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Parameters Used for Evaluation of the Response to Treatment with Recombinant Human Growth Hormone in Paediatric and Adult Populations in Poland: Review

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Abstract

Introduction and purpose

Recombinant human growth hormone (rhGH) therapy has been the standard treatment for paediatric short stature for many years, and a therapeutic option for the replacement therapy of growth hormone deficiency in the post-growth patient population. Each country providing rhGH treatment has its own programms based on national recommendations and international guidelines. The aim of this review was to discuss selected parameters used for assessment of the response to rhGH treatment in the paediatric and the post-growth adult populations, using the example of Poland.

Description of state of knowledge

The rhGH therapy requires thorough monitoring to minimize potential adverse effects and to optimize treatment outcomes. Due to the differences in the final therapeutic effects of rhGH between pediatric and adult cohorts, different parameters are used to assess treatment efficacy. In children and adolescents, anthropometric measurements reflecting growth are primarily utilized. Considering the systemic effects of the rhGH, metabolic parameters are evaluated in both populations. In adults, additional assessments include quality of life, measured using standardized questionnaires, and bone mineral density. Computer predictive models can also be used to monitor the treatment.

Conclusion

Growth hormone therapy has been associated with a range of well-documented benefits both paediatric and adult populations. However, its administration necessitates comprehensive monitoring based on standardized parameters specific to each patient cohort.

Keywords: growth hormone; growth hormone deficiency; recombinant human growth hormone therapy

Introduction

Research into growth hormone (GH) and its clinical use in the treatment of growth disorders spans more than 100 years. Initial treatment with the human-derived GH started between 1958 and 1985. Since 1985, with the advent of recombinant technology and genetic engineering, recombinant human growth hormone has become the standard therapy for short stature in the paediatric population[1]. Based on study results and its safety profile, adults with severe growth hormone deficiency (GHD) have also been eligible for therapy for about 30 years, with treatment being administered primarily for metabolic indications[2]. According to the latest research, rhGH treatment is considered safe; however, close monitoring is always required throughout therapy, both to optimise its beneficial effects and to detect potential side effects[3,4].

In Poland, qualification for the Growth Hormone Treatment Drug Programme is handled by (1) the Coordination Team for Growth Hormone Treatment, dedicated to the paediatric population, and (2) the Coordination Team for the Use of Growth Hormone in Adult Patients and Adolescents after Completion of Growth-promoting Therapy. Since 2000, attempts have been made to introduce reimbursement for rhGH in adults and adolescents who have completed growth-promoting therapy. The programme was finally launched in Poland in 2022. Detailed eligibility and treatment guidelines are included in Drug Programmes dedicated to specific patient groups and are available [5–10]. Table 1 shows the groups covered by reimbursement for rhGH therapy in Poland.

Paediatric population	Post-growth adolescents and adults
Growth hormone deficiency / Multihormonal hypopituitarism	Adults not treated with rhGH in childhood with a diagnosis of hypopituitarism
Turner syndrome Prader-Willi syndrome Chronic kidney disease	Adolescents and adults previously treated with rhGH
Children born small for gestational age and/or with foetal growth restriction	Patients with multihormonal hypopituitary (except prolactin) and confirmation of an organic or genetic cause of the underlying condition

Table 1. Patient groups treated with growth hormone in Poland. (*rhGH – recombinant human growth hormone*)

The positive effects of the GH on metabolism have been repeatedly demonstrated[11]. Among these, its role in promoting growth by stimulating the proliferation of bone growth cartilage, improving the lipid profile, lowering blood pressure (thereby reducing cardiovascular risk), enhancing bone mineralisation and density, increasing muscle mass, and improving muscular strength are particularly significant[12].

When treating children, the primary benefit is improved growth, except in the case of the Prader-Willi Syndrome group, for whom rhGH treatment is introduced to improve metabolic profile and muscle tone[13].

In addition to promoting growth, patients with severe growth hormone deficiency — most commonly due to somatotropin hypopituitarism or multihormonal pituitary hypopituitarism —seem to derive the greatest metabolic benefit. These patients lack endogenous GH or have

insufficient pituitary synthesis, making it particularly important to continue rhGH treatment beyond the growth phase[14].

A distinct group of patients consists of children born small for gestational age (SGA). It has been demonstrated that neonates with intrauterine growth restriction are at a higher risk of both early and late complications[15]. In the context of growth hormone therapy, late complications are of greater concern, encompassing a range of disorders, including growth impairment, insulin resistance, adrenarche praecox, progressive puberty, subclinical hypothyroidism, neurodevelopmental disorders, and progressive deterioration of renal function[16].

In this group, the metabolic effects of GH treatment are transient, observed only during the course of therapy, with the sole lasting benefit being an improvement in final adult height[17].

In the adult and adolescent population after completion of growth, the most serious long-term consequences of GHD include an increased mortality rate due to cardiovascular complications, a higher incidence of osteoporotic fractures, and a decline in quality of life—secondary to persistent muscle weakness or pain associated with skeletal damage and/or sarcopenia. In this patient group, the favourable metabolic profile of rhGH therapy is of the utmost importance[18].

Currently, in Poland, treatment involves daily subcutaneous injections of rhGH. Since 2021, a new formulation of rhGH — somapacitan — administered once weekly has been introduced to the global market. In 2023, the use of somapacitan was approved in the United States and Germany for both children over 2.5 years of age and adults. Two-year analyses and clinical studies confirm the efficacy of somapacitan at a level comparable to that of somatotropin, with a similar safety profile and risk of adverse effects, while significantly reducing the frequency of injections[19]. In the coming months, approval for this preparation is expected in additional European countries.

To monitor the effects of therapy, the use of standardised and harmonised parameters is recommended[20]. In the paediatric population, growth-related parameters are most commonly utilised, whereas in adults, quality of life and metabolic outcomes are assessed. Table 2 presents selected parameters used to evaluate the response to rhGH therapy.

The aim of this review was to discuss selected parameters used to evaluate the response to rhGH treatment in both the paediatric population and in adults and adolescents after the completion of growth.

Paediatric population	Post-growth adolescents and adults
Anthropometric measurements	
Ht, weight	Ht, weight, BMI
head circumference, chest circumference	waist circumference, WHR
pubertal stage according to Tanner scale	body composition assessment using BIA
Metabolic measurements	
serum ionogram analysis (at minimum Na, Ca and K)	serum ionogram analysis (at minimum Na, Ca and K)
fasting blood glucose and HbA1c	HbA1c
IGF-1	IGF-1
TSH, FT4, FT3	TSH, FT4

TG, TC, LDL-C, HDL-C	TG, TC, LDL-C, HDL-C
Other	
Psychological consultation with an assessment of psychomotor and/or intellectual development	QoL
BPM	BPM
BA	bone mineral density (DXA scan)
other examinations and consultations as required	other examinations and consultations as required

Table 2. Selected parameters used to evaluate the response to rhGH therapy in Children, Adolescents and Adults *(Ht - Height, BMI - Body Mass Index, WHR - Waist-Hip Ratio, BIA - bioelectrical impedance analysis, TG - triglycerides, TC - total cholesterol, HDL-C - High-Density Lipoprotein Cholesterol, LDL-C - Low-Density Lipoprotein Cholesterol, Ca - Calcium, Na - Sodium, K - Potassium, HbA1c - glycated hemoglobin, IGF-1 - Insulin-like Growth Factor 1, TSH- Thyroid-Stimulating Hormone, FT3- Free Triiodothyronine, FT4 - Free Thyroxine, BPM - Blood Pressure Measurement, QoL - Quality of Life, BA - Bone Age, DXA - Dual-energy X-ray Absorptiometry)*

Parameters Used to Evaluate the Response to Treatment in the Paediatric Population

Height and Growth Velocity

To evaluate the efficacy and outcomes of growth hormone therapy, objective anthropometric parameters are assessed during follow-up visits. The most commonly used and literature-cited as the most reliable measures are height (Ht) measurements and the assessment of growth velocity (HV)[21].

Measurements should be performed using the same a stadiometer with an accuracy of one millimetre at each follow-up visit, certified by the relevant authority (in Poland, the Central Office of Measures). Three measurements are taken, and the arithmetic mean is calculated, converted into standard deviation scores (SDS), and analysed. The obtained values are plotted on percentile charts for the corresponding sex, enabling the observation of growth trends and demonstrating improvements in height.

A good response to treatment is defined as a height difference expressed as SDS of at least 0.3 (ΔHt SDS $\geq$ 0.3) and/or an increase in growth velocity of at least 3 cm per year

(ΔHV $\geq$ 3 cm/year)[22].

Studies by Bang et al. and Straetemans et al. have shown that HV is the best parameter for assessing treatment response, although it is also associated with the highest potential measurement error. Regardless of the parameter chosen, the response in the first year of treatment is considered one of the most important prognostic factors[20,22].

In order to accurately assess HV in the first year of treatment, it is essential to ascertain the patient's growth velocity prior to the initiation of therapy. In Poland, every patient eligible for the rhGH therapy undergoes a series of precise anthropometric measurements and examinations, which form the basis for final qualification. These data are recorded both in the patient’s medical documentation and in the Therapeutic Programmes Monitoring System, significantly facilitating the monitoring and management of therapy.

In some cases, patients are qualified for rhGH treatment during adolescence or at an advanced stage of puberty. To expedite the diagnostic process and optimise treatment outcomes in such

instances, the physician responsible for qualification relies on the patient's medical history, often obtained during routine preventive visits within primary healthcare. The regular measurement of anthropometric parameters in the offices of other medical specialists, and the consistent documentation of these values in the patient's medical records, appear to be beneficial for ensuring accurate assessment and effective treatment planning.

Concentration of Insulin-Like Growth Factor Type 1 (IGF-1)

The assessment of IGF-1 concentration is listed as one of the mandatory and most important tests performed during routine follow-up visits for patients treated with rhGH. IGF-1 is a metabolically active molecule at target sites (e.g. growth plates in bones, muscles) and is synthesised in the liver in response to stimulation by GH[23]. Consequently, it serves as a direct reflection of the bioavailability of GH within the body[24]. Numerous studies have demonstrated a positive correlation between increased IGF-1 concentrations and favourable treatment responses[25].

However, concentrations of IGF-1 that significantly exceed the established reference range have been demonstrated to be associated with an elevated risk of atherosclerosis and the development of malignant cancers. The modification of rhGH dosage is dependent on IGF-1 values[26]. Persistently elevated IGF-1 levels, exceeding the age- and sex-specific reference ranges, necessitate a temporary suspension or discontinuation of rhGH therapy.

To ensure accuracy, it is recommended that IGF-1 concentration be measured in serum collected in the morning, with the sample delivered to the laboratory within 60 minutes of collection. IGF-1 concentration is subject to fluctuations over time and is influenced by numerous factors, including gender, age, pubertal stage, liver function, nutritional status, and medications taken by the patient[25]. The immunoenzymatic method is the most common technique for measuring IGF-1 levels. The values thus obtained are then compared with the laboratory norms provided by the manufacturer of the tests used in the laboratory collaborating with the centre managing GH therapy.

The variability of this parameter was discussed by Glińska et al., who noted that depending on the laboratory norms used for monitoring, a significantly different proportion of patients with elevated IGF-1 levels and thus requiring a reduction in GH dose were distinguished[27]. The

standards employed by laboratories are derived from large groups of healthy individuals. However, no standards or centile grids have been developed to date for rhGH-treated patients. The existing literature suggests that transiently sustained IGF-1 elevation is safe and has no long-term consequences, whereas a reduction of the GH dose secondary to elevated IGF-1 concentrations can significantly affect the final effects of GH treatment[28].

Bone Age

Another parameter that is specific to the paediatric population is the assessment of bone age (BA). This examination involves the radiographic imaging of the wrist of the non-dominant hand, followed by a thorough evaluation of the ossification nuclei[29]. The images obtained are then compared with data from atlases to ensure accuracy. In Poland, the evaluation according to the Greulich-Pyle method is mandatory[30]. A discrepancy of up to 12 months between bone age and calendar age is considered within the normal range. Prior to the introduction of rhGH, a more delayed BA relative to CA was associated with greater growth potential and a more favourable response to treatment. This parameter is mentioned as mandatory during the course of therapy and is also one of the indications for termination of treatment (complete ossification of the nuclei is equivalent to termination of the growth process). However, the assessment of BA is subject to error, as it is based on the experience of the radiologist and is difficult to standardise. Furthermore, radiological atlases were created in the 1930s and included radiographs of Caucasian patients from a good socio-economic background. In an attempt to address this limitation, a comparative analysis was conducted between the radiological assessment of bone age based on radiographs and ultrasound of the metacarpal bones. The results of this study were comparable to those obtained during standard BA assessment[31].

Prediction Models

Some authors propose the implementation of computer-based growth prediction models, emphasizing their potential to enhance therapy personalization for individual patients, achieve better therapeutic outcomes, and optimize treatment costs. Over the years, numerous predictive models have been developed, with the most widely described being the KIGS System of Growth Prediction, the Cologne Model, and the Gothenburg Prediction Models[32–34]. These models are primarily designed for patients with severe GH deficiency. Additionally,

efforts have been made to introduce a new parameter—index of responsiveness (IoR), which compares the observed growth velocity during the first year of treatment to the predicted growth velocity estimated using predictive models[20]. More recently, models predicting final height after the first year of treatment have also been proposed.

Currently, no predictive model has been specifically developed for the Polish population. Moreover, as the exact reliability of the proposed predictive models has not been fully established, precise anthropometric measurements remain the most reliable method for assessing treatment outcomes to date.

Parameters Used to Evaluate the Response to Treatment in Adults and Adolescents After Growth Completion

Due to the completion of the growth process and the distinct therapeutic goals of rhGH substitution, the parameters used to evaluate treatment in the adult population differ (Table 2). The assessment of treatment response should primarily include biochemical and anthropometric measurements, body composition analysis, bone mineral density assessment, and a patient interview focused on quality of life[18,35].

Biochemical Parameters

One of the key therapeutic effects of rhGH treatment in adults and adolescents after growth completion is the correction of metabolic disturbances associated with GHD. It has been demonstrated that GHD contributes to the development of atherogenic dyslipidaemia, while substitution therapy helps to correct these abnormalities[36]. The metabolic effects of treatment are monitored by measuring the lipid profile (including triglycerides, total cholesterol, HDL-cholesterol, and LDL-cholesterol), glycemia, and glycated hemoglobin (HbA1c) at designated time points. Furthermore, numerous studies have indicated a beneficial effect of GH in reducing cardiovascular risk by inhibiting pro-inflammatory cytokines, coagulation-promoting factors, and oxidative stress[35,37].

The assessment of carbohydrate metabolism parameters is of significance due to the prevalence of insulin resistance and the increased risk of developing diabetes mellitus in patients with GHD. GH, acting directly on carbohydrate metabolism, has a hyperglycaemic effect, while acting indirectly via IGF-1, it has an insulin-like effect. The initial phase of

rhGH therapy may have a transient adverse effect on carbohydrate metabolism, leading to reduced tissue glucose utilisation and elevated blood glucose and insulin levels. However, in long-term therapy, apart from slightly elevated fasting blood glucose, no significant negative metabolic effects were observed[38]. Furthermore, the beneficial effects of long-term rhGH therapy on body composition and the reduction of visceral adipose tissue promote improved carbohydrate metabolism and reduced insulin resistance[14]. Given the complex mechanism of action of GH and the time-dependent metabolic effects, regular laboratory monitoring of carbohydrate metabolism parameters is necessary, including fasting glucose and HbA1C[39].

It is important to acknowledge that despite the beneficial effects of GH replacement therapy in reducing cardiovascular risk, hormone therapy alone does not resolve all cardiometabolic abnormalities linked to the condition[12]. Therefore, an individualised approach to each patient, encouraging the implementation of a healthy lifestyle based on general principles and meticulous monitoring of metabolic parameters are essential.

An additional significant biochemical parameter, analogous to the pediatric population, is the serum IGF-1 concentration, recognized as a key indicator of both the efficacy and safety of therapy. During the initial phase of treatment, IGF-1 measurements should be performed every 1–2 months and interpreted in relation to age- and sex-specific reference ranges. The rhGH dose is adjusted based on IGF-1 levels, the presence of adverse effects, and therapy tolerance. In the later stages of treatment, measurements are recommended on a quarterly basis. Similar to the pediatric population, there are no standardized IGF-1 reference ranges specifically established for adults undergoing GH therapy, highlighting the need for further research in this area[18].

Anthropometric Measurements and Body Composition Analysis

Obesity and abnormal fat distribution are common chronic conditions observed in patients with GHD. The literature highlights the important role of GH and IGF-1 in the development and function of adipose tissue, particularly visceral fat, which is associated with metabolic syndrome[40]. Therefore, a key component in evaluating the effects of rhGH therapy includes anthropometric measurements, such as height, body weight, and waist circumference, as well as the calculation of body mass index (BMI) and waist-hip ratio (WHR). Additionally, according to clinical guidelines, body composition assessment using bioelectrical impedance

analysis (BIA) or dual-energy X-ray absorptiometry (DXA) is recommended to monitor fat distribution and changes in body composition.

Studies conducted at the end of the twentieth century showed that adults with GHD have an average of 7% higher body fat compared to expected values[11,14]. The GH therapy leads to an increase in lean body mass and a reduction in body fat. In addition, GH promotes anabolic processes by stimulating protein synthesis in skeletal muscle and the heart. In adults with growth hormone deficiency, replacement therapy contributes to increased muscle mass and strength.

Bone Mineral Density

GHD is associated with a decrease in bone mineral density (BMD), which can result in the development of osteoporosis and an increased risk of fractures. A meta-analysis by Barake *et al.* demonstrated a favourable impact of GH therapy on BMD, with treatment response varying based on patient age, sex, and therapy duration[41].

Polish guidelines, drawn up by a group of experts, suggest regular monitoring of BMD by densitometry (DXA), performed every 18-24 months. This recommendation is supported by the literature, which has demonstrated that therapy shorter than 12 months may not result in the expected improvement and, in some cases, may even result in lower BMD values in DXA measurement[42]. Conversely, long-term therapy lasting at least 18–24 months has been shown to increase BMD by up to 4%[43].

Recent studies have indicated that patients with GHD who have experienced onset in childhood have lower BMD compared to those who develop the disease in adulthood. This finding further underscores the importance of rhGH replacement therapy in this patient population[44].

Quality of Life

Patients with GHD frequently report symptoms such as muscle weakness and bone pain, which contribute to a reduced quality of life. Therefore, assessing the quality of life using standardized questionnaires is a mandatory component of GH therapy monitoring[45].

In 2008, Karbownik-Lewińska *et al,* introduced the Polish version of 'The Quality of Life Assessment of Growth Hormone Deficiency in Adults (*QoL-AGHDA*)', based on the

European versions[46]. This tool includes questions covering various aspects of life, such as well-being, energy levels and fatigue, physical and cognitive functioning, and social relationships. Studies have demonstrated significant enhancements in quality of life in most of these domains already in the first year of rhGH therapy, as well as long-term persistence of positive treatment effects[47].

Conclusions

Growth hormone therapy offers numerous benefits both in the pediatric population and in individuals who have completed their growth. The most significant metabolic benefits appear to be observed in patients with severe GHD. In Poland, several patient groups qualify for reimbursed GH treatment under specific indications.

Each patient requires thorough monitoring, utilizing standardized parameters that differ between children and adults. These proposed parameters are supported by various scientific studies and aim to facilitate the selection of the most effective rhGH dose while minimizing potential adverse effects. Due to the limited number of studies describing the effects and safety of GH therapy in the Polish population, further research is necessary.

Disclosure

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References:

1. Ranke MB, Wit JM. Growth hormone — past, present and future. *Nat Rev Endocrinol*. 2018;14(5):285-300. doi:10.1038/nrendo.2018.22

2. Ho KKY. Consensus guidelines for the diagnosis and treatment of adults with GH deficiency II: a statement of the GH Research Society in association with the European Society for Pediatric Endocrinology, Lawson Wilkins Society, European Society of Endocrinology, . *Eur J Endocrinol*. 2007;157(6):695-700. doi:10.1530/EJE-07-0631

3. Johannsson G, Touraine P, Feldt-Rasmussen U, et al. Long-term Safety of Growth Hormone in Adults With Growth Hormone Deficiency: Overview of 15 809 GH-Treated Patients. *J Clin Endocrinol Metab*. 2022;107(7):1906-1919. doi:10.1210/clinem/dgac199

4. Bamba V, Kanakatti Shankar R. Approach to the Patient: Safety of Growth Hormone Replacement in Children and Adolescents. *J Clin Endocrinol Metab*. 2022;107(3):847-861. doi:10.1210/clinem/dgab746

5. Treatment of Severe Growth Hormone Deficiency in Adult and Adolescent Patients After Completion of Growth-promoting Therapy (ICD-10 E23.0). Notice of the Minister of Health of 19 March 2025 on the list of reimbursed medicines, foodstuffs. Available from: https://www.google.com/url?sa=t&source=web&rct=j&opi=89978449&url=https://www.gov.pl/attachment/622d9b89-9988-494e-9f1d-

3c7497388c13&ved=2ahUKEwjYl9aynaWMAxXyEhAIHVJoO9UQFnoECBQQAQ&usg=AOvVaw0_8qOa-EnVgVHz11htZj1d . (Accessed on 30.03.2025)

6. Treatment of Short-Statured Children with Chronic Kidney Failure (ICD-10 N18). Notice of the Minister of Health of 19 March 2025 on the List of Reimbursed Medicines, Foodstuffs for Special Medical Purposes, and Medical Devices. Available from: https://www.google.com/url?sa=t&source=web&rct=j&opi=89978449&url=https://www.archiwum.mz.gov.pl/wp-content/uploads/2014/11/B.38._nowy-od-07.2014.docx&ved=2ahUKEwjxgPjknKWMAxWgAxAIHQIiCdMQFnoECBcQAQ&usg=AOvVaw0ZFyVnqQ_JPQ6cwfqiRoop. (Accessed on 30.03.2025)

7. Treatment of Short-Statured Children with Turner Syndrome (ICD-10 Q96). Notice of the Minister of Health of 19 March 2025 on the List of Reimbursed Medicines, Foodstuffs for Special Medical Purposes, and Medical Devices. Available from: https://www.google.com/url?sa=t&source=web&rct=j&opi=89978449&url=https://www.gov.pl/attachment/24fb030d-07ac-44a5-afbb-866296323384&ved=2ahUKEwiC8cDLnKWMAxWsKhAIHWmWHdYQFnoECBcQAQ&usg=AOvVaw3j-jJgftOb6LSuyAOwqe0L. (Accessed on 30.03.2025)

8. Treatment of Short-Statured Children with Somatotropic Pituitary Insufficiency (ICD-10 E23). Notice of the Minister of Health of 19 March 2025 on the List of Reimbursed Medicines, Foodstuffs for Special Medical Purposes, and Medical Devices. Available from: https://www.google.com/url?sa=t&source=web&rct=j&opi=89978449&url=https://www.gov.pl/attachment/c2022097-fbd3-43fc-8629-f968b509df5f&ved=2ahUKEwi_ityTnKWMAxWkBxAIHd1KNtgQFnoECBcQAQ&usg=AOvVaw3eqIDwKJ_0tb93GVltt7OZ. (Accessed on 30.03.2025)

9. Growth Hormone Treatment of Short-Statured Children Born Small for Gestational Age (SGA) or with Intrauterine Growth Restriction (IUGR) (ICD-10 R62.9). Notice of the Minister of Health of 19 March 2025 on the List of Reimbursed Medicines, Foodstuffs for Special Medical Purposes, and Medical Devices. Available from: https://www.google.com/url?sa=t&source=web&rct=j&opi=89978449&url=https://www.gov.pl/attachment/e48d74fb-7298-472d-adc9-ffc096d91b6d&ved=2ahUKEwj8gtPAnKWMAxXNIxAIHSimF-

QQFnoECBgQAQ&usg=AOvVaw13yTFEqTqrdQq-za5Jm5vN. (Accessed on 30.03.2025)

10. Treatment of Prader-Willi Syndrome (ICD-10 Q87.1). Notice of the Minister of Health of 19 March 2025 on the List of Reimbursed Medicines, Foodstuffs for Special Medical Purposes, and Medical Devices as of 1 April 2025. Available from: https://www.google.com/url?sa=t&source=web&rct=j&opi=89978449&url=https://www.gov.pl/attachment/ef5919d8-51ad-49a7-9482-2a30b31d2e0f&ved=2ahUKEwjaoer7mqWMAxVKERAIHbV6LaAQFnoECBkQAQ&usg=AOvVaw00Xq3hZaKUNyBvZ1kmBvdj. (Accessed on 30.03.2025)

11. Salomon F, Cuneo RC, Hesp R, Sönksen PH. The effects of treatment with recombinant human growth hormone on body composition and metabolism in adults with growth hormone deficiency. *N Engl J Med*. 1989;321(26):1797-1803. doi:10.1056/NEJM198912283212605

12. Ratku B, Sebestyén V, Erdei A, Nagy E V, Szabó Z, Somodi S. Effects of adult growth hormone deficiency and replacement therapy on the cardiometabolic risk profile. *Pituitary*. 2022;25(2):211-228. doi:10.1007/s11102-022-01207-1

13. Grootjen LN, Trueba-Timmermans DJ, Damen L, Mahabier EF, Kerkhof GF, Hokken-Koelega ACS. Long-Term Growth Hormone Treatment of Children with PWS: The Earlier the Start, the Better the Outcomes? *J Clin Med*. 2022;11(9). doi:10.3390/jcm11092496

14. Carroll P V, Christ ER, Bengtsson BA, et al. Growth hormone deficiency in adulthood and the effects of growth hormone replacement: a review. Growth Hormone Research Society Scientific Committee. *J Clin Endocrinol Metab*. 1998;83(2):382-395. doi:10.1210/jcem.83.2.4594

15. Petriczko, Elżbieta; Korpysz, Alicja; Walczak, Mieczysław; Szalecki M. (SGA), Następstwa endokrynologiczne u dzieci urodzonych z za niską masą w stosunku do wieku ciążowego. *Klin Pediatryczna*. 2023;31(1):21-26. https://klinika.com.pl/produkt/kp1-2023-neonatologia/.

16. Lebl J, Lebenthal Y, Kolouskova S, et al. Metabolic impact of growth hormone treatment in short children born small for gestational age. *Horm Res Paediatr*. 2011;76(4):254-261. doi:10.1159/000329729

17. Hokken-Koelega A, van Pareren Y, Arends N, Boonstra V. Efficacy and Safety of Long-Term Continuous Growth Hormone Treatment of Children Born Small for Gestational Age. *Horm Res Paediatr*. 2004;62(suppl 3(Suppl. 3):149-154. doi:10.1159/000080518

18. Lewiński A, Smyczyńska J, Stawerska R, et al. Ogólnopolski Program Leczenia Ciężkiego Niedoboru Hormonu Wzrostu u Osób Dorosłych oraz u Młodzieży po Zakończeniu Terapii Promującej Wzrastanie. *Endokrynol Pol*. 2018;69(5):468-524. doi:10.5603/ep.a2018.0054

19. Miller BS, Blair JC, Rasmussen MH, et al. Weekly Somapacitan is Effective and Well Tolerated in Children With GH Deficiency: The Randomized Phase 3 REAL4 Trial. *J Clin Endocrinol Metab*. 2022;107(12):3378-3388. doi:10.1210/clinem/dgac513

20. Straetemans S, De Schepper J, Thomas M, Tenoutasse S, Beauloye V, Rooman R. Criteria for First-Year Growth Response to Growth Hormone Treatment in Prepubertal Children With Growth Hormone Deficiency: Do They Predict Poor Adult Height Outcome? *Front Endocrinol (Lausanne)*. 2019;10(November). doi:10.3389/fendo.2019.00792

21. Bang P, Bjerknes R, Dahlgren J, et al. A comparison of different definitions of growth response in short prepubertal children treated with growth hormone. *Horm Res Paediatr*. 2011;75(5):335-345. doi:10.1159/000322878

22. Straetemans S, Thomas M, Craen M, Rooman R, De Schepper J. Poor growth response during the first year of growth hormone treatment in short prepubertal children with growth hormone deficiency and born small for gestational age: a comparison of different criteria. *Int J Pediatr Endocrinol*. 2018;2018(1):1-10. doi:10.1186/s13633-018-0064-3

23. Laron Z. Insulin-like growth factor 1 (IGF-1): A growth hormone. *J Clin Pathol - Mol Pathol*. 2001;54(5):311-316. doi:10.1136/mp.54.5.311

24. Wang Y, Bikle DD, Chang W. Autocrine and Paracrine Actions of IGF-I Signaling in Skeletal Development. *Bone Res*. 2013;1(3):249-259. doi:10.4248/BR201303003

25. Kim JH, Kim SJ, Lee J, Shin CH, Seo JY. Factors affecting IGF-I level and correlation with growth response during growth hormone treatment in LG Growth Study. *PLoS One*. 2021;16(7 July):1-10. doi:10.1371/journal.pone.0252283

26. Deodati A, Ferroli BB, Cianfarani S. Association between growth hormone therapy and mortality, cancer and cardiovascular risk: Systematic review and meta-analysis. *Growth Horm IGF Res*. 2014;24(4):105-111. doi:10.1016/J.GHIR.2014.02.001

27. Glińska M, Walczak M, Wikiera B, et al. Difficulties in Interpreting IGF-1 Levels in Short Stature Children Born Small for Gestational Age (SGA) Treated with Recombinant Human Growth Hormone (rhGH) Based on Data from Six Clinical Centers in Poland. *J Clin Med*. 2023;12(13). doi:10.3390/jcm12134392

28. López-Siguero JP, Martínez-Aedo MJ, Bermúdez de la Vega JA, Bosch-Muñoz J, Lechuga-Sancho AM, Villalobos T. Growth hormone treatment does not to lead to insulin resistance nor excessive rise in IGF-1 levels, while improving height in patients small for gestational age A long-term observational study. *Clin Endocrinol (Oxf)*. 2022;96(4):558-568. doi:10.1111/cen.14626

29. Moon JE, Ko CW. Delayed Bone Age Might Accelerate the Response to Human Growth Hormone Treatment in Small for Gestational Age Children with Short Stature. *Int J Endocrinol*. 2019;2019. doi:10.1155/2019/8454303

30. Mentzel H-J, Vilser C, Eulenstein M, et al. Assessment of skeletal age at the wrist in children with a new ultrasound device. *Pediatr Radiol*. 2005;35(4):429-433. doi:10.1007/s00247-004-1385-3

31. Rachmiel M, Naugolni L, Mazor-Aronovitch K, Koren-Morag N, Bistritzer T. Bone Age Assessments by Quantitative Ultrasound (SonicBone) and Hand X-ray Based Methods are Comparable. *Isr Med Assoc J*. 2017;19(9):533-538.

32. Ranke MB, Lindberg A, Chatelain P, et al. Derivation and validation of a mathematical model for predicting the response to exogenous recombinant human growth hormone (GH) in prepubertal children with idiopathic GH deficiency. *J Clin Endocrinol Metab*. 1999;84(4):1174-1183. doi:10.1210/jcem.84.4.5634

33. Ranke MB, Lindberg A, Cowell CT, et al. Prediction of response to growth hormone treatment in short children born small for gestational age: Analysis of data from KIGS (Pharmacia International Growth Database). *J Clin Endocrinol Metab*. 2003;88(1):125-131. doi:10.1210/jc.2002-020867

34. Ly H-J, Fors H, Nilsson S, Dahlgren J. A prediction model could foresee adequate height response in children eligible for growth hormone treatment. *Acta Paediatr*. 2022;111(2):346-353. doi:10.1111/apa.16070

35. Hazem A, Elamin MB, Bancos I, et al. Body composition and quality of life in adults treated with GH therapy: a systematic review and meta-analysis. *Eur J Endocrinol*. 2012;166(1):13-20. doi:10.1530/EJE-11-0558

36. Bollerslev J, Ueland T, Jørgensen AP, et al. Positive effects of a physiological dose of GH on markers of atherogenesis: a placebo-controlled study in patients with adult-onset GH deficiency. *Eur J Endocrinol*. 2006;154(4):537-543. doi:10.1530/eje.1.02125

37. Gola M, Bonadonna S, Doga M, Giustina A. Clinical review: Growth hormone and cardiovascular risk factors. *J Clin Endocrinol Metab*. 2005;90(3):1864-1870. doi:10.1210/jc.2004-0545

38. Zhou H, Sun L, Zhang S, Wang Y, Wang G. Effect of long-term growth hormone replacement on glucose metabolism in adults with growth hormone deficiency: a systematic review and meta-analysis. *Pituitary*. 2021;24(1):130-142. doi:10.1007/s11102-020-01079-3

39. Hoffman AR, Kuntze JE, Baptista J, et al. Growth hormone (GH) replacement therapy in adult-onset gh deficiency: effects on body composition in men and women in a double-blind, randomized, placebo-controlled trial. *J Clin Endocrinol Metab*. 2004;89(5):2048-2056. doi:10.1210/jc.2003-030346

40. Lewitt MS. The Role of the Growth Hormone/Insulin-Like Growth Factor System in Visceral Adiposity. *Biochem insights*. 2017;10:1178626417703995. doi:10.1177/1178626417703995

41. Barake M, Klibanski A, Tritos NA. Effects of recombinant human growth hormone therapy on bone mineral density in adults with growth hormone deficiency: a meta-analysis. *J Clin Endocrinol Metab*. 2014;99(3):852-860. doi:10.1210/jc.2013-3921

42. Hansen TB, Brixen K, Vahl N, et al. Effects of 12 months of growth hormone (GH) treatment on calciotropic hormones, calcium homeostasis, and bone metabolism in adults with acquired GH deficiency: a double blind, randomized, placebo-controlled study. *J Clin Endocrinol Metab*. 1996;81(9):3352-3359. doi:10.1210/jcem.81.9.8784096

43. Holmes SJ, Whitehouse RW, Swindell R, Economou G, Adams JE, Shalet SM. Effect of growth hormone replacement on bone mass in adults with adult onset growth hormone deficiency. *Clin Endocrinol (Oxf)*. 1995;42(6):627-633. doi:10.1111/j.1365-2265.1995.tb02690.x

44. Yang H, Chen M, Xu H, et al. Bone mineral density in adults growth hormone deficiency with different ages of onset: a real-world retrospective study. *Endocrine*. 2024;85(1):347-355. doi:10.1007/s12020-024-03786-4

45. Webb SM. Measurements of quality of life in patients with growth hormone deficiency. *J Endocrinol Invest*. 2008;31(9 Suppl):52-55.

46. Karbownik-Lewińska M, Lewiński A, McKenna S, et al. The Polish version of the Quality of Life Assessment of Growth Hormone Deficiency in Adults (QoL-AGHDA) - four-stage translation and validation. *Endokrynol Pol*. 2008;59(5):374-384.

47. Elbornsson M, Horvath A, Götherström G, Bengtsson B-Å, Johannsson G, Svensson J. Seven years of growth hormone (GH) replacement improves quality of life in hypopituitary patients with adult-onset GH deficiency. *Eur J Endocrinol*. 2017;176(2):99-109. doi:10.1530/EJE-16-0875