RETROSPECTIVE STUDY OF RECOMBINANT GROWTH HORMONE THERAPY IN PRADER-WILLI SYNDROME: IMPACT ON LINEAR GROWTH AND METABOLIC PROFILES

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ABSTRACT

Prader-Willi syndrome (PWS) is a rare, multisystemic genetic disorder involving a lack of expression of the paternally inherited genes in the 15q11-q13 region. Clinically, it is characterized by hypotonia, failure to thrive in infancy, subsequent hyperphagia, morbid obesity, hypogonadism, and intellectual disability. Growth hormone (GH) deficiency is also common, prompting the use of recombinant human GH (rhGH) therapy as a key intervention. **Aim of the Study** This research investigates the impact of rhGH therapy on growth parameters, body composition, and metabolic profiles in pediatric patients with genetically confirmed PWS. **Materials and Methods** A retrospective observational descriptive study was conducted between 2023 and 2025 at the Regional Center for Medical Genetics Iași, in collaboration with the Endocrinology Clinic at "Sf. Spiridon" Emergency County Hospital Iași. Patients aged 1 month to 19 years were enrolled based on clinical and molecular confirmation (DNA methylation analysis and MLPA). Anthropometric data (height, weight, body mass index), biochemical parameters (lipid profile, IGF-1, thyroid function), and clinical findings were collected. Statistical analyses were performed using Python libraries. **Results** Children receiving rhGH therapy demonstrated a significant increase in height standard deviation scores, alongside improvements in lipid parameters (including total cholesterol and LDL-cholesterol). IGF-1 levels normalized in most patients, reflecting enhanced somatotropic function. However, variations in therapy response underscored the need for individualized follow-up. **Conclusions** These preliminary findings support the efficacy of rhGH in improving growth, metabolic outcomes, and overall clinical status in PWS. Close multidisciplinary monitoring of anthropometric and metabolic indices remains essential to optimize therapeutic benefits and limit potential adverse effects.

Keywords: prader-willi syndrome, growth hormone treatment, metabolic profile, growth parameters

INTRODUCTION

Prader-Willi syndrome (PWS) is a rare, multisystemic genetic disorder caused by the absence of paternally expressed genes in the 15q11-q13 chromosomal region. It affects individuals of all ethnic backgrounds and both sexes equally, with a global prevalence estimated at 1 in 10,000 to 30,000 people(1). PWS is recognized as the most common genetic syndrome linked to morbid obesity and results from several possible genetic mechanisms, primarily deletions, maternal uniparental disomy (UPD), or imprinting defects. Each mechanism prevents the normal expression of paternal genes critical for metabolic regulation and hypothalamic function(2).

Clinically, PWS presents a broad spectrum of manifestations, starting in the neonatal period with marked hypotonia and feeding difficulties. Infants often struggle to nurse or suckle effectively, requiring specialized feeding interventions. Over time, hypotonia may persist, although it usually improves somewhat as children grow(3). A defining feature of the syndrome, typically appearing between two and six years of age, is hyperphagia. This persistent appetite surge and lack of satiety lead to rapid weight gain, with severe obesity developing unless strict dietary control is enforced. Individuals experience reduced

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energy expenditure, further compounding obesity risk (Table I). Furthermore, many patients develop an abnormal body composition characterized by increased fat mass and decreased muscle mass. While insulin levels can be normal or even lower than expected, individuals with PWS generally exhibit higher insulin sensitivity than similarly obese peers, but they remain at risk for type 2 diabetes(4). Lipid metabolism disturbances, such as elevated total cholesterol and LDL, along with low HDL, can heighten cardiovascular risk (5).

Table I. Nutritional phases in Prader-Willi syndrome (Whitmann et all, 2024)

Phases	Description
Phase 0- in utero	Decreased fetal movements Growth restriction compared to unaffected siblings
Phase 1 (birth)	Hypothonic non-obese infant
Phase 1a (birth-15 months)	Dificulty feeding Failure to thrive may be present
Phase 1b (5-15 months)	Weight increases at normal rate for individual growth curve
Phase 2 (2-4,5 years)	Weight gain
Phase 2a	Weight gain without increased caloric intake of interest in food
Phase 2b	Weight gain and increased interest in food
Phase 3 (5-13 years)	Lifelong hyperphagia, food-seeking, a feeling of persistent hunger coupled with a decreased sensation of satiety
Phase 4	In some individuals, there may be some blunting of hyperphagia and a new ability to feel full

Oral and dental manifestations are also common. Patients with PWS frequently present with a broad spectrum of oral conditions, including dental caries, enamel hypoplasia, periodontal disease, oral microsomia, malocclusion, candidiasis, xerostomia, hypotonic tongue, and delayed tooth eruption(6). Hypotonia of the orofacial muscles can further complicate articulation and chewing. These factors underscore the need for careful dental assessments and interventions, as well as consistent oral hygiene practices(7).

Obstructive sleep apnea syndrome is a respiratory disorder frequently associated with PWS and it affects up to 60% of children and adolescents with obesity. It is characterized by recurrent episodes of partial or complete upper airway collapse during sleep, leading to disrupted ventilation, sleep fragmentation, and snoring. Moreover, it is linked to a spectrum of complications, including cardiometabolic

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syndrome, neurocognitive impairments, and behavioral issues (8,9).
Low bone mineral density and an increased risk of scoliosis are common in patients with PWS, influenced by muscle hypotonia and hypogonadism. Regular monitoring of bone mineral density is crucial to prevent long-term complications. Regular physical exercise and supplementation with vitamin D and calcium are recommended to maintain bone health(10).

Diagnostic criteria for PWS rely on both clinical presentation and genetic confirmation. The classic clinical diagnosis incorporates criteria organized into major and minor categories. Major criteria include neonatal hypotonia with a weak suck, childhood obesity triggered by hyperphagia, motor and cognitive delays, hypogonadism manifesting as underdeveloped external genitalia or infertility, and distinct facial features (such as almond-shaped eyes and a thin upper lip). Minor criteria include decreased fetal movement, short stature uncorrected by GH therapy, skin or hair pigmentation anomalies, and compulsive behaviors. A formal diagnosis typically requires four major criteria or a combination of three major plus three minor criteria. Definitive confirmation comes from genetic testing, most commonly DNA methylation analysis, which detects abnormal imprinting regardless of the underlying mechanism (deletion, UPD, or imprinting defect). For more detailed characterization, multiplex ligation-dependent probe amplification (MLPA) can identify deletions and pinpoint imprinting errors. Additional molecular tools include FISH assays, karyotype analysis, and SNP microarrays (3).

Management of PWS is multidisciplinary and focuses on preventing or addressing complications like obesity, endocrine imbalances, and behavioral challenges(11). Nutritional supervision is essential, beginning with specialized feeding support in infancy and transitioning to caloric restriction or structured meal plans in later childhood. Physical activity plays a central role by counteracting obesity and helping maintain muscle tone. Endocrine therapies address deficits such as hypogonadism and hypothyroidism, while behavioral interventions, including therapy and sometimes medication, help manage compulsivity, irritability, and outbursts. Respiratory evaluations are critical for detecting sleep apnea or other respiratory issues, which can become life-threatening if unchecked (2,12)

Genetic counseling is essential for families. Most cases are sporadic, implying a recurrence risk under 1%. However, certain genetic rearrangements or imprinting center defects can significantly increase recurrence risk, justifying further chromosomal or molecular analyses in specific cases. A clear understanding of the underlying genetic mechanism helps guide prenatal testing, clarify prognosis, and ensure informed family planning (11,13).

One of the most transformative therapies for PWS is recombinant human growth hormone (rhGH) administration. Originally introduced to correct short stature, GH treatment confers multiple additional benefits, including improved body composition (less fat mass, more lean mass), enhanced metabolic profile, and, in many instances, better respiratory function (14). The recommended dose typically ranges from 0.35 to 0.5 mg/m²/day for children, adjusted upward to maintain optimal IGF-1 levels. Early initiation—ideally before two years of age—can yield long-term advantages by helping control weight gain, mitigate adiposity, and support normal growth. Moreover, GH can positively influence cognition, motor skills, and overall quality of life. Nonetheless, clinicians must monitor for potential side effects, such as exacerbation of sleep apnea or fluid retention, and coordinate with specialists to tailor therapy to each patient's unique needs(15).

MATHERIAL AND METHODS

The study is a retrospective, observational descriptive analysis that evaluates the impact of recombinant human growth hormone treatment on patients with Prader-Willi syndrome in Romania. The research was carried out at the

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Regional Center for Medical Genetics in Iași, in collaboration with the Endocrinology Department of the "Sf. Spiridon" Clinical County Emergency Hospital in Iași. The original contribution lies in the inclusion of a well-defined cohort of 19 patients, aged 1 month to 19 years, with Prader-Willi syndrome confirmed both clinically and molecularly. This dataset is unique for the Romanian population and was collected to complement existing international literature with locally specific clinical and genetic data.

Patients meeting the following inclusion criteria were enrolled: a confirmed molecular diagnosis of Prader-Willi syndrome via DNA methylation analysis and Multiplex Ligation-dependent Probe Amplification, a body mass index below 39.9 kg/m² and written informed consent obtained from patients or their legal representatives.

Exclusion criteria included patients over 19 years of age, those with severe comorbidities such as severe sleep apnea or morbid obesity, and anyone who refused participation. Clinical parameters such as height, weight, and BMI, as well as biochemical markers including lipid profiles, were systematically recorded, while molecular confirmation was achieved through established genetic tests.

Data collection involved periodic updates of clinical and biochemical parameters in a secure electronic database. Statistical analysis was conducted using Python with libraries including pandas, scikit-learn for statistical computations, and matplotlib plus plotly for graphical visualization. This robust data processing protocol allowed for detailed monitoring of treatment effects and contributed to the study's original insights.

Patient enrollment was performed only after receiving approval from the Ethics Committee of the Grigore T. Popa University of Medicine and Pharmacy Iași, and all procedures adhered to GDPR standards.

This methodological approach not only establishes a comprehensive framework for assessing the therapeutic impact of rhGH in PWS patients but also generates original contributions through the integration of detailed clinical, biochemical, and molecular data from a specific regional cohort.

RESULTS

This study investigated the effects of recombinant human growth hormone (rhGH) therapy on a cohort of patients with Prader-Willi syndrome (PWS), comparing them to a control group that did not receive rhGH. The primary outcomes included anthropometric measurements (height, weight and BMI), metabolic indicators (lipid parameters, thyroid hormone levels), and IGF-1 as a key marker of GH bioactivity.

ANTHROPOMETRIC OUTCOMES

At baseline, the cohort showed a slight predominance of female patients and a mean therapy initiation age of 38.3 months (3.2 years), with an average treatment duration of 79.2 months (6.6 years). Notably, four patients began recombinant human growth hormone (rhGH) treatment before 24 months of age, underscoring the potential benefits of early intervention on growth and metabolic parameters.

The evolution of height in PWS patients treated with rhGH shows significant improvement. For example, patient AS-F improved from −5 SDS before treatment to −2.9 SDS after treatment, narrowing the gap toward normal values. This confirms rhGH's efficacy in stimulating linear growth, especially in those with severe deficits (Fig. 1).

Fig 1. Mean height deviations before and after rhGH in Prader-Willi syndrome

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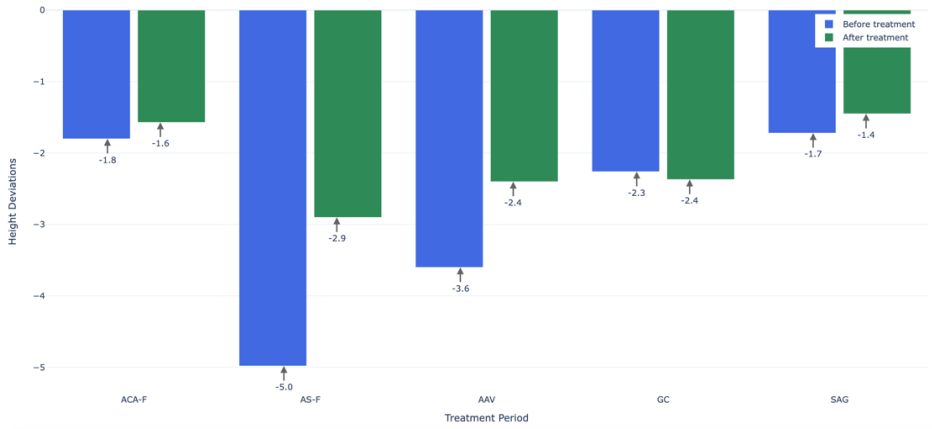
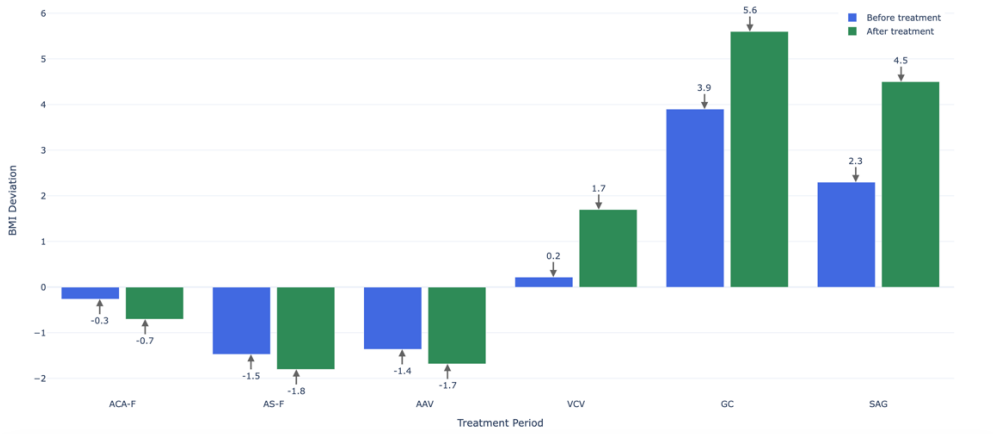


Regarding BMI, rhGH produced different outcomes. Patients with low initial BMI (e.g., ACA-F: −0.3 SDS to −0.7 SDS) maintained lean profiles, while those with high initial BMI (e.g., patient GC: 3.9 SDS to 5.6 SDS) saw little improvement. This indicates that rhGH alone may not sufficiently address elevated BMI without additional nutritional and lifestyle interventions (Fig. 2).

Fig 2. BMI evolution (SD) before and after rhGH in Prader-Willi syndrome



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CLINICAL CHARACTERISTICS

Figure 3. Clinical characteristics of patients with Prader-Willi syndrome

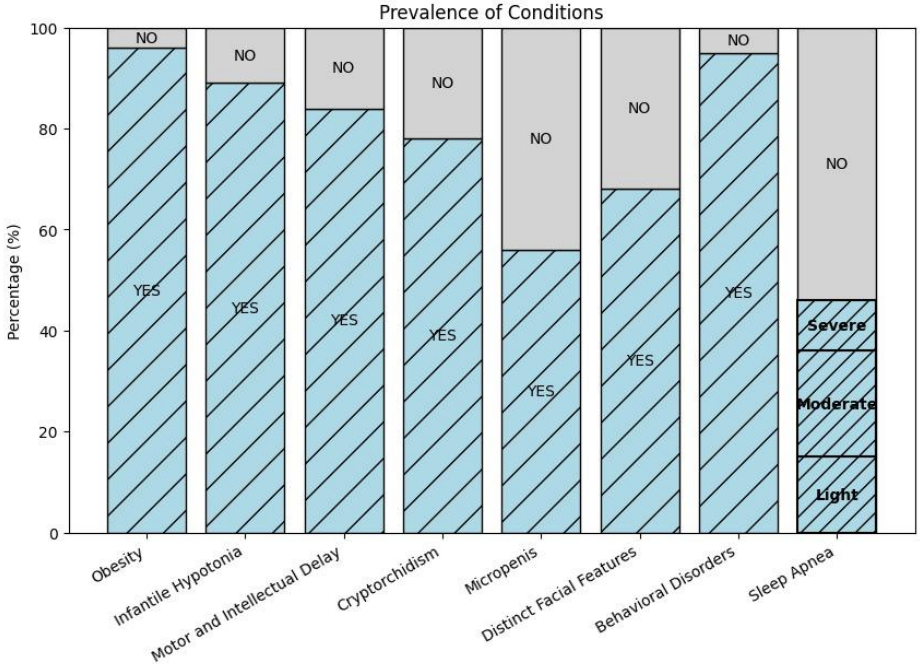

Fig. 3 shows the prevalence of key clinical features in this genetic syndrome. Obesity, present in 94% of patients, underscores the profound impact of hypothalamic dysfunction on metabolism and appetite control. A characteristic behavioral profile—including cognitive rigidity, impulsivity, and emotional dysregulation—occurs in 95% of cases, reflecting the syndrome's neuropsychiatric component (16).

Infantile hypotonia (89%) remains a cardinal sign, frequently causing feeding difficulties in the neonatal period and subsequent motor delays. Intellectual disability affects 84% of patients and significantly impacts cognitive development and autonomy (3). Among endocrine manifestations, cryptorchidism is reported in 78% of males, and micropenis in 56%, emphasizing the importance of early endocrine intervention (17).

Respiratory complications, notably sleep apnea (mild in 15%, moderate in 21%, and severe in 10%), require careful monitoring—particularly when administering growth hormone therapy. Lastly, eating disorders (53%), such as hyperphagia and reduced satiety, drive early obesity and complicate dietary management in Prader-Willi syndrome (18).

METABOLIC PROFILE AND LIPID PARAMETERS

In terms of total cholesterol dynamics in the rhGH group, it was discovered that levels declined on average from 179.89 mg/dL before treatment to 174.33 mg/dL afterward. Although this decrease is modest, it underscores rhGH's potential to stabilize lipid metabolism.

Fig. 4 further details total cholesterol variations for individual treated patients, demonstrating that most participants maintained or modestly reduced their cholesterol values. Consistent with literature, these findings highlight the therapy's favorable influence on cardiovascular risk parameters.

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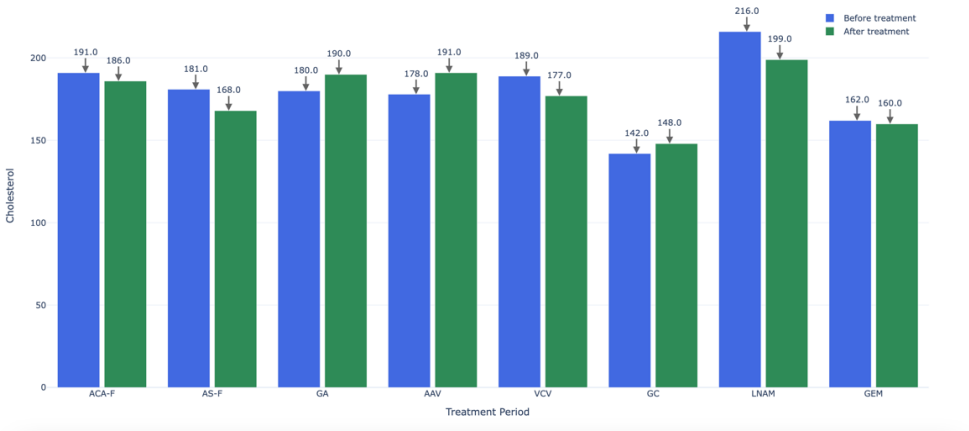
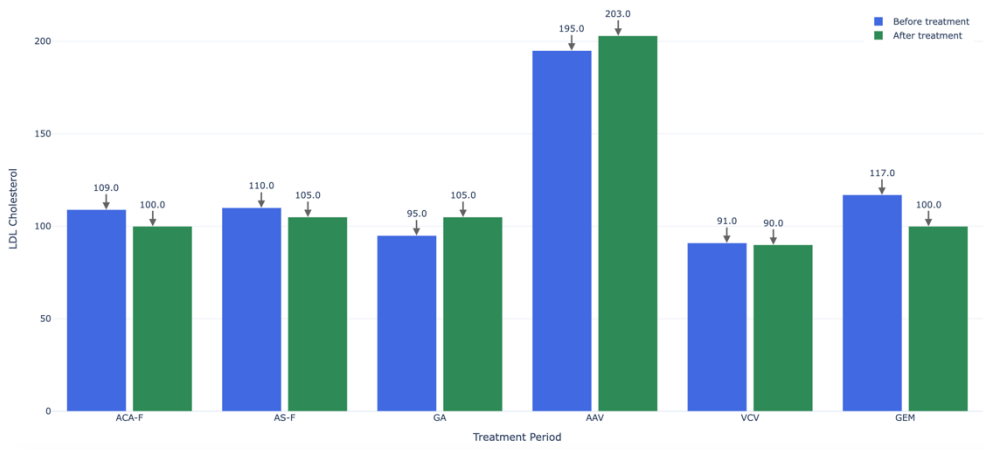
Fig 4. Variation in mean total cholesterol levels before and after GH treatment



A key focus was LDL-cholesterol levels, depicted in Fig. 5. Patients who began therapy with elevated LDL-cholesterol generally showed improvements, as seen in ACA-F, AS-F, VCV, and GEM. However, patient AAV exhibited a post-treatment increase, underscoring the need for individualized monitoring and possible adjunct interventions. Since LDL-cholesterol contributes significantly to cardiovascular morbidity, even modest changes can carry clinical relevance.

Fig 5. Variation in LDL-cholesterol levels before and after GH treatment



Triglyceride levels revealed notably positive outcomes. Individuals presenting with hypertriglyceridemia at baseline—particularly GC and GA—experienced normalization after rhGH initiation. Given the link between elevated triglycerides and heightened cardiovascular risk, this result emphasizes the broader metabolic benefits of GH therapy.

THYROID FUNCTION AND IGF-1 LEVELS

Although not the primary focus of the present analysis, thyroid hormone status (measured via free thyroxine, fT4) also improved in several patients. Initially low levels returned to normal during rhGH therapy, suggesting an indirect role of GH in modulating thyroid metabolism (Fig 6). Meanwhile, IGF-1 emerged as a reliable indicator of treatment adherence and anabolic response. Most patients achieved normal or even elevated IGF-1 levels, confirming rhGH's efficacy. However, the literature indicates that immunoreactive IGF-1 does not always represent the bioactive fraction, pointing to the importance of IGF-1/IGFBP-3 ratios for a deeper understanding of GH activity(15).

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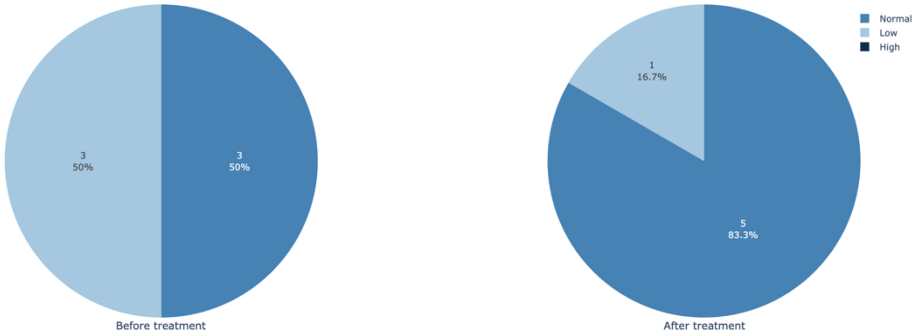
Fig 6. Distribution of fT4 levels before and after GH treatment



DISCUSSIONS

The study findings align with existing literature. Stipančić et al. demonstrated that rhGH treatment significantly improves growth and BMI in children with PWS. In a study of four patients aged between 2.8 and 10.5 years, monitored for 3–8 years, height SDS improved from values ranging between –0.62 and –2.5 to between 0.45 and 1.12; for instance, one patient treated for 8 years reached a final height of 172.7 cm (–0.14 SDS), closely approaching normal values (19).

Similarly, Passone et al. conducted a meta-analysis that highlighted significant benefits of rhGH on growth, body composition, and BMI. Treated patients experienced an average height increase of 1.67 SDS compared to controls and an improved growth rate of 5.44 cm per year, while BMI decreased by –0.67 SDS. These effects were most pronounced in patients who began treatment at an early age (under 3.5 years), underscoring the critical importance of early intervention (20).

One important limitation of this study is its relatively small sample size, which diminishes statistical power and restricts the external validity of our findings. The retrospective, observational design also introduces potential selection biases and confounding variables, such as differences in nutrition and lifestyle, that could influence results. Furthermore, the patient cohort exhibited notable heterogeneity—varying in age at treatment initiation, baseline anthropometric status, and metabolic profiles—which can complicate the interpretation of treatment outcomes. Larger-scale, prospective studies across multiple centers are warranted to validate and extend these preliminary observations.

Overall, the data indicate that rhGH therapy contributes to tangible benefits in PWS, including improved linear growth, reduced abdominal adiposity, and more favorable lipid profiles. Nevertheless, individual variability underscores the necessity for a comprehensive approach that integrates nutritional counseling, regular physical activity, and ongoing endocrine evaluation. Early initiation of GH therapy—preferably before two years of age—can optimize outcomes by supporting not only growth parameters but also metabolic stability and developmental progress.

CONCLUSIONS

Prader-Willi syndrome (PWS) is a rare genetic disorder characterized by a wide spectrum of manifestations affecting both physical and neurocognitive development. This study highlights significant benefits in improving linear growth and optimizing body composition following treatment with rhGH. The increase in height measurements and the reduction in height-weight deviations reflect the therapy's effectiveness in stimulating growth processes and reducing anthropometric imbalances. Furthermore, the evaluation of the metabolic profile showed a trend toward stabilization of cholesterol and triglyceride levels, suggesting a beneficial effect of rhGH on lipid metabolism. In conclusion, the preliminary data support the

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use of rhGH therapy as an essential intervention in the management of Prader-Willi syndrome, while emphasizing the need for rigorous monitoring of anthropometric and metabolic parameters to optimize treatment and minimize associated risks.

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