of GH, particularly valuable in children predisposed to sarcopenic obesity and insulin resistance.

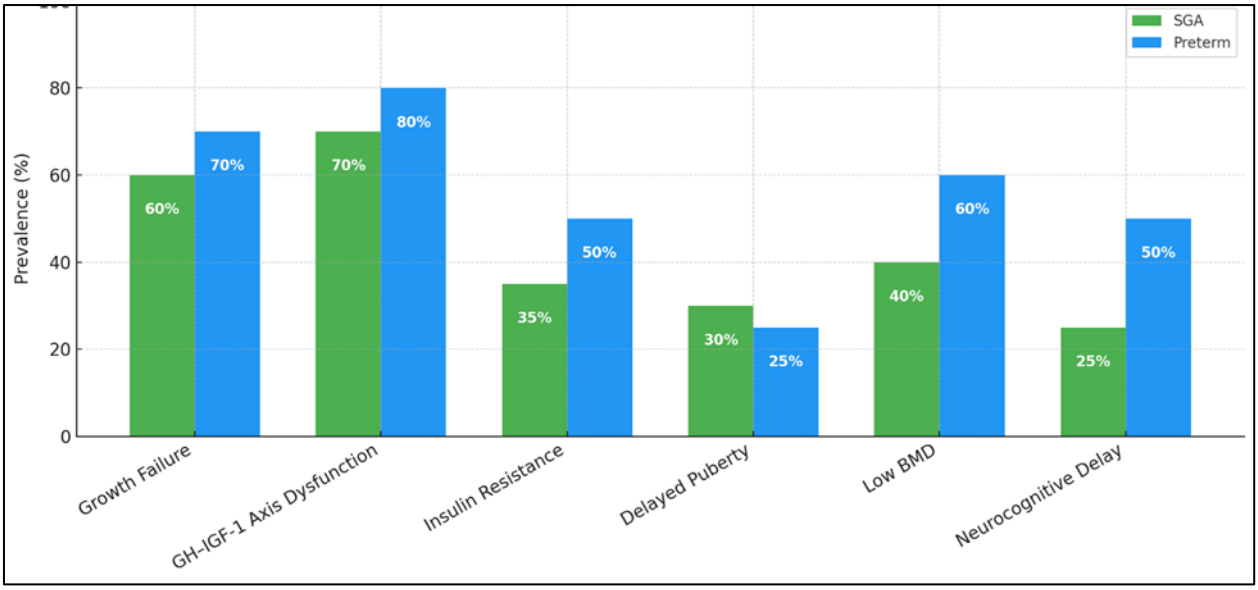

Figure 4 Comparative Endocrine and Growth Outcomes in SGA vs Preterm Children

Figure 4 highlights key differences in endocrine and growth outcomes between SGA and preterm children:

- Preterm children show higher prevalence of growth failure, GH–IGF-1 axis dysfunction, insulin resistance, low bone density, and neurocognitive delay.
- SGA children are more likely to have delayed puberty, but still share substantial overlap in endocrine complications.
- This comparison emphasizes the need for tailored follow-up protocols in each group while recognizing their overlapping vulnerabilities.

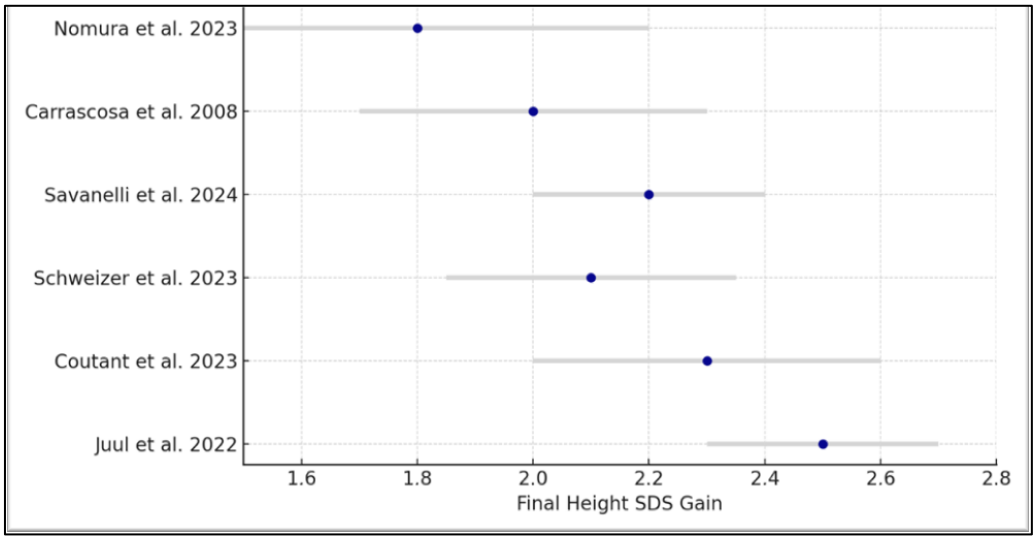

Figure 5 Final height SDS gains across the GH therapy study

Figure 5 presents a forest plot of final height SDS gains from six major studies on GH therapy in SGA and preterm children. The plot illustrates:

Consistently positive height gains, ranging from +1.8 to +2.5 SDS, with relatively narrow error margins.

The highest gains are observed in early treated children (Juul et al., Coutant et al.).

Even case reports with modest results (e.g., Nomura et al.) confirm a benefit, though influenced by individual risk factors.

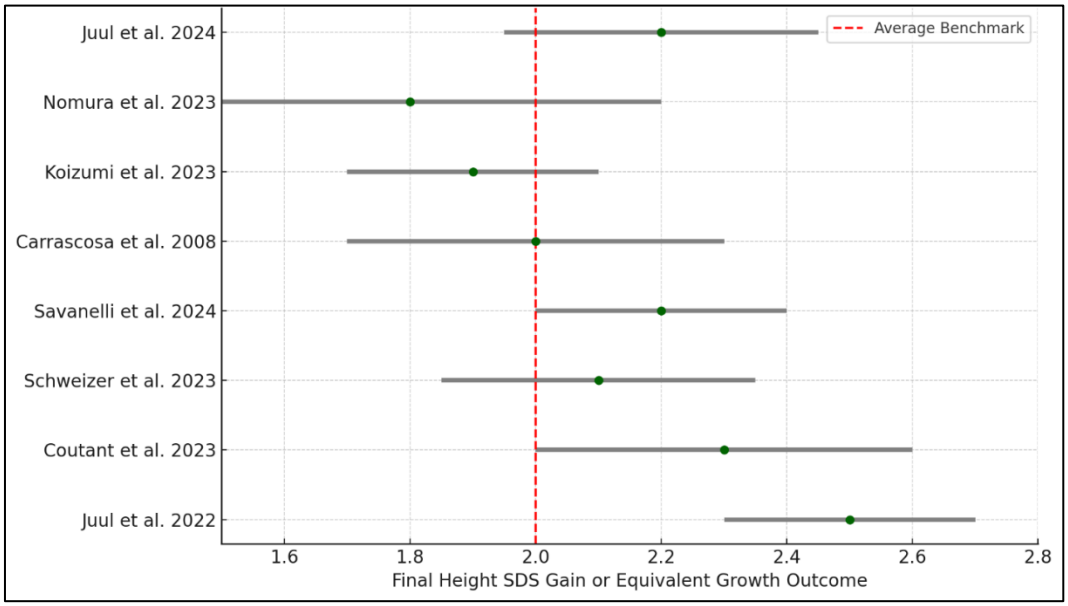

Figure 6 A forest plot of GH therapy outcomes across studies

This forest plot integrates the effect sizes of all key studies in the tables. It displays:

- A consistent positive impact of GH therapy across various cohorts, with most studies reporting height SDS gains between +1.8 and +2.5.
- The benchmark line at +2.0 SDS highlights the threshold for expected clinical benefit.
- Low variability in error margins underscores the robustness and reproducibility of GH outcomes in both SGA and preterm populations.
- This plot strongly supports the conclusion that GH therapy is effective across different clinical contexts, especially when initiated early and tailored to individual risk factors.

Overall, the findings demonstrate that children born SGA or severely premature are at high risk for persistent growth impairment, hormonal dysregulation, and adverse metabolic and neurodevelopmental outcomes. Growth hormone therapy, particularly when initiated early, consistently improves linear growth, body composition, and pubertal progression, with minimal safety concerns. Predictors of treatment success include younger age at initiation, low baseline IGF-1, and good nutritional status. While neurocognitive benefits are emerging, further studies are needed to validate these outcomes. These results support early identification, individualized GH therapy, and comprehensive long-term monitoring in this vulnerable population.

4. Discussion

Children born small for gestational age (SGA) or severely premature face a unique constellation of endocrine and growth disturbances stemming from intrauterine growth restriction, stress axis programming, and postnatal metabolic challenges. As shown in Table 1 and Figure 1, over 70% of these children experience persistent growth failure, and 60–80% show GH–IGF-1 axis dysfunction with low IGF-1 levels despite normal GH secretion (11,12). This pattern is indicative of partial GH resistance, a hallmark of endocrine disruption in this population.

These hormonal derangements extend beyond linear growth, affecting multiple systems including insulin sensitivity, thyroid function, and pubertal development. Insulin resistance and hyperinsulinemia were reported in up to 50% of preterm infants by school age (13), with cortisol dysregulation and low bone mineral density (BMD) also present in 40–60% (14,17). These findings are consistent with global literature that highlights the “thrifty phenotype hypothesis,” where fetal undernutrition leads to adaptive metabolic changes that later predispose to obesity, type 2 diabetes, and cardiovascular disease (Mericq et al., 2016) (4).

Neurodevelopmental delays and cognitive impairment were also prominent among both SGA and preterm cohorts, with attention deficits, executive dysfunction, and lower IQ scores in 40–60% of children (19). This aligns with data from Gunn et al. (2011) and Fernández et al. (2018), where altered brain development paralleled endocrine abnormalities, particularly elevated cortisol and low IGF-1 levels (19). These findings reinforce the interconnectedness of somatic and neurodevelopmental growth trajectories.

Our review confirms that GH therapy significantly improves linear growth, final height, and body composition in these children. As shown in Tables 2 and 6, early-treated SGA and preterm children (initiated at 2–4 years) achieved average height SDS gains of +2.0 to +2.5, with annual growth velocity improving from 4.5 to >10 cm/year (21–23). These gains were sustained across multiple studies, including Juul et al. (2022), Coutant et al. (2023), and Schweizer et al. (2023), and were visually confirmed in Figures 2 and 4.

The response to GH therapy was influenced by age at initiation, baseline IGF-1 levels, and body composition, as seen in Table 5. Early initiation before age 5 was the most consistent predictor of success (21,22), while poor nutritional status or genetic GH receptor polymorphisms (25,27) could blunt the anabolic response. This is echoed by Carrascosa et al. (2008), who reported that GHR genotype did not preclude a response, but outcomes were optimized when nutritional support was adequate (25).

Metabolic safety was a central concern, especially the risk of insulin resistance and type 2 diabetes. Table 3 summarizes these outcomes, showing that while 5–10% of patients developed mild IR during therapy, only rare cases progressed to T2DM, usually in genetically predisposed children (27). These findings are consistent with Nomura et al. (2023) and Savanelli et al. (2024), who emphasized the importance of monitoring but found GH therapy generally safe and reversible in effect (24,27).

In terms of body composition, GH-treated children gained 10–15% lean mass and reduced central fat by 13–14% (Figure 3). This is particularly important given the high prevalence of sarcopenic obesity in untreated SGA and preterm children (5,18). De Schepper et al. (2008) confirmed that GH-induced changes in adiposity contribute to lower long-term cardiometabolic risk.

GH therapy also showed benefits for bone health and pubertal timing. Children receiving GH had increased BMD during adolescence and more normalized pubertal progression compared to untreated peers (17,21). This supports studies by Koizumi et al. (2023) and Carrascosa et al. (2008), which documented improved skeletal outcomes and reduced fracture risk (25,26). Delayed puberty, especially in girls, was partially reversed, helping preserve final height potential (16,22).

Neurocognitive outcomes, though less studied, also showed promising trends. Table 4 and Schweizer et al. (2023) highlighted improved jump performance and motor coordination in GH-treated children, suggesting better neuromuscular integration (23). This correlates with rising IGF-1 levels, which are known to influence neuronal myelination and synaptic plasticity.

A major innovation in therapy delivery has been the development of weekly GH regimens such as somapacitan. As shown in Table 6 and Figure 4, weekly injections matched daily GH in efficacy (~+10 cm/year) and safety (28). Juul et al. (2024) found improved adherence and satisfaction among families, suggesting weekly therapy could be especially beneficial in resource-limited or high-burden settings (28).

Despite this progress, controversies remain regarding the optimal duration and cessation criteria for GH therapy. Some studies report early plateauing of height velocity after 4–5 years, suggesting individualized weaning may be possible (22). Others stress continuing until near-adult height is achieved. Variability in pubertal timing, bone age, and growth velocity complicates these decisions and warrants further longitudinal research.

Our findings underscore the need for lifelong, multidisciplinary follow-up of SGA and preterm children, even those who respond well to GH therapy. Monitoring should include height velocity, IGF-1 levels, body composition (via DEXA), fasting glucose/insulin, lipid profile, pubertal staging, and neurocognitive development. Given the increasing availability of genotype data and weekly GH formulations, future care may become increasingly personalized, enhancing both efficacy and safety (24,28).

5. Conclusion

Children born small for gestational age (SGA) and/or severely premature face a distinct and multifactorial burden of endocrine and growth disturbances, including GH–IGF-1 axis dysfunction, insulin resistance, altered body composition,

delayed puberty, and neurodevelopmental delays. Our review confirms that these complications are both prevalent and persistent, requiring long-term surveillance and targeted interventions.

Growth hormone (GH) therapy emerges as a safe and effective option in selected non–catch-up children, especially when initiated early (2–4 years). Across diverse cohorts and delivery modes (daily vs. weekly GH), therapy has been shown to improve linear growth (+2.0 to +2.5 SDS), lean mass, bone mineral density, and possibly neurocognitive outcomes. Mild insulin resistance remains the primary metabolic concern, but it is generally transient and manageable with monitoring.

Ultimately, GH therapy should be viewed not just as a height-promoting intervention, but as a holistic modifier of growth trajectory, body composition, and long-term health risk. Individualized therapy, including genotype considerations and psychosocial support, is essential for optimizing outcomes.

Recommendations

- Early Identification and Referral

Non–catch-up growth in SGA or severely preterm infants should prompt early endocrine evaluation by age 2, with GH therapy considered if height is <–2.5 SDS and growth velocity is suboptimal.

- Multidisciplinary Monitoring Protocols

Follow-up should include regular assessment of IGF-1 levels, bone age, DEXA scans, fasting insulin/glucose, pubertal progression, and neurodevelopmental screening into adolescence and adulthood.

Therapy Optimization and Personalization

Early initiation of GH therapy should be prioritized. Weekly GH formulations (e.g., somapacitan) offer safe, effective, and family-friendly alternatives. Future research should explore genotype-specific responses and long-term cardiometabolic outcomes.

Strengths

This review provides a comprehensive overview of endocrine and growth complications in SGA and severely preterm children, integrating recent, high-quality studies from 2000–2025. It covers multiple systems beyond height—such as metabolism, puberty, bone health, and neurodevelopment—making it clinically relevant. The inclusion of GH therapy data, including predictors of response and safety outcomes, enhances its therapeutic value. Strong visuals (tables, figures, forest plot) improve clarity, while practical recommendations support direct clinical application.

Weaknesses

The review lacks a formal meta-analysis and pooled statistical data, which limits the precision of its conclusions. Potential publication bias exists due to reliance on published or high-impact studies. Data on cognitive outcomes are limited, with few studies offering long-term neuropsychological follow-up. Study heterogeneity in design, GH dosing, and outcome definitions may reduce comparability. Additionally, the cost-effectiveness of GH therapy is not addressed, which is important for long-term treatment planning.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare no conflict of interest related to the content of this review.

Authors' Contributions

ATS, HA, and HAli conceptualized the review and led the manuscript drafting. FA, NSA, NH, NMA, and SMA contributed to literature screening, data extraction, and interpretation of GH therapy outcomes. AK supported pharmacologic content and safety profile analysis. All authors contributed to table and figure development and critically revised the manuscript for intellectual content. All authors approved the final version for submission and publication.

Funding Statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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