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ORIGINAL PAPER

Twenty-five years of growth hormone treatment in non-dialyzed children with chronic kidney disease in Poland – efficacy, safety, metabolic effects, and factors influencing response

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ABSTRACT

Introduction: Recombinant human growth hormone (rhGH) treatment has been a well-established means of dealing with chronic kidney disease (CKD)-related short-stature for over 25 years. The aim of this study was to evaluate the safety, efficacy, metabolic effects, and factors influencing response to rhGH treatment in Poland.
Material and methods: 156 non-dialyzed children with different stages of CKD were analysed regarding anthropometric features, biochemical parameters, calcium-phosphorus metabolism, bone mineral density (BMD), and CKD progression. The analysis comprised 24 months of treatment
Results: The median height velocity during the whole course of treatment in the analysed group was 8 cm/year. In the first year of treatment, it was significantly faster than in the second year (9.5 cm/year and 7.6 cm/year, respectively, $p < 0.01$) and did not differ between children with CKD stage 2–3 (group A) and with CKD stage 4–5 (group B). Age of therapy onset correlated negatively with total ΔheightSDS ($r = –0.21$, $p < 0.05$). Throughout the treatment we observed a decrease of hypercalcemia (both groups) and an increase of hyperphosphatemia (group A). In the first year parathyroid hormone (PTH), IGF-1, CaxP, and ALP increased. In the second year PTH, IGF-1, and CaxP stabilized, and ALP decreased. ΔheightSDS correlated negatively with initial and mean serum cholesterol. Serum triglyceride concentration increased in the course of treatment. After 24 months, total body BMD increased in group A, and lumbar spine BMD increased in both groups (A and B). The mean decrease of glomerular filtration rate was 2.5 ml/min/1.73 m^2/year.
Conclusions: rhGH treatment is safe and effective, and should include the youngest CKD patients. Our results suggest that there might be a relationship between rhGH treatment and lipid profile, which necessitates further research.

KEY WORDS:
children, chronic kidney disease, growth hormone, short stature, growth velocity.

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INTRODUCTION

Short stature negatively impacts the quality of life, self-acceptance, and psychosocial relations. Almost 40% of children with kidney failure reach a height below the third percentile compared to their peers. According to the data from North American Pediatric Renal Transplant Cooperative Studies (NAPRTCS) registry, severe growth retardation (height standard deviation scores – SDS, below –1.88) affects 31% of children with glomerular filtration rate (GFR) > 25 ml/min/1.73 m^2. A correlation between the severity of growth retardation and GFR was shown: height SDS –3.2, –1.9, –1.5, and –0.9 for GFR < 10, 10–25, 25–50, and > 50 ml/min/1.73 m^2, respectively [1]. At the start of kidney replacement therapy, the mean height SDS was reported to be between v1.5 and v2.2 SDS [2, 3]. In the chronic kidney disease (CKD) in children study, the largest prospective study of paediatric patients with CKD to date, 15% of participants were below the third percentile for age- and sex-specific height at baseline [4, 5], and the percentage of those with growth failure increased further as GFR declined [6].

The first reports of the use of growth hormone (GH) in treating CKD-related growth retardation date back to 1989 [7]. In Poland, the National Program for recombinant human growth hormone (rhGH) treatment of short-statured children with CKD was launched in 1994.

The underlying causes of growth disorders in CKD are multifactorial. They include abnormalities in foetal development, malnutrition, mineral and bone disorders (MBD), metabolic acidosis, electrolyte imbalance, and diseases of the somatotropic and gonadotropic axis [8]. The release of GH from the pituitary gland is pulsatile. Somatotropin binds with its receptor (GH receptor) and activates insulin-like growth factor 1 (IGF1) synthesis. CKD is characterized by receptor resistance to GH with the proper serum GH levels and low IGF1 bioactivity.

The study aimed to analyse the efficacy, safety, and metabolic effects of rhGH treatment, and factors influencing response to the therapy in children with CKD-related short stature, treated conservatively for CKD stages II–V between the years 1994 and 2020 in Poland.

MATERIAL AND METHODS

PATIENTS

In Poland, between 1994 and 2020, 335 children with CKD-related short stature were treated with rhGH as part of the National Program: 145 children on chronic dialysis, 166 patients on conservative treatment, and 24 kidney transplant recipients.

The present study comprises 156 children with CKD stages II–V treated conservatively, who maintained therapy for at least 6 months. Chronically dialyzed children and patients after kidney transplantation were excluded from the analysis. Out of the children on conservative treatment, 8 underwent 2 courses of rhGH treatment. In those patients, the analysis included the course of longer duration. This study comprised the first 24 months of rhGH treatment (Figure 1).

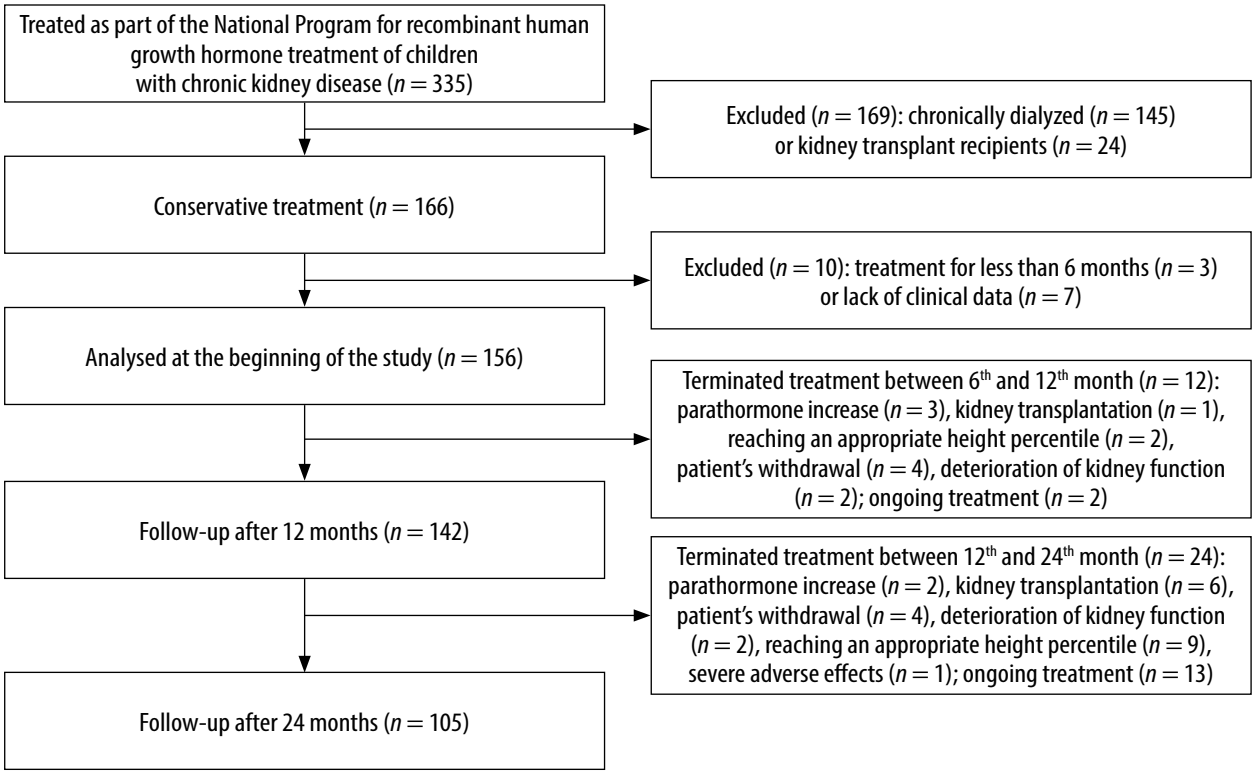

FIGURE 1. Participant flow chart, kidney transplantation

The inclusion criteria for the national program of rhGH treatment in children with CKD [9] were as follows:

- GFR below 75 ml/min/1.73 m^2 calculated using the Schwartz formula [10],
- age- and sex-adjusted height SDS (hSDS) below –1.88 SDS or growth velocity below –2.0 SDS,
- skeletal age below 12.5 years in boys and below 11.5 years in girls (according to Greulich Pyle normative values [11].

The exclusion criteria were as follows: cause of growth retardation other than CKD, glucose metabolism disorder, neoplasms.

The treatment with rhGH was discontinued in the following clinical situations:

- rapid deterioration of kidney function,
- adverse effects of rhGH treatment,
- achieving the final height, defined as skeletal age of 16 years in girls and 18 years in boys, or lack of treatment effect – growth velocity below 3 cm/year,
- achieving the 10^{th} percentile of sex- and age-adjusted height (1994–2005), 25th percentile of sex and age-adjusted height (2006–2010), and the percentile of target height calculated from mid-parental height following Tanner's formula (2011-now) [12],
- patient's voluntary withdrawal from treatment,
- kidney transplantation,
- serum parathyroid hormone (PTH) concentration above 500 pg/ml, with the possibility of resuming treatment after PTH level decreases below 300 pg/ml.

All children with CKD qualified for the Polish National Program for rhGH treatment were referred to a single tertiary care centre of paediatric nephrology, where the treatment was initiated, conducted, and coordinated.

DRUG ADMINISTRATION

Since 1994, two somatotropin preparations have been used in Poland: Genotropin (Pfizer) in 1994–2008 and 2018–2019, and Omnitrope (Novartis) in 2008–2018 and from 2019 to date. The drug administration was the same: subcutaneously every night before bedtime, in the standard dose of 0.33–0.37 mg/kg body weight/week. A qualified doctor trained all patients or their caregivers in using a GH set before initiating the therapy.

ANALYSED PARAMETERS

The following parameters were analysed:

- age of rhGH treatment onset,
- age of CKD diagnosis,
- cause of CKD according to the ESPN/ERA-EDTA registry [13],
- skeletal age at baseline and after consecutive years of treatment,
- bone mineral density (BMD) determined by dual-energy X-ray absorptiometry (DEXA) at baseline and after every consecutive year of the therapy evaluated as total body BMD and lumbar spine (L2–L4) BMD expressed in SDS,
- anthropometric measurements performed by an anthropologist, including height (cm) *via* a Harpenden Wall Mounted Stadiometer and weight (kg). For 25 years, the children were qualified for the National Program based on different growth charts. In this study, age- and sex-specific height, weight, and body mass index BMI were standardized using World Health Organization growth charts and expressed as SDS. Due to growth impairment, BMI SDS values were obtained by height and age [14] as indicated in [15, 16],
- biochemical parameters: albumin (g/dl), glucose (mg/l), cholesterol (mg/dl), triglycerides (mg/dl), calcium (mg/dl), phosphorus (mg/dl), calcium-phosphorus product (mg^2/dl^2), intact PTH (pg/ml), alkaline phosphatase (ALP) (U/l), blood gases, IGF1 (ng/ml), GFR (ml/min/1.73 m^2) calculated using the Schwartz formula, hypercalcemia, and hyperphosphatemia were assessed using age-appropriate normal ranges according to the manufacturers' recommendations. The normal concentrations of calcium were as follows: children < 3 years – 8.7–9.8 (mg/dl), 3–11 years – 8.9–10.1 (mg/dl), 11–13 years – 8.8–10.6 (mg/dl), 13–15 years – 9.2–10.7 (mg/dl), and > 15 years – 8.9–10.7 (mg/dl), and of phosphorus: < 3 years – 3.9–6.5 (mg/dl), 3–6 years – 4.0–5.4 (mg/dl), 6–11 years – 3.7–5.6 (mg/dl), 11–13 years – 3.3–5.4 (mg/dl), 13–15 years – 2.9–5.4 (mg/dl), and > 15 years – 2.8–4.6 (mg/dl).

Following the National Program, anthropometric measurements and serum calcium, phosphorus, ALP, PTH, glucose, blood gases, and GFR were assessed every 3 months; serum cholesterol, triglycerides, total protein, albumin – every 6 months; and IGF1 every year.

This study analyses the parameters mentioned above at the initiation of the rhGH treatment, after 12 months, and after 24 months of treatment.

STATISTICAL ANALYSIS

Statistical analysis was performed using Dell Statistica 13.3 software. The normality of data was evaluated using the Shapiro-Wilk test. The results are expressed as median (IQR) or mean ±SD. Quantitative variables were compared for homogeneity using the Mann-Whitney *U* test or Kruskal-Wallis ANOVA test with appropriate corrections. Paired observations were compared using a sign test. The numbers of patients in subgroups were compared using the χ^2 test. The correlations between growth velocity (expressed as ΔheightSDS – ΔhSDS) and clinical and biochemical parameters were analysed using Spearman's rank correlation. A p-value of < 0.05 was considered statistically significant.

TABLE 1. Clinical characteristics of the study group at the onset of recombinant human growth hormone treatment

Parameters	Whole group	Group A	Group B	*p*
Number	156	58	98	
Girls/boys	38/118	13/45	25/73	
Age of rhGH treatment onset (years, median, IQR)	10.8 (7.2–13.0)	11.4 (7.6–13.5)	10.2 (7.1–12.8)	0.208*
Time from CKD diagnosis to rhGH therapy onset (years, median, IQR)	5.8 (2.8–8.8)	4.4 (2.4–7.8)	6.1 (3.7–9.1)	0.048*
Skeletal age at the onset of rhGH treatment (years, median, IQR)	8.0 (4.5–11.0)	9.0 (5.0–10.5)	7.0 (4.5–11.0)	0.303*
Causes of CKD (%)				
CAKUT	104 (66.7)	34 (58.6)	70 (71.4)	0.269**
Hereditary kidney diseases	29 (18.6)	14 (24.1)	15 (15.3)	
Glomerulopathies	10 (6.4)	6 (10.3)	4 (4.1)	
AKI (HUS included)	8 (5.1)	2 (3.4)	6 (6.1)	
Other[1]	5 (3.2)	2 (3.4)	3 (3.1)	

AKI – acute kidney injury, CAKUT – congenital anomalies of the kidney and urinary tract, CKD – chronic kidney disease, HUS – hemolytic-uremic syndrome, rhGH – recombinant human growth hormone
[1] – unclassified family nephropathy – 1, rhabdomyosarcoma of the urinary bladder – 1, unknown – 3
** Mann-Whitney U test; ** χ^2 test*

RESULTS

CLINICAL DATA

The clinical characteristics of 156 patients are shown in Table 1.

The patients were divided into 2 groups regarding the CKD stage at rhGH treatment initiation: group A – CKD stage 2–3 (n = 58) and group B – CKD stage 4–5 (n = 98). The dominant gender was male (75.6%). At the rhGH therapy initiation, the median age was 10.8 years and was slightly higher in group A, but with no statistical significance. We found a weak negative correlation between the age of therapy onset and total change in height SDS during 24 months (r = –0.21, p < 0.05).

The time between CKD diagnosis and the introduction of rhGH therapy was significantly longer in children with more advanced kidney disease. The median skeletal age in both groups was equal and was delayed by 2.3 (1.3–3.6) years compared to chronological age (Table 1).

Regardless of the CKD stage, the most common causes of CKD were congenital anomalies of the kidney and urinary tract (CAKUT) (Table 1).

The median duration of rhGH treatment in the analysed group was 28 (18–28) months and was significantly longer in group A than B (33.5 months vs. 26 months, respectively, p < 0.01).

The causes of rhGH treatment withdrawal in the entire analysed group are shown in Table 2.

Because the growth rate deteriorated again, rhGH was repeatedly started in 9 patients: 2 children after kidney transplantation and 7 children in CKD stage 5 during dialysis therapy. We did not analyse the second treatment period in this manuscript.

ANTHROPOMETRY

The median height velocity during the whole course of treatment in the analysed group was 8 cm/year. In the first year of treatment, it was significantly faster than in the second year (9.5 cm/year and 7.6 cm/year, respectively, p < 0.01) but did not differ regarding the initial stage of CKD (Figure 2 A).

Median hSDS at the treatment initiation was –2.1 and did not differ between groups A and B. The improvement of hSDS in the first year was significantly greater than in the second year (ΔhSDS 0.7 and 0.4, respectively), with no differences between the groups (Figure 2 B). The total change of hSDS between the treatment initiation and 24 months ($\Delta hSDS_{0-24}$) showed no correlation with baseline GFR.

We found no differences in BMI (kg/m^2) and BMI SDS regarding the stage of CKD neither on treatment initiation nor after 12 and 24 months of therapy. Also, both BMI (kg/m^2) and BMI SDS did not change after 12 and

TABLE 2. Causes of recombinant human growth hormone treatment withdrawal during the entire treatment period

Cause of treatment discontinuation	*n*	%
PTH elevation	16	14.5
Kidney transplantation	18	16.4
Reaching the target height	14	12.7
Patient's voluntary withdrawal	25	22.7
Deterioration of kidney function	5	4.5
Reaching the appropriate height percentile	27	24.5
Adverse effects	5	4.5

PTH – parathyroid hormone

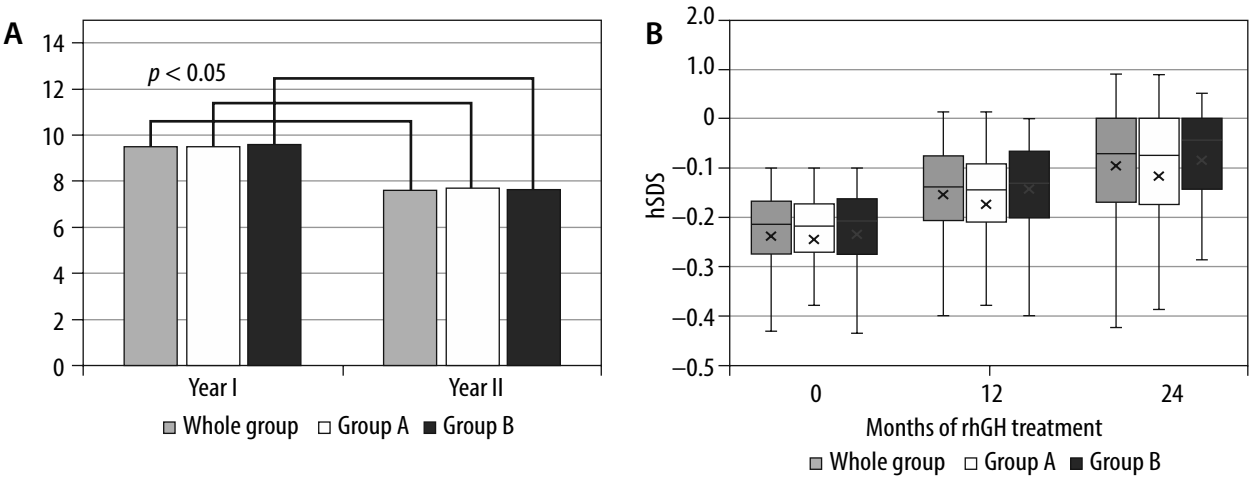

FIGURE 2. Growth during the observation period. **A**) Growth velocity during year I and II of recombinant human growth hormone (rhGH) treatment (cm/year). **B**) Height standard deviation scores before and throughout rhGH treatment

TABLE 3. Body mass index before, and after 12 and 24 months of recombinant human growth hormone treatment

BMI		Whole group	Group A	Group B	*p**
Onset of rhGH treatment	*n*	156	58	98	
	kg/m^2	15.5 (14.4–17.7)	15.6 (14.5–17.5)	15.5 (14.3–17.8)	0.805
	SDS	–0.3 (–0.9–0.5)	–0.2 (–0.9–0.5)	–0.3 (–0.9–0.6)	0.905
12 months of treatment	*n*	142	56	86	
	kg/m^2	16.0 (15.0–17.5)	16.1 (15.0–17.6)	15.9 (15.0–17.4)	0.618
	SDS	–0.3 (–0.9–0.4)	–0.1 (–0.8–0.4)	–0.3 (–0.9–0.3)	0.522
24 months of treatment	*n*	105	47	58	
	kg/m^2	16.6 (15.3–18.1)	16.7 (15.7–18.3)	16.5 (15.2–18.0)	0.503
	SDS	–0.2 (–0.7–0.5)	–0.2 (–0.7–0.5)	–0.2 (–0.8–0.5)	0.948

BMI – body mass index, rhGH – recombinant human growth hormone, SDS – standard deviation scores
** Mann-Whitney U test*

24 months compared to values at the onset of the treatment in the whole group and both groups (A and B) (Table 3).

The growth velocity during rhGH treatment regarding the patients' age was analysed. The cohort was divided into 3 groups based on the age at treatment onset (group I: < 8 years, group II: 8–12 years, group III: > 12 years).

Growth velocity was significantly higher in the first than in the second year of treatment in all groups (*p*-values: 0.005, 0.004, < 0.001, respectively) and did not differ between the age groups. At the treatment initiation, the oldest patients (group III) presented the lowest hSDS compared to the other groups, with borderline statistical significance ($p = 0.053$). During rhGH therapy, the hSDS in group III was the lowest of all groups. Post-hoc analysis showed significant hSDS differences between the youngest and the oldest groups after 12 and 24 months of treatment. After 2 years of therapy, ΔhSDS was the highest in the youngest children (group I) compared to the 2 other groups (Table 4).

The oldest children were characterized by significantly higher BMI SDS than the remaining 2 groups at treatment onset. There were no differences in BMI SDS after 1 and 2 years.

Throughout the treatment, BMI SDS increased significantly in the youngest children ($p = 0.002$); no differences were found in the 2 other age groups ($p = 0.174$ and $p = 0.266$, respectively) (Table 4).

Skeletal age did not differ between groups A and B at onset, and after 12 and 24 months. Skeletal age advanced proportionally throughout the observation period, and skeletal age delay remained comparable over 2 years (Table 5).

Forty-eight patients were treated with rhGH for 3 years, 23 children were treated for 4 years, and only 6 subjects received rhGH for 5 or more years. The growth rate in these individuals is presented in Supplementary Table S1.

BIOCHEMICAL PARAMETERS

Before the introduction of rhGH the median haemoglobin (Hb) concentration was significantly higher in group A than in group B (12.6 g/dl vs. 11.3 g/dl, respectively, $p < 0.001$), the triglyceride concentration was higher in group B (141 mg/dl vs. 94 mg/dl, $p = 0.007$), and the base excess (BE) level was higher in group A (–1.9 mmol/l vs. –2.9 mmol/l, $p = 0.022$).

TABLE 4. Anthropometric parameters regarding the patients' age at the onset, and after 12 and 24 months of recombinant human growth hormone treatment

Parameters	Group I	Group II	Group III	*p*-value*
N at the onset of rhGH treatment (group A/group B)	44 (15/29)	55 (20/35)	57 (23/34)	0.802***
N after 12 months (group A/group B)	39 (15/24)	53 (20/33)	50 (21/29)	0.897***
N after 24 months (group A/group B)	28 (12/16)	38 (16/22)	39 (19/20)	0.820***
Duration of rhGH treatment (months, median, IQR)	29.5 (18.0–41.5)	28.0 (18.0–42.0)	27.0 (18.0–36.0)	0.364
Δh 0–12 months [cm]	10.1 (8.3–11.5)	9.4 (8.4–10.3)	9.5 (8.0–11.5)	0.198
Δh 12–24 months [cm]	8.4 (7.2–9.4)	7.6 (6.3–8.3)	7.3 (6.4–8.6)	0.112
hSDS at the onset of rhGH treatment	–2.0 (–2.6 to –1.7)	–1.9 (–2.5 to –1.6)	–2.4 (–3.0 to –1.8)	0.053
hSDS after 12 months	–1.0 (–1.7 to –0.6)	–1.4 (–2.0 to –0.9)	–1.8 (–2.5 to –1.3)	0.002 **I vs. III
hSDS after 24 months	–0.8 (–1.4–0.1)	–1.2 (–1.8 to –0.7)	–1.8 (–2.2 to –1.0)	0.002 **I vs. III
ΔhSDS 0–24 months	1.6 (1.1–1.9)	0.9 (0.6–1.1)	1.0 (07–1.4)	< 0.001 **I vs. II , III
BMI SDS at the onset of rhGH treatment	–0.5 (–1.1–0.2)	–0.5 (–0.9–0.0)	0.4 (–0.5–1.1)	0.005 **I vs. II, III
BMI SDS after 12 months	–0.2 (–0.9–0.4)	–0.4 (–0.9–0.0)	0.0 (–0.6–0.8)	0.158
BMI SDS after 24 months	0.0 (–0.7–0.5)	–0.4 (–0.7–0.4)	–0.3 (–0.8–0.5)	0.940

ΔhSDS – ΔheightSDS, hSDS – height standard deviation scores, rhGH – recombinant human growth hormone
** Kruskal-Wallis test; **post-hoc analysis – Dunn's test; *** χ^2 test*

TABLE 5. Skeletal age before, and after 12 and 24 months of recombinant human growth hormone treatment

Parameters		Whole group	Group A	Group B	*p*-value*
Skeletal age at onset of rhGH treatment	Years	8.0 (4.5–11.0)	9.0 (5.0–10.5)	7.0 (4.5–11.0)	0.303
Skeletal age at 12 months of treatment	Years	10.0 (6.5–11.5)	10.0 (6.5–11.5)	9.5 (6.0–11.5)	0.269
Skeletal age at 24 months of treatment	Years	10.5 (7.0–12.8)	11.0 (7.3–13.0)	10.0 (7.0–12.5)	0.281
Skeletal age delay at onset of rhGH treatment	Years	2.3 (1.3–3.6)	2.0 (1.1–3.3)	2.6 (1.4–3.8)	0.221
Skeletal age delay at 12 months of treatment	Years	2.2 (1.1–3.0)	1.8 (0.8–2.7)	2.6 (1.8–3.7)	0.028
Skeletal age delay at 24 months of treatment	Years	2.3 (1.3–3.0)	2.1 (0.8–2.9)	2.6 (1.6–3.1)	0.183

rhGH – recombinant human growth hormone
** Mann-Whitney U test*

Total ΔhSDS (0–24 months) correlated negatively with baseline cholesterol ($r = -0.34$, $p < 0.001$ – weak correlation) and IGF1 ($r = -0.33$, $p = 0.047$ – weak correlation). Also, weak positive correlations were found between total ΔhSDS and HCO_3 ($r = 0.24$, $p = 0.018$) and BE ($r = 0.22$, $p = 0.049$). Considering the mean values of biochemical parameters from the 24 months of treatment, the only significant correlation was found between ΔhSDS and mean serum cholesterol ($r = -0.23$, $p = 0.022$ – weak correlation).

In the course of treatment, we observed a statistically significant change in Hb after 24 months, an increase in triglycerides, and a decrease in BE (Table 6).

CALCIUM-PHOSPHORUS METABOLISM

At treatment, initiation hypercalcemia was found in 26% of patients from group B and 31.6% from group A (NS). 26.3% of patients from group B and 7% patients from group A presented with hyperphosphatemia

TABLE 6. Haemoglobin and biochemical parameters in the whole group at the onset, and after 12 and 24 months of recombinant human growth hormone treatment

Parameters	rhGH treatment onset	12 months	24 months	*p*-value*
Hb [g/dl]	11.8 (10.9–12.8)	11.5 (10.6–12.9)	11.5 (10.3–12.6)	0.045
Serum albumin [g/dl]	4.3 (3.9–4.6)	4.3 (3.9–4.5)	4.3 (4.0–4.6)	0.965
Glucose [mg/dl]	88.0 (81.5–96.0)	91.0 (83.8–96.8)	90.0 (84.0–95.8)	0.176
Total cholesterol [mg/dl]	189.0 (159.0–209.5)	177.0 (153.4–211.0)	179.0 (157.5–211.5)	0.088
TG [mg/dl]	116.0 (80.5–177.1)	142.0 (101.0–198.0)	148.4 (99.0–189.0)	< 0.001
HCO_3 [mmol/l]	22.4 (20.5–24.2)	22.5 (20.4–24.4)	21.9 (20.2–24.1)	0.183
BE [mmol/l)	–2.5 (–4.7 to –0.4)	–2.5 (–4.7 to –0.3)	–2.9 (–4.9 to –0.3)	0.045

BE – base excess, Hb – haemoglobin, rhGH – recombinant human growth hormone, TG – tyreoglobulina
** Friedman's test*

TABLE 7. Number of patients with hypercalcemia and hyperphosphatemia at the onset, and after 12 and 24 months of recombinant human growth hormone treatment

Parameters	Months of treatment (*n*)	Whole group (%)	Group A (%)	Group B (%)	*p*-value*
Ca > *n* (%)	0 (156)	43/156 (27.6)	18/58 (31.0)	25/98 (25.5)	0.456
	12 (142)	29/142 (20.4)	13/56 (23.2)	16/86 (18.6)	0.506
	24 (105)	14/105 (13.3)	7/47 (14.9)	7/58 (12.1)	0.672
p-value*		0.006	0.053	0.045	–
p > *n* (%)	0 (156)	30/156 (19.3)	4/58 (6.9)	26/98 (25.5)	0.003
	12 (142)	54/142 (38.0)	20/56 (35.7)	34/86 (39.5)	0.647
	24 (105)	38/105 (36.2)	15/47 (31.9)	23/58 (39.7)	0.412
p-value*		< 0.001	< 0.001	0.088	–

** χ^2 test*

($p = 0.003$) (Table 7). Throughout the observation period, the ratio of hypercalcaemic patients decreased in both groups (group A – borderline statistical significance). The ratio of hyperphosphatemic patients increased in group A, while it did not change in group B.

Before rhGH initiation, the calcium-phosphorus product (Ca × P) was higher in group B compared to group A ($p = 0.028$). No differences were found after 12 and 24 months of treatment (p-values 0.877 and 0.268, respectively). In the first year, Ca × P increased significantly in both groups, and in the second year it did not change. The median Ca × P in groups A and B remained below 60 mg^2/dl^2 throughout the observation period (Figure 3 A).

After one year of treatment, PTH concentration increased significantly in both groups. Parathyroid hormone slightly decreased in groups A and B after the second year but with no statistical significance. Median PTH concentrations were significantly higher in group B both at onset ($p < 0.001$) and after 12 ($p < 0.001$) and 24 months of treatment ($p < 0.05$) (Figure 3 B).

In the first year of observation, we observed a significant rise in the serum ALP activity regardless of the baseline CKD stage. After the second year, ALP decreased significantly in groups A and B. ALP activity did not differ between the groups at any time (Figure 3 C).

After 12 months of treatment, IGF1 levels increased significantly in both groups. In group A the IGF1 concentration continued to rise. It stabilized in group B. No differences in serum IGF1 between the groups were found at the onset or throughout the observation period (Figure 3 D).

DENSITOMETRIC EVALUATION

Because of incomplete data, we analysed total body BMD (TB BMD) in 64 patients (41%) and lumbar spine BMD (L2–L4 BMD) in 76 patients (48.7%) at the beginning of the study.

Total body BMD Z-score improved in group A. There was no change in TB BMD Z-score in group B (Figure 4 A). L2–L4 BMD *Z*-score after 24 months of treatment improved in groups A and B (Figure 4 B).

CHRONIC KIDNEY DISEASE PROGRESSION

Chronic kidney disease progression during rhGH treatment was evaluated using GFR. The mean GFR at treatment initiation in the whole analysed group was 29.5 ml/min/1.73 m^2, after 12 months – 28.8 ml/min/1.73 m^2, and after 24 months – 27.5 ml/min/1.73 m^2. Exploring the impact of rhGH on GFR during 24 months of treatment,

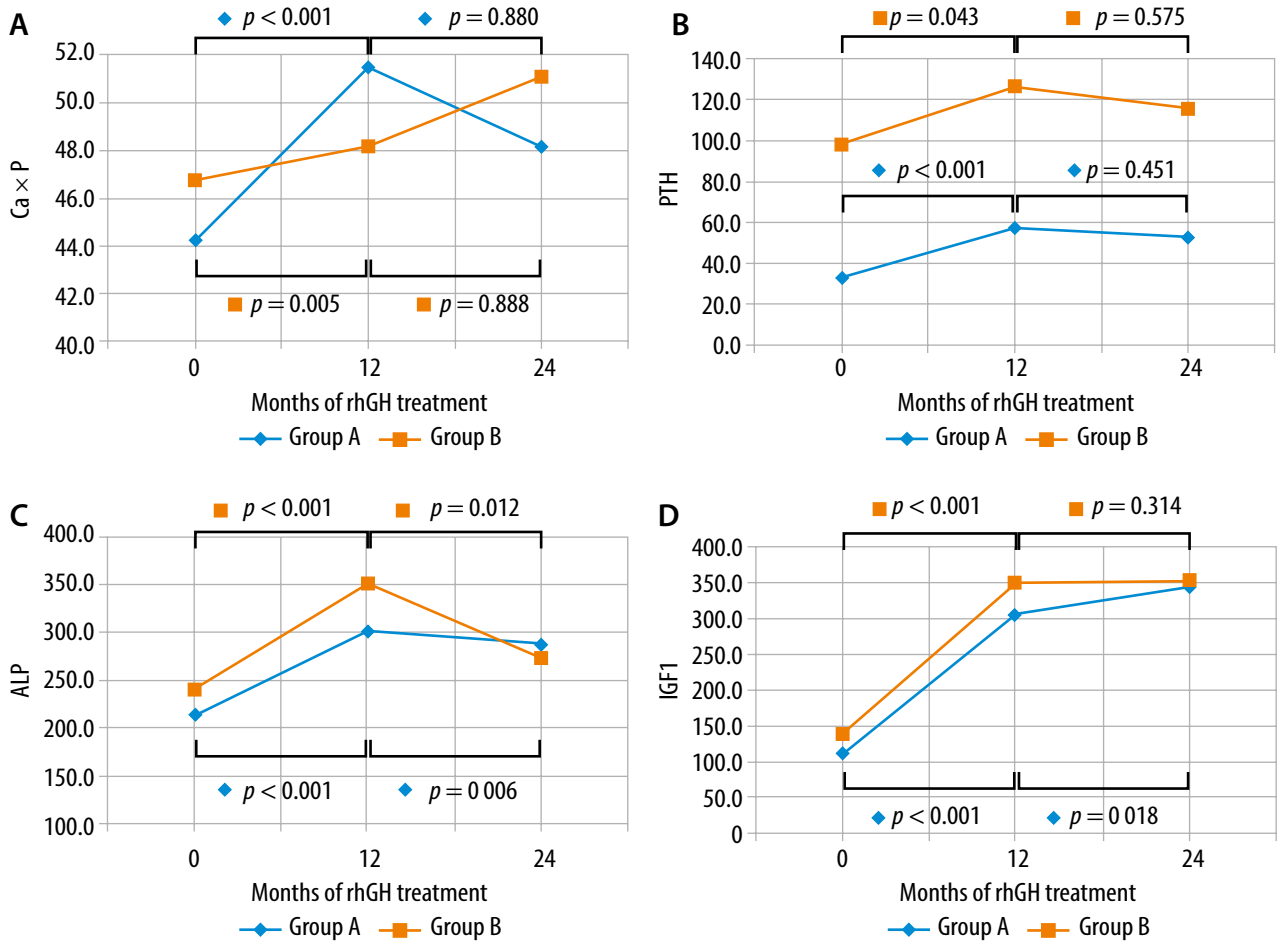

FIGURE 3. Calcium-phosphorus metabolism parameters throughout the treatment in groups **A** and **B**. **A**) Calcium-phosphorus product [mg²/dl²]. **B**) Parathyroid hormone [pg/ml]. **C**) Alkaline phosphatase [U/l]. **D**) Insulin-like growth factor-1 [ng/ml]; *p*-values calculated using sign test

in the whole group the GFR decreased by 2.5 ±5.5 ml/min/1.73 m²/year. We found no GFR deterioration in the youngest group (group I), but in the other age groups the mean GFR decreased by 2.8 ±5.6 ml/min/1.73 m²/year (Figure 5). We analysed changes in GFR during the treatment regarding the underlying aetiology of CKD. A significant decrease in GFR after 24 months was observed in patients with CKD caused by CAKUT and hereditary diseases (Table 8).

DISCUSSION

This report summarizes 25 years of GH treatment in non-dialyzed children with different stages of CKD

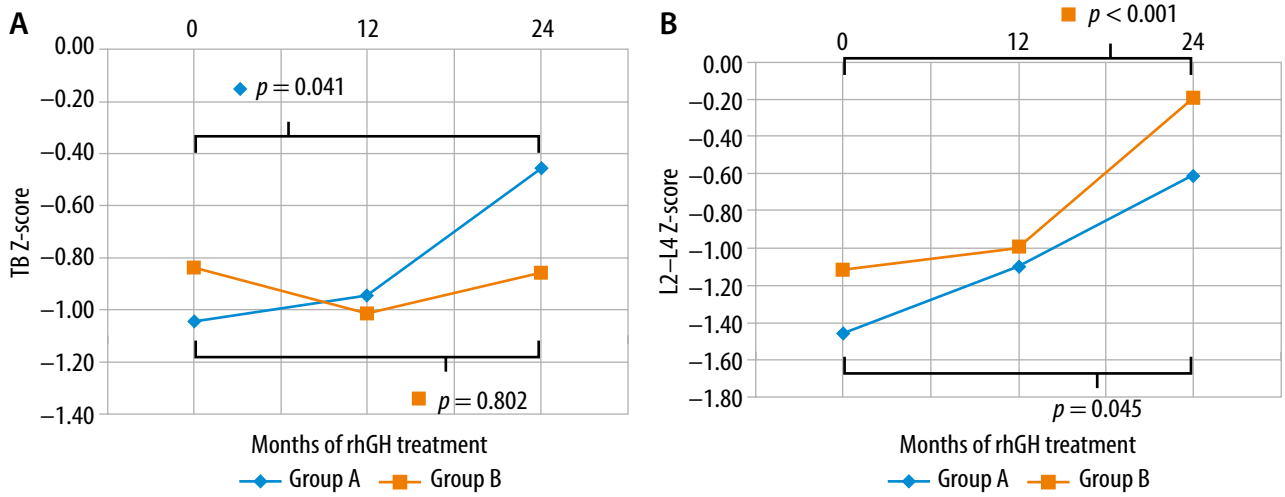

FIGURE 4. Densitometric bone mineral density (BMD) Z-score values throughout the recombinant human growth hormone treatment. **A**) Total body BMD in groups A (initial $n = 20$) and B (initial $n = 44$). **B**) L2–L4 BMD in groups A (initial $n = 24$) and B (initial $n = 52$); *p*-values calculated using sign test

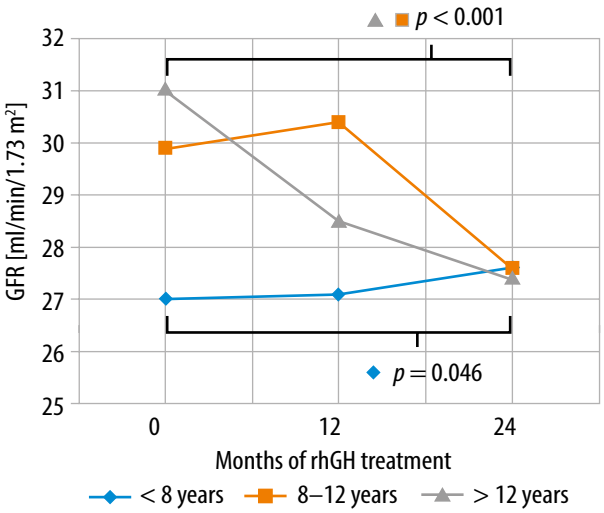

FIGURE 5. Changes of glomerular filtration rate throughout the recombinant human growth hormone treatment in the age groups; *p*-values calculated using sign test

in Poland. In the first 15 years, due to economic motives, the National Program established termination of treatment once a child reached the 10th and later the 25th age- and sex-adjusted height percentile. For the last 10 years, short-statured CKD patients have been treated with rhGH until they reach their final height or the percentile of target height.

In the analysed cohort, consistent with other studies, height velocity was greater in the first year of treatment (9.5 cm/year compared to 7.6 cm/year in the second year). Fine *et al.* reported in a 24-month study that patients treated with rhGH had a greater growth rate during the first year of treatment [17]. Similarly, Kari *et al.* [18] observed an improvement of hSDS in children with CKD on conservative treatment both after the first and second year of the rhGH therapy (hSDS amounted to –2.1 before treatment, –1.5 after one year, –1.2 after 2 years).

We found no difference in response to the rhGH treatment regarding the CKD stage, even though children with less advanced kidney disease (stage II and III) were slightly older. The time from CKD diagnosis to the initiation of GH therapy was significantly shorter than in CKD stages IV and V. According to the literature, younger age, lower hSDS, more significant target-height deficit, lower growth velocity, and greater skeletal age retardation at the initiation of rhGH therapy, target height, and hereditary kidney disease as an underlying kidney disorder are positively associated with the final height achieved in children with CKD treated with rhGH. In contrast, poor prognostic factors for the rhGH treatment response are advanced age at the start of the therapy, initiation after puberty, the duration of dialysis, steroid therapy, and multisystemic syndromes, e.g. Schimke or nail-patella syndrome [8, 19–21].

In our cohort, children below 8 years old improved hSDS significantly more than the older patients, both after the first and second year of treatment. This confirms the previous reports showing that younger children achieve faster growth velocity [20, 22, 23].

During the rhGH treatment, no change in BMI SDS regarding the CKD stage was found. Patients from the oldest group (above 12 years of age) had significantly higher BMI SDS after the treatment onset. In contrast, no differences were found after the first and second years of treatment. In the youngest group, an increase in BMI SDS during rhGH therapy was found, similarly to data in children with an idiopathic GH deficiency, small for gestational age, Turner syndrome, and dialyzed patients [24, 25]. However, no correlation was found between the initial BMI SDS and total ΔhSDS, consistent with the previous findings [19, 21].

BIOCHEMICAL DATA

In our study, the serum cholesterol levels were stable during the analysed treatment period. Still, we found a weak negative correlation between ΔhSDS and both initial serum cholesterol levels and mean cholesterol levels from 24 months of treatment. This suggests that there might be an interrelation between serum cholesterol concentration and the response to rhGH treatment.

In the analysed cohort, serum triglyceride concentrations increased during rhGH treatment. Although most studies show no influence of rhGH treatment on the lipid profile [26], a rise in serum triglycerides during

TABLE 8. Changes of glomerular filtration rate during the first 2 years of recombinant human growth hormone treatment regarding the underlying cause of chronic kidney disease

Cause of CKD	GFR 0	GFR 12	GFR 24	*p*-value*
CAKUT	27.7 ±14.0	26.7 ±15.5	25.3 ±15.5	< 0.001
Glomerulopathies	43.2 ±26.9	42.2 ±34.3	41.3 ±41.3	0.277
Hereditary diseases	32.5 ±16.0	33.0 ±21.1	31.6 ±15.1	0.024
AKI (HUS included)	22.9 ±7.9	22.8 ±12.3	22.4 ±15.2	0.549
Other/unknown	31.1 ±19.8	29.1 ±16.6	26.8 ±16.6	0.549
p-value**	0.346	0.585	0.535	

**Friedman's test; **Kruskal-Wallis test*
AKI – acute kidney injury, CAKUT – congenital anomalies of the kidney and urinary tract, CKD – chronic kidney disease, GFR – glomerular filtration rate, HUS – hemolytic-uremic syndrome

GH therapy was previously found in children on peritoneal dialysis [27]. Labarta *et al.* showed that in children with SGA (small for gestational age) treated with rhGH, tyreoglobulina levels increased significantly but remained within the normal range. On the other hand, total and LDL cholesterol decreased in the study period [28]. Another study on SGA children showed no changes in lipid profile during rhGH treatment [29]. This finding might suggest the negative impact of rhGH treatment on triglycerides and requires further attention.

During the treatment period, Hb and BE changed in the studied children, while albumin remained stable. Both these slight alterations were without clinical significance. Similarly, in the studies by Hokken-Koelega and Jedrzejowski, biochemical parameters did not change significantly during rhGH treatment in transplanted patients and PD patients, respectively [20, 27].

BONE METABOLISM

The study showed no significant correlations between initial traditional calcium-phosphorus metabolism markers and response to rhGH treatment.

The increase of hyperphosphatemic patients during the treatment appeared in the entire cohort. An increase in serum phosphorus levels is typical for CKD associated with mineral and bone disease (CKD-MBD). However, the CKD progression, presented as a reduction of GFR in the analysed cohort, was relatively slow and did not advocate for the observed rise in hyperphosphatemia. This may be due to GH therapy itself. It was demonstrated to stimulate phosphate retention by increased intestinal absorption and augmented renal retention in the mechanism mediated by IGF1 and independent of PTH [30]. It is recommended that in patients with CKD, serum calcium and phosphorus levels are lowered to age-appropriate referential values [31, 32] because phosphate is a vascular toxin [33], and elevated calcium levels may lead to nephrocalcinosis and vascular calcification [34]. It often proves to be a challenge in clinical practice due to, e.g., dietary non-compliance. Despite the increased number of hyperphosphatemic children and values of calcium-phosphorus product throughout the rhGH treatment in our study, the latter was kept within the referential value of $< 60\ mg^2/dl^2$.

CKD-MBD is associated with low serum calcium levels, resulting from decreased calcitriol synthesis and impaired intestinal calcium resorption [35]. Surprisingly, in this study, a relatively high ratio of patients presented with hypercalcemia before the initiation of rhGH therapy. This may be due to the common use of calcium-based phosphate binders in treating hyperphosphatemia.

Interestingly, we observed a decrease in the number of patients with hypercalcemia throughout rhGH treatment. IGF1 stimulates renal hydroxylation of vitamin D, resulting in augmented calcitriol synthesis and, consequently, increased renal calcium resorption. In CKD, this mechanism is impaired due to the previously mentioned defect of calcitriol synthesis. However, IGF1 also increases intestinal calcium absorption independently from GH/IGF1-regulated renal vitamin D hydroxylation [36]. The observed decrease in the hypercalcemic patient ratio after the introduction of GH treatment may be explained by high calcium demands during accelerated bone formation [37].

The incidence of hypercalcemia decreased in the whole group and group B. In group A, the decrease in the number of patients with hypercalcemia was on the verge of statistical significance. Probably, this difference was due to there being fewer patients in group B.

The increase in the frequency of hyperphosphatemia was significant in children with less advanced CKD, but there was no significant increase in the group with more advanced CKD. We suppose that this difference could be a derivative of a higher prevalence of hyperphosphatemia before the start of treatment in group B and, therefore, more frequent use of phosphate binders from the beginning of rhGH therapy. Unfortunately, the treatment data were incomplete and were not analysed in the manuscript.

GH-induced hyperparathyroidism is rarely reported [26, 38], and several studies showed no consistent changes in PTH levels during growth hormone therapy [37]. However, our study showed a significant increase in PTH after the first year of rhGH treatment, with further stabilization in the second year. Hyperparathyroidism occurs in the course of CKD, but the slow progression of CKD in the presented cohort and the fact that PTH levels increased regardless of the initial CKD stage suggest that the changes may be associated with GH. Nevertheless, the median PTH remained within the recommended range for children with CKD on conservative treatment [39, 40] throughout the observation period, regardless of the initial CKD stage.

The study showed a rise in bone turnover parameters after 12 months of rhGH treatment, followed by stabilization of PTH, IGF1, and calcium-phosphorus product and a decrease of ALP in the second year. This, together with high Δh, suggests that the first year of GH treatment is the period of critical changes in bone turnover and enhanced bone metabolism.

Studies on rhGH treatment effects on BMD do not bring conclusive results. One of the studies showed no changes in BMD but reported improvement in bone mineral mass [41]. A study regarding children with idiopathic short stature and GH deficiency also showed no changes in the lumbar spine BMD during 24 months of GH therapy [42]. One study showed no BMD improvement in CKD rats after one week of human GH therapy [43]. In another study, 2-week-long GH treatment combined with exercise improved trabecular bone mass, while GH treatment alone did not [44]. In our cohort, however, after 24 months of GH treatment, BMD of the lumbar spine improved regardless of the initial CKD stage. Total body BMD is only enhanced in children with lower stages of

CKD (2–3), with no change in children with CKD 4–5. These outcomes are partially consistent with van der Sluis *et al.*, whose study showed an increase in lumbar spine BMD and no change in total body BMD [45].

In advanced CKD (stages 4 and 5), bone structure disturbances are more pronounced in cortical bone than in trabecular bone [46]. Of note, when we analysed the bone biopsies of dialyzed children treated with rhGH, we found a trend towards lower and more heterogeneous matrix mineralization in cortical than in trabecular bone [47]. Thus, we think that the positive impact of rhGH treatment on osseous tissue in stage 4 and stage 5 is expressed more in trabecular bone (e.g. in vertebrae). Conversely, as revealed in our cohort, in children with CKD stages 2 and 3, rhGH might improve trabecular and cortical bone.

CHRONIC KIDNEY DISEASE PROGRESSION

Mean GFR at treatment initiation in the whole analysed cohort was 29.5 ml/min/1.73 m^2, after 12 months – 28.8 ml/min/1.73 m^2, and after 24 months – 27.5 ml/min/1.73 m^2 ($p < 0.01$). Mehls *et al.* [48] compared the progression of CKD expressed as a change in GFR between patients on rhGH treatment (the KIGS registry) and those without rhGH treatment (ESCAPE trial) [49]. At 5-year follow-up, the mean loss of eGFR in KIGS children did not differ significantly from that in controls (ESCAPE trial): – 5.8 vs. –8.6 ml/1.73 m^2/5 years, respectively ($p = 0.17$). In another study, GFR decreased by 3.5 ml/min/1.73 m^2/year [50]. Similarly, in our study, mean GFR decreased by 2.5 ±5.6 ml/min/1.73 m^2/year. Therefore, the decline in eGFR during rhGH treatment is probably the natural consequence of CKD progression, independent from the GH treatment itself, and is of no clinical significance for the individual patient. Interestingly, the analysis of eGFR changes showed a significant improvement after 2 years of rhGH treatment in children below 8 years old. The predominant cause of CKD in the analysed population was CAKUT (66.7%). In most patients with renal hypodysplasia, kidney function deteriorates in puberty, which could explain the observed improvement of GFR in the youngest children.

A significant decrease in GFR after 24 months was observed in patients with CKD caused by CAKUT and hereditary diseases. In the ESCAPE trial, the decline in kidney function was higher in patients with glomerulopathies than in patients with congenital primary renal disorders; in contrast, it was the lowest in rhGH-treated patients with glomerulopathies. This was an unexpected result and may suggest that rhGH treatment does not pose a particular threat to patients with glomerulopathies [49].

STRENGTHS AND LIMITATIONS

The strengths of our article are the large study group allowing reliable conclusions based on statistical calculations, the homogeneity of the group in terms of CKD stage, and extensive analysis of anthropometric and biochemical data. Our study summarizes more than 25 years of rhGH therapy in non-dialyzed children with CKD and is one of the most complete papers written on this group of patients. In light of our knowledge, we have demonstrated for the first time a clinically and statistically significant increase in triglycerides in non-dialyzed children with CKD treated with rhGH, which warrants further analysis and is a stimulus for further research. So far, as we mentioned above, such a phenomenon has been found in children on peritoneal dialysis [27]. A separate assessment of the mineralization in the entire skeleton and the lumbar spine, taking into account the degree of CKD, is also valuable. Johnson *et al.* only analysed total bone mineral mass (TBBM) calcification [41]. The only studies investigating total body and BMD in rhGH-treated non-dialyzed children with CKD include small numbers of patients (4 and 15 children, respectively) [45, 51]. The statistically significant differences in the effect of rhGH on skeletal calcification according to the degree of CKD we have shown are another argument for initiating rhGH as early as possible.

The limitations of our work include the large number of patients who discontinued treatment, which may have affected the results' reliability. Furthermore, it was impossible to perform a reliable analysis of multiple subgroups due to the small number of patients (e.g. analysis by CKD causes). In addition, the analysis of skeletal calcification included only a subset of patients due to incomplete data. Moreover, we did not consider the possible effect of puberty on bone mineralization. We did not compare our patients with children with CKD not treated with rhGH. Adding such an analysis would have increased the reliability of the results. Finally, we included only height and BMI among the anthropometric data in the study. We did not analyse other parameters such as waist-hip ratio, skinfold thickness, and body proportions.

CONCLUSIONS

Younger children with CKD grow faster than older children treated with rhGH, indicating the necessity of rapid qualification of the youngest CKD patients for rhGH treatment.

Recombinant human GH treatment of patients with varying degrees of CKD is safe and significantly improves the growth rate.

Children with CKD require thorough monitoring of calcium-phosphorus metabolism parameters, particularly in the first year of rhGH treatment because it is the period in which the most dynamic changes in bone turnover parameters take place.

Response to rhGH treatment might be related to serum cholesterol levels, and the treatment might have a negative impact on serum triglyceride concentration in non-

dialyzed children with CKD. These should entail further research on the interrelations between lipid profile and rhGH treatment.

DISCLOSURE

The authors declare no conflict of interest.

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