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Original research article

Twenty years of growth hormone treatment in dialyzed children in Poland—Results of national multicenter study

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ABSTRACT

Purpose: The aim of the study was to analyze the effect of recombinant human growth hormone (rhGH) therapy and to establish factors influencing growth rate in dialyzed children in Poland.

Methods: We retrospectively analyzed medical records of 81 children with end-stage renal disease (ESRD) on chronic dialysis treated with rhGH for ≥12 months between 1994 and 2014. The following data were recorded: cause of ESRD, dialysis modality, age at the dialysis and rhGH initiation [years]. In addition, growth [cm], [standard deviation score - SDS], body mass index [SDS], skeletal age [years], bone mineral density [SDS], hemoglobin, total protein, albumin, urea, creatinine, calcium, phosphorus, calcium phosphorus product, PTH, and alkaline phosphatase were measured at the baseline and after 12 months.

Results: Growth velocity in 81 children during one-year rhGH treatment was 7.33 ± 2.63 cm (ΔSDS 0.36 ± 0.43). Height SDS increased significantly (-3.31 ± 1.12 vs. -2.94 ± 1.15, $p < 0.001$). Children on peritoneal dialysis (PD) (n = 51) were younger than children on hemodialysis (HD) (n = 30) (9.92 ± 3.72 vs. 12.32 ± 3.11 years, $p = 0.003$). ΔSDS did not differ between PD and HD children (0.40 ± 0.33 vs. 0.30 ± 0.47, $p = 0.311$). Growth velocity (ΔSDS) correlated with age at dialysis initiation ($r = -0.30$, $p = 0.009$), age at rhGH treatment initiation ($r = -0.35$, $p = 0.002$), skeletal age ($r = -0.36$, $p = 0.002$), BMI SDS ($r = -0.27$, $p = 0.019$), and PTH ($r = -0.27$, $p = 0.017$). No correlation between growth velocity and other parameters was observed.

Conclusions: Treatment with rhGH in children with ESRD is effective and safe irrespective of dialysis modality. Early initiation of rhGH therapy is a crucial factor determining response to the treatment in children with ESRD.

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1. Introduction

Growth retardation is one of the major problems in children with chronic kidney disease (CKD) with great impact on future life activity and quality of life. Growth impairment can already begin when glomerular filtration rate (GFR) falls to 50% of normal value and becomes an increasing problem when GFR drops below 25% [1]. According to the United States Renal Data System 2007 annual data report (USRDS), the height and weight of approximately half of the children on dialysis were below the 20th percentile for the normal population [2]. Similarly, The British Association for Paediatric Nephrology (BAPN) 2006 report showed that 61% and 44% of patients on dialysis were below the 10th and 2nd percentile for height, respectively [3]. Also data on longitudinal growth on dialysis show a constant decrease in height standard deviation score (HtSDS) over time. According to The North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) 2006 report, HtSDS decreases from -1.61 to -1.71 and -1.84 after the first and second year of dialysis, respectively, and growth does not differ depending on dialysis modality [4]. NAPRTCS database data show that kidney transplantation improves mean HtSDS only in children who were younger than 5 years of age at the moment of the transplantation [5]. This fact proves the importance of height achievement before the kidney transplant. Approximately 60% of boys and 41% of girls who started renal replacement therapy before 15 years of age attain a final height more than -2 SD (12 cm) below the mean height for healthy adults [6].

Growth impairment in children with CKD is of multifactorial origin. The causes include low caloric intake, bone and mineral disturbances, water-electrolyte imbalance, endocrine disorders, anaemia, metabolic acidosis, and dysregulation of growth hormone (GH) – insulin like-growth factor 1 (IGF1) axis. Although GH plasma levels are usually normal or increased in patients with CKD (due to decreased renal clearance), IGF-1 bioactivity is low. IGF-1 deficiency is caused by tissue GH resistance due to down-regulation of GH receptor leading to decreased IGF-1 synthesis in the liver and growth plate. Moreover, the balance between GH-induced transcriptional activation of IGF-1 and suppressor activity of cytokine signaling (SOCS) is shifted towards SOCS. In addition, patients with advanced CKD are insensitive to IGF-1 due to accumulation of the IGF-binding proteins. Metabolic acidosis and steroid therapy also directly decrease secretion of GH [7,8].

In the last decades the growth of CKD pediatric patients has been constantly improving due to early recognition and treatment of congenital abnormalities of urinary tract that result in slower loss of GFR. Other factors improving final height are intensive nutritional management, adequate treatment of renal osteodystrophy, anemia, and metabolic disorders, and finally, growth hormone therapy.

Disturbances of the GH - IGF-1 axis in children with CKD provide the rationale for the supplementation of growth hormone in these patients. The first study on the use of recombinant human growth hormone (rhGH) in children with chronic renal failure was published in 1988 [9]. Since then, rhGH treatment has been successfully used to improve growth velocity and final growth in children with CKD. The treatment is proven to be safe and effective [7,10]. In Poland, the National Program for rhGH treatment in children with CKD was established in 1994.

The aim of the study is to analyze the effect of rhGH therapy in dialyzed children in 1994–2014 in Poland and to evaluate factors influencing growth rate in these children.

2. Material and methods

2.1. Treatment with rhGH

The study group included 145 children treated with chronic dialysis, qualified to the National Program of rhGH treatment in years 1994–2014.

The inclusion criteria for the National Program of rhGH treatment in children with CKD were [11]:

1) glomerular filtration rate (GFR) below 75 mL/min/1.73m^2 calculated using Schwartz formula [12],
2) height SDS for chronological age and gender below -1.88 SD or growth velocity below -2.0 SD;
3) skeletal age below 12.5 years in boys and below 11.5 years in girls (according to Greulich-Pyle normative values [13]).

The following exclusion criteria were applied:

1) cause of growth retardation other than CKD;
2) glucose metabolism disorder;
3) neoplasms.

The treatment with rhGH was discontinued in the following conditions:

1) receiving renal transplant;
2) severe side effects of the treatment;
3) poor outcome of rhGH treatment defined as growth rate of less than 3 cm/year while on treatment, with exclusion of girls with skeletal age over 14 years and boys with skeletal age over 16 years;
4) achieving skeletal age of 16 years in girls and 18 years in boys.

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

In this study, only the results of rhGH treatment in chronically dialyzed children with end-stage renal disease (ESRD) were analyzed.

The following inclusion criteria were applied in this analysis:

1) CKD stage V (GFR below 15 mL/min./1.73m^2) [12] and chronic dialysis program
2) Treatment with rhGH after inclusion to the National Program of rhGH treatment in children with CKD

RhGH (Genotropin®, Pfizer Inc., New York City, New York, USA, in 1994–2008; Omnitrope®, Novartis International AG, Basel, Switzerland since 2008) was administered subcutaneously every bedtime, in the standard dose of 0.33-0.37 mg/kg body weight/week. All patients were trained by a qualified doctor in the use of growth hormone set before the initiation of the treatment.

2.2. Analyzed parameters

Final analysis was performed in children treated continuously for at least 12 months. The following parameters were analyzed in this group: cause of CKD according to the European Society for Paediatric Nephrology/European Renal Association-European Dialysis and Transplantation Association Registry (ESPN/ERA-EDTA) [14], dialysis modality (hemodialysis [HD] or peritoneal dialysis [PD]), dialysis duration [years], skeletal age at baseline and after every consecutive year of the treatment [years] determined according to Greulich-Pyle normative values [13], 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 (TB BMD) and lumbar spine (L2-L4) BMD expressed in [SDS], and anthropometric measurements performed by professional anthropologist, including: height [cm] and weight [kg] determined as the mean of three independent measurements via Harpenden Wall Mounted Stadiometer (Holtain Ltd., Crosswell, United Kingdom). Age-sex-specific height, weight, and body mass index (BMI) standard deviation scores (SDS) were calculated using growth charts with Polish normative data [15]. In

addition, the following parameters were controlled every three months: anamnesis on possible adverse events, physical examination including blood pressure control, and laboratory tests including: serum creatinine (Crea) [mg/dL], urea [mg/dL], glucose [mg/dL], alkaline phosphatase (ALP) [IU/L], intact parathormone (PTH) [pg/mL], calcium (Ca) [mg/dL], phosphate (P) [mg/dL], calcium-phosphorus product (Ca x P), blood gases, total protein [g/dL], serum albumin [g/dL], cholesterol [mg/dL], and triglycerides [mg/dL]. The reason for the treatment discontinuation were analyzed in all patients.

In addition to rhGH, the following medications were administered in all study participants: oral iron supplements, erythropoiesis stimulating agents, alphacalcidol, and calcium carbonate. The dose was adjusted according to contemporary pediatric guidelines.

2.3. Ethical issues

The research project was approved by Bioethics Committee of Medical University of Warsaw, Warsaw, Poland (date of decision: 19th January 1995). All procedures were performed in accordance with the ethical standards of our institution and the 1964 Declaration of Helsinki as amended on the treatment of human subjects. Informed consent for the treatment with rhGH was obtained from all participants (≥16 years) and their representatives.

2.4. Statistical analysis

Statistical analysis was performed using Dell Statistica 13.0 software (Dell Inc., Aliso Viejo, CA, USA). Normality of data was analyzed using Shapiro-Wilk test. The results were expressed as mean ± SD. Quantitative variables were compared for homogeneity using Student *t*-test (normal distribution) or using Mann-Whitney U test and Wilcoxon test (nonparametric distribution). The numbers of patients in subgroups were compared using chi-square test and Fisher exact test. The relation between growth rate and clinical and biochemical parameters were analyzed using Pearson correlation or Spearman's rank correlation, when appropriate. P value of < 0.05 was considered statistically significant.

3. Results

3.1. Characteristics of the study group

Between 1994 and 2014, a total of 145 Polish children (46 girls and 99 boys) with stage 5 CKD treated with chronic dialysis were qualified to rhGH treatment. In 64 (44.1%) of them, rhGH treatment was discontinued before 12 months. The causes of early discontinuation were: kidney transplantation (n = 27, 42.1%), non-compliance (n = 13, 20.3%), elevated PTH > [500 pg/mL] (n = 12, 18.8%), adverse events (n = 8, 12.5%) (poor control of hypertension in 6, diabetes in 1, and seizures in 1 patient), poor response to the treatment (n = 3, 4.7%) (2 children were on steroid therapy, 1 had nail-patella syndrome), and complications of dialysis (n = 1,1.6%). Further analysis was performed in a subgroup of 81 patients (25 girls, 56 boys) who were treated for at least 12 months.

Baseline characteristics of these 81 children is presented in Table 1. More than a half of the study participants were treated with peritoneal dialysis. The most common causes of CKD were congenital anomalies of kidney and urinary tract and chronic glomerulonephritis. The age at chronic kidney disease diagnosis did not differ between children on PD and HD but age at the initiation of both dialysis and rhGH therapy were significantly lower in patients on PD compared to those on HD. Mean time between the initiation of dialysis and introduction of rhGH treatment was approx. 2 years. There was no difference in skeletal age between PD and HD subgroups.

The study group consisted of 7 (8.64%) children below 5 years of age, 21 (25.93%) aged 5–10 years, 44 (54.32%) aged 10–15 years, and 9 (11.11%) over 15 years. Mean height SDS at the beginning of the rhGH therapy was the lowest in children over 15 years old (-4.18 ± 1.63); mean HtSDS was -4.06 ± 1.34 in children under 5 years, -3.24 ± 0.91 in children aged 5–10 years, and -3.04 ± 0.93 in children aged 10–15 years. The differences were not statistically significant (p = 0.509) (Fig. 1).

3.2. Duration of the treatment and causes of the treatment discontinuation

Mean duration of rhGH treatment in the group of 81 dialyzed children was 25.68 ± 12.03 months (range from 12.13 to 64.80 months). In this group, 24 (29.6%), 36 (44.4%), 12 (14.8%), 7 (8.6%), and 2 (2.6%) children were treated for 1, 2, 3, 4, and 5 years, respectively.

The causes of discontinuation of rhGH therapy were: kidney transplantation in 34 (41.98%), poor response to the treatment in 12 (14.81%), increase in PTH over 500 pg/mL in 9 (11.11%), achievement of satisfactory height in 5 (6.17%), orthopedic complications in 4 (4.94%), reluctance to the treatment (non-compliance) in 4 (2.47%), arterial hypertension in 3 (3.70%), seizures in 1 (1.23%), dialysis

Table 1
Clinical characteristics of the study group.

Analyzed parameter	All patients	PD	HD	P[1]
Number of patients (%)	81 (100%)	51 (62.96%)	30 (37.04%)	–
Female/male n (%)	25/56 (30.86%/69.14%)	15/36 (29.41%/70.59%)	10/20 (33.33%/66.67%)	NS (P = 0.805)
Etiology of ESRD	32 (39.51)	19 (37.25)	13 (43.33)	NS
Congenital anomalies of urinary tract	24 (29.63)	16 (31.37)	8 (26.67)	(P = 0.794)
Glomerulonephritis	10 (12.35)	7 (13.73)	3 (10.00)	
Cystic kidney diseases	7 (8.64)	4 (7.84)	3 (10.00)	
Haemolytic uremic syndrome	5 (6.17)	4 (7.84)	1 (3.33)	
Hereditary kidney disease	3 (3.70)	1 (1.96)	2 (6.67)	
Unknown				
Age of CKD diagnosis [years]	5.09 ± 4.72	4.68 ± 4.28	6.03 ± 5.61	NS (P = 0.275)
Age of dialysis initiation [years]	8.55 ± 3.98	7.78 ± 4.09	9.93 ± 3.45	P = 0.024
Age at onset of rhGH treatment [years]	10.81 ± 3.68	9.92 ± 3.72	12.32 ± 3.11	P = 0.003
Skeletal age at onset of rhGH treatment	7.76 ± 3.22	7.30 ± 3.22	8.54 ± 3.13	NS (P = 0.105)

PD – peritoneal dialysis, HD – hemodialysis, NS – not significant, ESRD – end-stage renal disease, CKD – chronic kidney disease, rhGH – recombinant human growth hormone.
[1] - HD vs. PD.

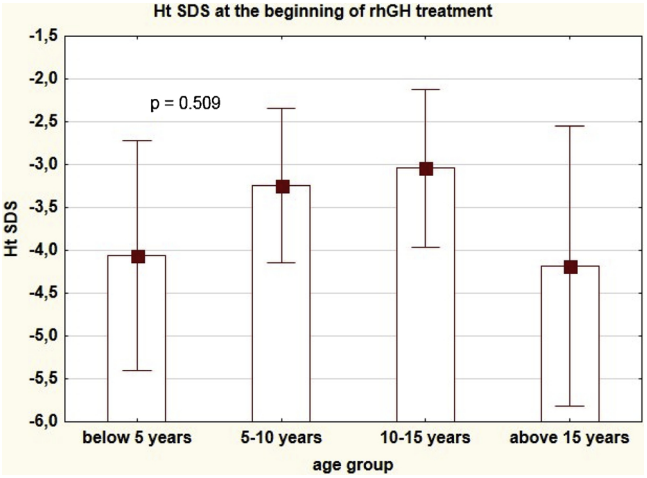

Fig. 1. Height SDS at the beginning of the rhGH treatment in the age groups. (Ht SDS – height standard deviation score, rhGH – recombinant human growth hormone).

complications in 1 (1.23%), and liver transplantation in 1 patient (1.23%). The reason for discontinuation in 7 (8.64%) children was not documented (Fig. 2).

The subgroup of children with poor treatment response (non-responders, n = 12) was significantly older compared to the rest of the study group (13.88 ± 2.70 vs. 10.25 ± 3.52 [years], p = 0.001).

3.3. The results of rhGH treatment

The results of rhGH therapy in the first year of the treatment are presented in Table 2. At baseline, no significant difference in height expressed as SDS between children treated with PD and HD was observed. Similarly, after one-year rhGH treatment, height expressed in [SDS] did not differ between the groups. Height expressed both in [cm] and in [SDS] increased significantly during one-year rhGH treatment in the whole group and in the PD subgroup, whereas in HD subgroup the difference was significant only when height was expressed in SDS. Growth velocity in [cm] was significantly faster in children on PD but ΔSDS 0–12 did not differ between the groups.

The analysis of skeletal age and bone mineral density is presented in Table 3.

In the subgroup of 44 children with complete analysis of skeletal age (n = 44, PD/HD 12/32) at baseline, no significant differences in chronological and skeletal age between patients on PD and HD were found. At baseline, skeletal age was significantly delayed in all participants. After 12 months, we found no differences in skeletal age between children on PD and HD. In the study group as well as in subgroup analysis (HD/PD), although skeletal age advanced parallelly to chronological age during one year rhGH treatment, it still remained significantly delayed compared to chronological age.

In the subgroup of 32 children with complete analysis of bone mineral density (n = 32, PD/HD 13/19), no significant differences in chronological age and bone mineral density between PD and HD patients was found, both at baseline and after 12 months of rhGH treatment. In 13 children treated with HD, total body BMD SDS worsened significantly during 12-month rhGH therapy (p = 0.022).

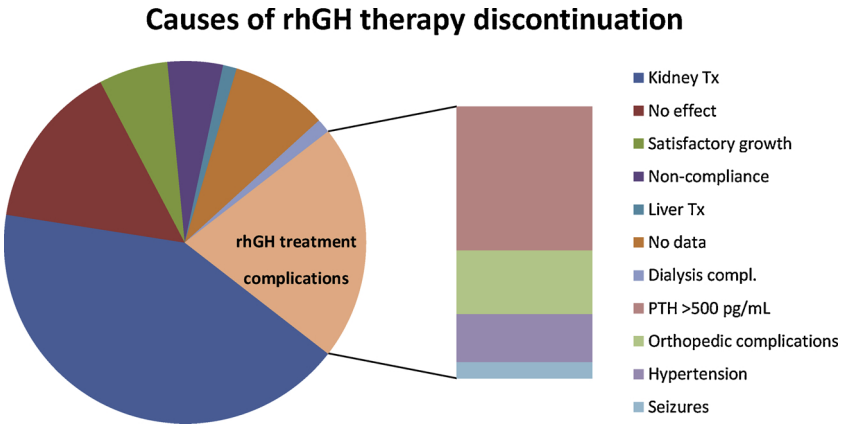

Fig. 2. Causes of rhGH therapy discontinuation.
(rhGH – recombinant human growth hormone, Tx – transplantation, PTH – parathormone).

Table 2
Results of growth hormone treatment in dialysed children treated with rhGH.

	All patients	PD	HD	P[1]
Height 0 [cm]	122.50 ± 18.84[2]	118.78 ± 20.00[4]	128.84 ± 14.96	P = 0.019
Height 0 [SDS]	−3.31 ± 1.12[3]	−3.22 ± 1.12[5]	−3.45 ± 1.11[6]	NS (P = 0.363)
Height 12 [cm]	129.83 ± 17.78[2]	126.57 ± 19.03[4]	135.39 ± 14.04	P = 0.030
Height 12 [SDS]	−2.94 ± 1.15[3]	−2.82 ± 1.15[5]	−3.15 ± 1.14[6]	P = 0.210
Growth velocity 0-12 months [cm]	7.33 ± 2.63	7.79 ± 2.79	6.55 ± 2.21	P = 0.039
ΔSDS 0-12 months	0.36 ± 0.43	0.40 ± 0.33	0.30 ± 0.47	NS (P = 0.311)

PD – peritoneal dialysis, HD – hemodialysis, NS – not significant, SDS – standard deviation score.
[1] – PD vs. HD.
[2] – p = 0.012, [3] – p < 0.001, [4] – p = 0.046, [5] – p < 0.001, [6] – p < 0.001.

Table 3
Skeletal age and bone mineral density in dialysed children treated with rhGH.

	All patients	PD	HD	P[1]
Skeletal age				
Number of patients	44	32	12	–
Age at onset of rhGH treatment	10.13 ± 3.44[2]	9.75 ± 3.45[3]	11.14 ± 3.36[4]	NS (P = 0.238)
Skeletal age at onset of rhGH treatment	7.10 ± 2.75[2,5]	6.95 ± 2.64[3,6]	7.48 ± 3.12[4,7]	NS (P = 0.576)
Age after one-year rhGH treatment	11.13 ± 3.44[8]	10.75 ± 3.45[9]	12.14 ± 3.36[10]	NS (P = 0.238)
Skeletal age after one-year rhGH treatment	7.85 ± 2.82[5,8]	7.73 ± 2.60[9]	8.17 ± 3.46[10]	NS (P = 0.650)
Bone mineral density				
Number of patients	32	19	13	–
Age at onset of rhGH treatment	11.01 ± 2.70	10.79 ± 2.57	11.34 ± 2.94	NS (P = 0.580)
TB BMD "0" SDS	–0.84 ± 0.88	–0.96 ± 0.86	–0.66 ± 0.92[11]	NS (P = 0.349)
L2-L4 BMD "0" SDS	–1.20 ± 1.54	–1.49 ± 1.63	–0.78 ± 1.34	NS (P = 0.200)
TB BMD "12" SDS	–1.06 ± 1.14	–0.96 ± 0.99	–1.21 ± 1.36[11]	NS (P = 0.566)
L2-L4 BMD "12" SDS	–0.88 ± 1.70	–1.03 ± 1.81	–0.65 ± 1.56	NS (P = 0.542)

PD – peritoneal dialysis, HD – hemodialysis, NS – not significant, rhGH – recombinant human growth hormone, TB – total body, BMD – bone mineral density.
[1]PD vs. HD.
[2]$p < 0.001$, [3] – $p < 0.001$, [4] – $p < 0.001$, [5] – $p < 0.001$, [6] – $p = 0.006$, [7] – $p < 0.001$, [8] – $p < 0.001$, [9] – $p < 0.001$, [10] – $p < 0.001$, [11] – $p = 0.022$.

Table 4
Mean annual biochemical results in children on PD and HD treated with rhGH.

	PD	HD	P
Total protein [g/dL]	6.15 ± 0.63	6.65 ± 0.53	P = 0.001
Serum albumin [g/dL]	3.37 ± 0.50	3.90 ± 0.43	P < 0.001
Cholesterol [mg/dL]	229.90 ± 54.63	208.35 ± 59.20	NS
Triglycerides [mg/dL]	203.47 ± 83.67	178.65 ± 78.87	NS
Hemoglobin [g/dL]	10.59 ± 1.04	9.93 ± 1.09	P = 0.009
PTH [pg/mL]	168.06 ± 119.75	177.28 ± 132.12	NS
ALP [U/L]	366.28 ± 162.37	326.23 ± 209.44	NS
Calcium [mg/dL]	9.38 ± 0.99	9.56 ± 0.83	NS
Phosphate [mg/dL]	5.02 ± 0.93	5.39 ± 0.97	NS
CaxP [mg^2/dL^2]	47.37 ± 11.81	50.55 ± 11.15	NS
HCO3- [mmol/L]	22.42 ± 2.97	22.92 ± 4.18	NS
Base Excess [mmol/L]	–2.04 ± 3.47	–2.31 ± 4.28	NS

PD – peritoneal dialysis, HD – hemodialysis, NS – not significant, PTH – parathormone, ALP – alkaline phosphatase, CaxP – calcium phosphate product.

The analysis of laboratory tests results obtained within the first year of rhGH treatment in PD and HD groups are presented in Table 4.

3.4. Factors influencing the response to rhGH treatment

The analysis of growth velocity in age subgroups revealed that mean growth velocity in the first year of rhGH treatment in the youngest children (0–5 years) was 9.80 ± 3.09 cm (ΔSDS 0.73 ± 0.69), compared to 8.20 ± 2.01 cm (ΔSDS 0.55 ± 0.25) in the group aged 5–10 years, 7.18 ± 2.41 cm (ΔSDS 0.23 ± 0.41), and 4.10 ± 1.23 cm (ΔSDS 0.31 ± 0.31) in children aged 10–15 and over 15 years of life, respectively ($p < 0.001$ and $p = 0.002$ for growth velocity in [cm] and SDS, respectively). Post-hoc analysis by Tukey test revealed that growth velocity [cm] in the oldest subgroup was significantly slower compared to the velocity observed in the remaining patients (children < 5 years: $p < 0.001$, children aged 5–10 years: $p = 0.002$, children aged 10–15 years $p = 0.027$). ΔSDS 0–12 differed significantly only between children aged 5–10 years and 10–15 years ($p = 0.047$) (Fig. 3).

Mean BMI at the beginning of the treatment was 16.08 ± 2.46 kg/m^2 (BMI SDS -0.31 ± 0.95) in the entire study population, and 16.58 ± 2.66 (BMI SDS -0.01 ± 0.80) and 15.79 ± 2.30 kg/m^2 (BMI SDS -0.49 ± 1.0) in HD and PD subgroups, respectively. After one year of the treatment, mean BMI was 16.55 ± 2.45 kg/m^2 (BMI SDS -0.14 ± 0.78) in the entire study population, and 16.98 ± 2.72 (BMI SDS 0.00 ± 0.75) and 16.29 ± 2.26 kg/m^2 (BMI SDS -0,23 ± 0.79) in HD and PD groups, respectively. The differences between children on HD and PD in terms of BMI and BMI SDS were not significant (at baseline: $p = 0.169$ and $p = 0.08$, after one-year treatment: $p = 0.257$ and $p = 0.388$, in HD and PD groups, respectively). In the entire study group, both BMI and BMI SDS increased significantly ($p < 0.001$ and $p = 0.028$, respectively). Similarly, significant increase in BMI and BMI SDS was observed in PD patients ($p < 0.001$ and $p = 0.004$, respectively) but not in HD patients ($p = 0.221$ and $p = 0.755$, respectively).

In the study group, growth velocity during the first year of the treatment (Δ0–12 SDS) correlated negatively with: age of dialysis initiation ($r = -0.30$, $p = 0.009$), chronological and skeletal age at rhGH initiation ($r = -0.35$, $p = 0.002$ and $r = -0.36$, $p = 0.002$, respectively), and BMI SDS ($r = -0.27$, $p = 0.019$) (Fig. 4). We found no significant correlation between growth velocity (Δ0–12 HtSDS) and sex, cause of CKD, HtSDS at rhGH initiation, bone mineral density parameters, mean annual hemoglobin, total protein, albumin, urea, creatinine, calcium, phosphate, Ca x P, PTH, and alkaline phosphatase. We found only a negative correlation between Δ0–12 SDS and PTH at baseline ($r = -0.27$, $p = 0.017$)

In the group of 57 children treated for at least two years, growth velocity in the second year was: 6.26 ± 2.42 [cm] while Δ12-24 SDS was 0.08 ± 0.53. Growth velocity and Δ12-24 SDS were significantly lower in the second year of the treatment compared to the first year ($p < 0.001$ and $p = 0.010$, respectively). Growth velocity and Δ12-24 SDS in the second year of the rhGH treatment did not differ significantly between PD and HD groups (6.45 ± 2.36 vs. 6.01 ± 2.55 [cm], $p = 0.593$ and 0.10 ± 0.65 vs. 0.04 ± 0.30, $p = 0.732$, respectively).

3.5. The comparison of the first decade of rhGH treatment in Poland with later experience

In the first decade of program implementation (1994–2003), a total of 94 children on chronic RRT were enrolled to rhGH treatment in Poland, whereas in a second decade, 51 children were enrolled.

Sixty and 21 dialyzed children were treated with rhGH for more than 12 months in the first and second decade of the program, respectively. The clinical data and response to rhGH therapy in the first year of the treatment in both groups are presented in Table 5. The children treated in 1994–2003 and 2004–2014 did not differ significantly in terms of dialysis modality, sex, age at CKD diagnosis, age at dialysis and rhGH treatment initiation, skeletal age, and time between CKD diagnosis and initiation of rhGH therapy.

At baseline and after 12 months of therapy, no differences between the groups in height expressed both in [cm] and SDS were observed. Also, growth velocity and ΔSDS did not differ significantly between

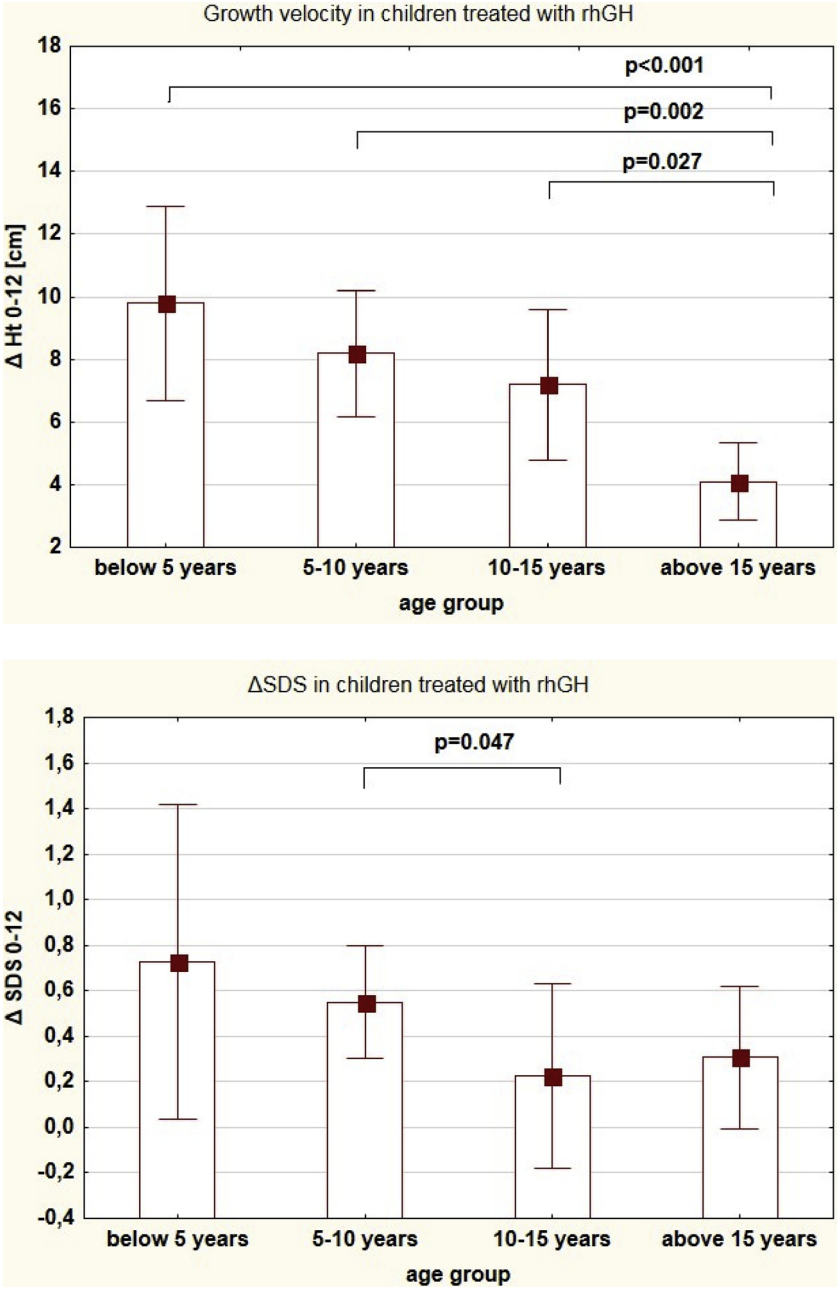

Fig. 3. Growth velocity [cm] and Δ height SDS in age groups in children treated with rhGH.
(rhGH – recombinant human growth hormone, SDS – height standard deviation score).

children treated in both analyzed periods. The analysis of biochemical parameters revealed that children treated in the first period were characterized by significantly lower values of hemoglobin, PTH, Ca, and Ca x P compared to those treated in the second period.

4. Discussion

This study summarizes 20-year Polish experience in rhGH treatment of growth retarded dialyzed children with chronic kidney disease. Our results proved that treatment with rhGH is effective in children with end-stage renal disease, irrespective of dialysis modality. We have also found that the key determinant of satisfactory response to rhGH therapy in the first year of the treatment is patient's age – the response was inversely correlated to patient's age, skeletal age, and age of dialysis initiation. On the contrary, we found no significant influence of sex, primary kidney disease, dialysis modality, hemoglobin, protein, and lipid parameters. In addition, we confirmed in Polish pediatric population that response to the treatment is more pronounced in the first year. No significant differences in the treatment outcome between the first and the second decade of the program were observed.

Mean age-sex-specific height SDS at baseline was < -3. Considering the fact, that the inclusion criteria for the rhGH therapy in Poland is HtSDS < -1.88 SD, rhGH therapy initiation is delayed in Polish patients. Similarly, mean time from the diagnosis of CKD to the initiation of rhGh therapy was 5.38 ± 3.91 years and did not change significantly between the first and the second decade of the program. To improve program implementation and its results, rhGH treatment should be popularized among Polish pediatric nephrologists as an established, safe, and effective method of growth and quality of life improvement in children with end-stage renal disease.

Growth velocity in the first year of the treatment is comparable to previous studies from other countries. Mean growth velocity on rhGH

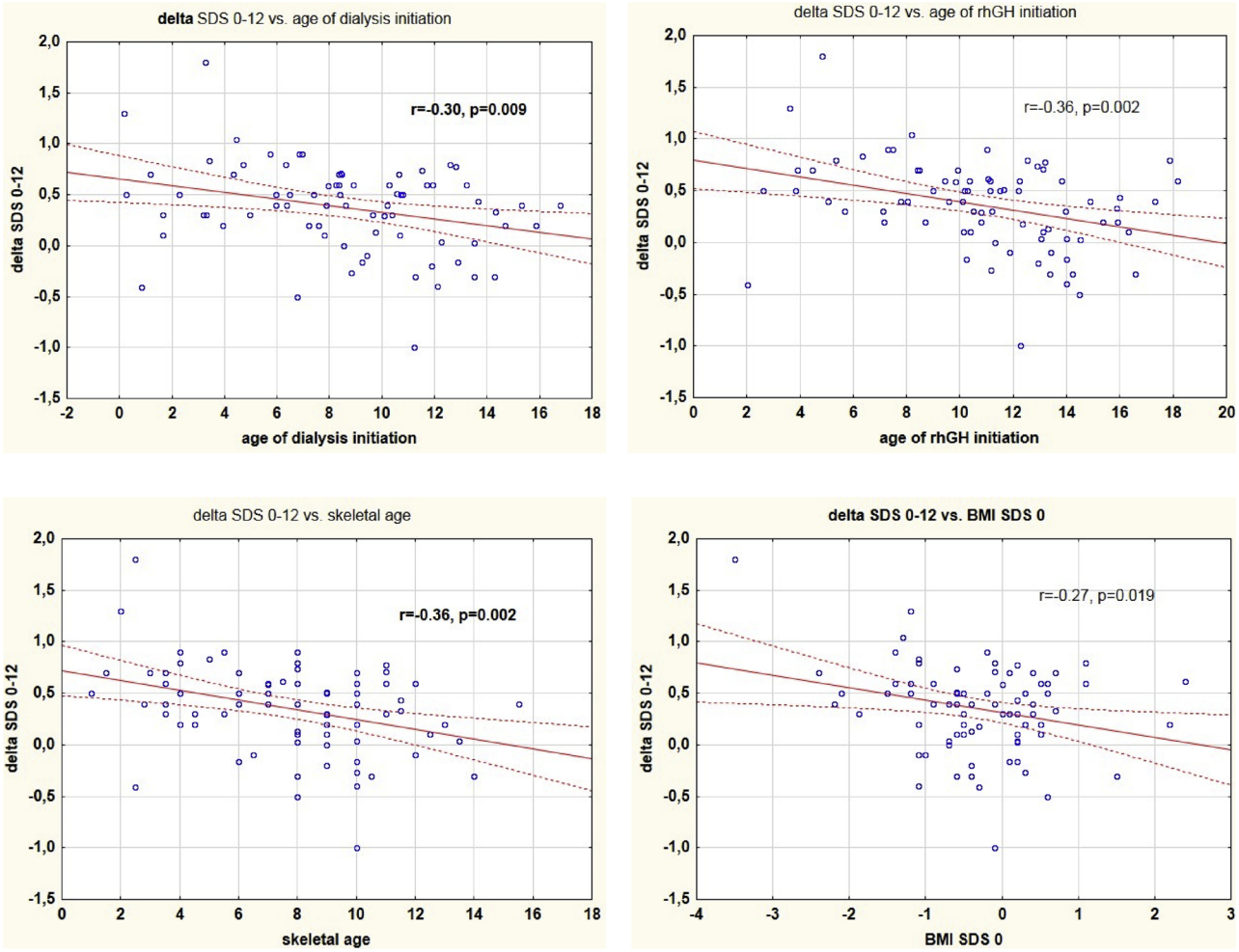

Fig. 4. The relation between age of dialysis initiation, age of rhGH initiation, skeletal age, BMI and Δ height SDS.
(rhGH – recombinant human growth hormone, SDS – height standard deviation score, BMI – body mass index).

therapy in our study group was 7.33 ± 2.63 cm during the first year of the treatment. Similar effect of rhGH at 1 IU/kg/week was described in dialyzed children by Haffner et al. (7.2 cm/year) [16] and Kawaguchi et al. (8.3 cm/year) [17].

The response to rhGH therapy was influenced by age at dialysis initiation, age at initiation of rhGH therapy, skeletal age, BMI, and PTH level. According to the literature, younger age, lower HtSDS, greater target-height deficit, lower growth velocity, and greater skeletal age retardation at the initiation of rhGH therapy, along with the target height and hereditary kidney disease as an underlying renal disorder, are positively associated with the final height achieved in children with CKD treated with rhGH. Other determinants of poor response to the treatment included: advanced age at the start of the therapy, initiation after the onset of puberty, the duration of dialysis, steroid therapy and multisystemic syndromes (e.g. Schimke syndrome or nail-patella syndrome) [16,18–20]. Numerous reports revealed that long-term growth response to rhGH was much more pronounced in children on conservative treatment than in children on dialysis [16,21,22]. In children in pre-dialysis stages of CKD, the response positively correlated with GFR [20].

The patients with poor response to rhGH who discontinued the treatment were older compared to responders. This finding highlights the necessity for early qualification for the therapy.

The study group included only 7 children below 5 years. In these youngest children, similarly to the previous findings, we observed poor HtSDS at the beginning of the rhGH treatment. According to the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) report including 5615 children with a GFR < 75 ml/min/1.73m^2 treated between 1994 and 2004, growth retardation is the most pronounced in the youngest children [23]. In our cohort, the response to rhGH in the youngest children was the best among all age groups but due to small number of patients the differences did not reach statistical significance.

The youngest patient enrolled to our study was 2 years old. Growth during the first years of life mainly depends on nutrition, which exerts greater impact on growth than the GH IGF-1 axis. Optimization of nutritional intake (using special formulas, nasogastric tubes or gastrostomy) is therefore considered as the most important factor in achieving appropriate height in these patients. Nevertheless, even intensive nutrition does not result in complete catch up growth, so rhGH has been used in trials in infants. These studies showed a significant improvement in growth without change in GFR, bone maturation, plasma lipids, calcium-phosphorus metabolism or serious side effects [24–27].

We observed a significant increase in BMI SDS during one-year treatment, suggesting a positive impact of rhGH supplementation on nutritional status. Similarly, increase in BMI SDS during rhGH therapy was found in children with idiopathic growth hormone deficiency, small for gestational age, and Turner syndrome [28]. We have also revealed a weak negative correlation between Δ height SDS and BMI SDS at baseline. However, this observation was not confirmed in the study of German children with CKD treated with rhGH [16,20].

The growth velocity defined as ΔSDS was significantly higher within the first year of treatment in comparison to the second year. This observation is consistent with the results obtained by other

Table 5
Comparison of clinical parameters and response to rhGH in children treated with rhGH for at least 12 months in years 1994–2003 and 2003-2014.

Analyzed parameter	Years of the treatment		P[1]
	1994–2003	2003–2014	
Number of patients (%)	60 (74.07%)	21 (25,93%)	–
Peritoneal dialysis/hemodialysis (%)	36/24 (60.00%/40.00%)	15/6 (71.43%/28.57%)	NS
Male/female (%)	39/21 (65.00%/35.00%)	17/4 (80.95%/19.05%)	NS
Age of CKD diagnosis [years]	5.12 ± 4.63	5.04 ± 5.04	NS
Age of dialysis initiation [years]	8.88 ± 3.53	7.65 ± 5.02	NS
Age at onset of rhGH treatment [years]	11.10 ± 2.99	9.95 ± 5.17	NS
Skeletal age at onset of rhGH treatment [years]	7.96 ± 2.83	7.18 ± 4.22	NS
Height 0 [cm]	123.55 ± 15.55	119.51 ± 26.33	NS
Height 0 [SDS]	–3.27 ± 1.01	–3.40 ± 1.38	NS
Height 12 [cm]	131.09 ± 14.71	126.24 ± 24.66	NS
Height 12 [SDS]	–2.93 ± 1.06	–3.00 ± 1.40	NS
Growth velocity 0-12 months [cm]	7.54 ± 2.42	6.73 ± 3.16	NS
ΔSDS 0-12 months	0.35 ± 0.44	0.41 ± 0.38	NS
Total protein [g/dL]	6.32 ± 0.65	6.45 ± 0.61	NS
Serum albumin [g/dL]	3.52 ± 0.56	3.78 ± 0.43	NS
Cholesterol [mg/dL]	225.34 ± 52.24	212.88 ± 69.56	NS
Triglycerides [mg/dL]	202.22 ± 86.24	173.34 ± 67.73	NS
Hemoglobin [g/dL]	10.13 ± 0.89	10.92 ± 1.40	P = 0.004
PTH [pg/mL]	158.50 ± 123.24	208.68 ± 119.71	P = 0.046
ALP [U/L]	363.30 ± 182.22	315.83 ± 173.25	NS
Calcium [mg/dL]	9.23 ± 0.90	10.05 ± 0.77	P < 0.001
Phosphate [mg/dL]	5.02 ± 0.70	5.51 ± 1.43	NS
CaxP [mg^2/dL^2]	46.06 ± 8.93	55.61 ± 15.32	P = 0.001
HCO3- [mmol/L]	22.31 ± 3.06	23.43 ± 4.34	NS
Base Excess [mmol/L]	–2.23 ± 3.30	–1.74 ± 4.88	NS

NS – not significant, CKD – chronic kidney disease, rhGH – recombinant human growth hormone, SDS – standard deviation score, PTH – parathormone, ALP – alkaline phosphatase, CaxP – calcium phosphate product.
[1]1994–2003 vs. 2004–2014.

authors. The results of 24-month study by Fine et al. and Berard et al. showed that patients treated with rhGH had greater growth velocity during the first than the second year of treatment [10,29]. The longer the follow-up period, the higher risk of drop out, change of treatment modality, and progression into puberty. Nevertheless, many studies demonstrate a positive response to rhGH for up to 8 years of the treatment [18,29,30].

The analysis of skeletal age changes in our patients treated with rhGH showed that bone maturation was appropriate and did not lead to disproportionate acceleration of bone age. If rhGH advanced bone age quicker than chronological age, this would lead to an initial acceleration of growth, but no potential for improvement of final height. Similarly to our observations, many studies have demonstrated that bone age does not accelerate and final height is not limited [10,18,31,32].

The results of bone mineral density measurement during the first year were inconsistent. Except for significant decrease in total body BMD Z-score in a small group of children on hemodialysis, we did not observe any negative influence of rhGH therapy on bone composition. The surprising finding in HD children could result from small sample size. The worsening of BMD in HD group could also be caused by low compliance in adolescent patients regarding diet and regular medication intake (e.g. calcium carbonate). The increased requirements for calcium and phosphate due to accelerated growth on rhGH therapy can theoretically lead to hyperparathyroidism and negative bone alterations. Children treated with rhGH should have their calcium-phopsphorus metabolism evaluated on regular basis and, according to Polish National Program, rhGH therapy must be ceased temporarily once PTH reaches 500 pg/mL.

The studies evaluating bone mineralization by DEXA in children treated with rhGH bring inconsistent results. One study showed an improvement in total bone mineral mass and no change in bone mineral density (BMD) [33]; in the second study, lumbar spine BMD increased, whereas total body BMD did not change [34]. The analysis of bone metabolism markers in CKD patients from 4C Study showed that rhGH induced an osteoanabolic pattern and normalized osteocyte activity. The level of osteocyte markers, cFGF23 (c-terminal fibroblast growth factor 23) and sclerostin, positively correlated with HtSDS, while the level of bone turnover markers, i.e. bone alkaline phosphatase (BAP) and tartrate-resistant acid phosphatase (TRAP), positively correlated with height velocity [35]. The study of tetracycline-labeled bone biopsies from our center have shown that low bone turnover and high mineralization densities are normalized by rhGH [36]. Another study of bone biopsies from pediatric dialysis patients showed that bone formation increased on rhGH therapy, irrespective of underlying bone abnormalities [37].

No impact of calcium-phosphorus metabolism parameters on growth of dialyzed children treated with rhGH was found, except a weak negative correlation between ΔHtSDS and parathormone at baseline. The desired PTH level for children with ESRD is still under debate. Both European and American guidelines recommend higher PTH concentrations [38,39], as elevated concentrations are required to maintain normal bone turnover in dialyzed patients [40]. The need for supraphysiologic PTH concentrations have been justified with the concept of “skeletal resistance to PTH” with unclear mechanism. In addition, no correlation between ΔHtSDS and PTH level in dialyzed children without rhGH treatment was observed [41,42]. On the other hand, the analysis of patients from IPPN (International Pediatric PD Network) revealed weak inverse correlation between ΔHtSDS and PTH and patients with PTH > 500 ng/mL exhibited a significant loss in height SDS compared to children with lower PTH levels [43]. In addition, the analysis of rhGH therapy results in 33 dialyzed children showed that the therapy improved height, irrespective of underlying bone histologic features [37].

No significant correlation was found between lipid parameters and ΔHtSDS during first year of rhGH therapy. Children with ESRD, especially those treated with chronic peritoneal dialysis exhibit severe lipid abnormalities, including elevation of total cholesterol, LDL (low density

lipoprotein) cholesterol and triglycerides with reduced level of HDL (high density lipoprotein) cholesterol [44,45]. Jędrzejowski et al. showed that administration of rhGH to children treated with peritoneal dialysis resulted in transient increase of serum triglycerides without significant effect on other serum lipids levels [46].

The comparison of the first decade of rhGH treatment and the following period revealed similar outcome of the therapy, despite substantial biochemical differences between the cohorts. Higher hemoglobin level is a clear consequence of easier access to erythropoiesis-stimulating agents. We think that poor calcium-phosphorus parameters in children treated after 2003 could be caused by excess consumption of highly-processed rich-in-phosphate food by children and adolescents.

Twenty five-year experience in the use of rhGH in children with different stages of CKD has showed that the therapy is safe [7]. Our analysis also confirmed the safety of the procedure in the dialyzed children. Adverse events were rare and reversible after treatment cessation. Many of the anticipated potential side effects (e.g. neoplasms) have not occurred or occurred sporadically (e.g. benign intracranial hypertension or slipped capital femoral epiphysis).

The main limitation of our study is lack of data on bone mineral density and skeletal age in some of our patients and low number of patients treated for 3 years and longer. The missing data could not have been completed due to retrospective nature of the study. Decreasing number of long-term treated patients is caused by CKD complications or is a consequence of the successful outcomes of kidney transplantation program in our country.

5. Conclusions

Treatment with rhGH in children with ESRD is effective and safe irrespective of dialysis modality. Early initiation of rhGH therapy is a crucial factor determining response to the treatment in children with ESRD.

Conflict of interests

The authors declare no conflict of interest.

Financial disclosure

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The author contribution

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Manuscript preparation: Dominika Adamczuk, Beata Leszczyńska, Piotr Skrzypczyk, Małgorzata Pańczyk-Tomaszewska.

Literature search: Dominika Adamczuk, Beata Leszczyńska, Piotr Skrzypczyk, Małgorzata Pańczyk-Tomaszewska.

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