Nutrition and growth in European children with end-stage renal disease

Bonthuis, M.

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CONSIDERABLE VARIATIONS IN GROWTH HORMONE POLICIES IN PAEDIATRIC END-STAGE RENAL DISEASE ACROSS 38 EUROPEAN COUNTRIES- A REPORT FROM THE ESPN/ERA-EDTA REGISTRY

Maike van Huis, **Marjolein Bonthuis**, Kitty J Jager, Franz Schaefer, Karlijn J van Stralen, Jaap W Groothoff

In progress

Background: Growth retardation is a major complication of paediatric end-stage renal disease (ESRD) with serious impact on adult life. Growth retardation is potentially treatable with recombinant growth hormone (rGH). In this study, we aimed to quantify the variation in rGH policies and actual provided care in this patient group across Europe.

Methods: A structured questionnaire on rGH policy was sent to renal registry representatives of 38 European countries. Data on height and actual use of rGH on children with ESRD aged less than 18 years were retrieved from the ESPN/ERA-EDTA Registry.

Results: In 22 (78%) out of 28 responding countries rGH is reimbursed in children with ESRD. However, the specific conditions for reimbursement, such as the minimum age (range 0-60 months), the maximum age (range 14 to no limit), as well as CKD stage (range 1-5) vary considerably. Mean height standard deviation scores (SDS) at RRT [95% CI] were significantly higher in countries where rGH was reimbursed -1.80 [-2.06; -1.53] compared with countries in which it was not reimbursed (-2.34 [-2.49;-2.18], $P<0.001$). Comparison of the mean height SDS at the start of RRT and final height SDS yielded similar results. Among the 13 countries for which both data on actual rGH use between 2007 and 2011 and data from the questionnaire was available, 30.1% of dialysis and 42.3% of transplanted patients had a short stature, while 24.1% and 7.6% of those children used rGH, respectively.

Conclusion: There is considerable variation in rGH policies across Europe which is associated with (final) height. In addition, not all patients that would be eligible according to their national policy, are receiving rGH. Therefore, differences in short stature in paediatric patients with ESRD among European countries may not only be explained by differences in access to growth hormone therapy, but also by doctors' and patients' attitudes towards rGH therapy.

ABSTRACT

INTRODUCTION

Recent data have shown that currently 43% of patients with childhood onset end-stage renal disease (ESRD) do not achieve an adult height within the normal range [1]. At the same time short stature affects health outcomes, especially health-related quality of life and psychosocial development [2–6]. Longitudinal growth can therefore be considered as a marker of quality of paediatric renal care.
Treatment of growth failure in paediatric ESRD consists of correcting any nutritional, water and salt deficiencies as well as metabolic abnormalities. In case of persistent growth failure, recombinant Growth Hormone (rGH) might be indicated [7]. Although rGH use is found to be safe and efficient in children with ESRD [8–12], its use has been reported as limited [13].

Although some national guidelines are available, general European guidelines on rGH use in paediatric ESRD are lacking and therefore the care provided to growth retarded children could differ between countries. Previous studies have highlighted the variation in management of children with ESRD between European countries [14–16]. As the use of rGH is expensive, reimbursement and subsequently the possibility to prescribe rGH to every patient may also vary per country. These factors may lead to different policies and actual provided care per country, which could possibly explain the variation in the extent of growth retardation among the European countries [17]. Furthermore, because of the lack of international guidelines, variation might occur in the Chronic Kidney Disease (CKD) stage in which rGH therapy is initiated –only at the time of dialysis or already in CKD stage 2-4 -, in the age range in which rGH is being provided, as well as in the measures used to identify growth retardation, for example short stature or a decline in growth velocity.

In this study we aimed to describe the variation in growth hormone policies in paediatric nephrology patients across European countries and to relate these policies to outcome, including height at start of renal replacement therapy (RRT), height during childhood RRT and final height by using data from the ESPN/ERA-EDTA registry.

METHODS

Data sources

We developed a structured questionnaire on growth hormone policies in European paediatric renal care. To ensure content validity we used input from four paediatric nephrologists from different countries. An overview of all questions in the questionnaire is shown in Appendix 1.
The questionnaire was sent to the paediatric renal registry representatives in 38 countries in the European region.

Data on growth of children on RRT were retrieved from the ESPN/ERA-EDTA Registry. Within this registry demographic data on all European children starting RRT are collected annually. Moreover, a variable set of data on anthropometric, clinical, and medication related parameters is collected [18]. For this study height data collected from 2007 onwards were used.

Definition of variables

Standard deviation scores (SDS) for height were calculated according to recent national growth charts whenever available or according to the recently developed Northern and Southern European growth charts [17]: SDS = (individual patient height – mean height for age- and sex-related healthy peers)/ SD of height for age- and sex-related healthy peers.
Macro-economic indicators were obtained from the World bank [19] and expressed as Gross Domestic Product (GDP) per capita. We compared national growth hormone policies with actual use of rGH and with the percentage of children with a short stature defined as height SDS of -2 or below. Within the registry data on growth hormone use are limited and no data are available on the duration of rGH treatment. Therefore, to study the effect of actual growth hormone use we calculated the percentage of patients with a short stature that used growth hormone (yes/no) during five years of follow-up (2007-2012, whenever available). Data on actual rGH use of each specific country was included in the analyses when data on both rGH use and growth parameters was available for at least 50% of the patients. The paediatric renal registry representatives were asked in a qualitative manner to explain any differences between the actual provided care of rGH and the number of eligible patient for rGH.

Statistical analysis

In the ESPN/ERA-EDTA registry the number of height measurements differed largely by patient and country. To correct for the correlation of measurements within the same patient we used linear mixed models. Only countries for which height data were available for a sufficient number of patients (at least 10 or all patients in case of a particular small country) were included in the analyses. Chi square analysis, Kruskal Wallis one-way analysis of variance and One-way ANOVA were used to compare differences between groups. For Italy and the FYR of Macedonia only height data on dialysis patients were available from the registry. Therefore, to test the possible confounding effect –of country policy in combination with information only on the (shorter) dialysis patients -, we performed a sensitivity analysis excluding these patients from these countries. In order to adjust for differences in economic indicators across countries, we included GDP per capita in our analyses. Values are presented as mean [SE] unless stated otherwise. P values of <0.05 were considered statistically significant. All analyses were performed in SAS version 9.3 (SAS Institute Inc., Cary, NC, USA) and SPSS version 20 (IBM, SPSS Statistics 20, Chicago, IL, USA).

RESULTS

Policies in rGH use

28 out of 38 (response rate 74%) of the countries completed the questionnaire. The mean height SDS at start of RRT, mean height SDS during RRT and final height SDS by country are presented in Table 1.

In 22 (78%) out of 28 countries rGH was reimbursed in children with CKD, and in six it was not reimbursed. From these six countries where it was not reimbursed, two countries indicated that in exceptional cases (e.g. in case of strict endocrinological criteria being satisfied) its use was allowed.

Out of the 22 countries where rGH was reimbursed, sixteen reported to have a national policy on growth hormone in CKD. Policies were based on either international guidelines (50%), national consensus (32%), local consensus among either paediatric nephrologists or paediatric endocrinologists (25%), government policies (11%) or health insurance companies (18%). The minimum age to prescribe growth hormone varied between 0 and 60 months, whereas the maximum age for prescription varied between 14 years and no maximum age. Countries were either allowed to prescribe growth hormone in CKD stage 1-4 and when glomerular filtration rate was reduced in transplanted patients or in CKD patients only (not on dialysis or after renal transplantation). One country was allowed to prescribe growth hormone in dialysis patients only. An overview of all reported policies is presented in Appendix 2.

Height SDS criteria for prescribing rGH varied between -1.88 SDS and -3 SDS. Five countries only used height SDS as a criterion, whereas fourteen countries used both height SDS in combination with a stable or decrease in height SDS (stable or decrease of >0.25 SDS in the previous year) and/or growth velocity (> 1 SDS decrease in growth velocity) as a criteria, and six countries did not have specific height criteria for prescribing rGH.

Table 1. Mean height SDS at the start of RRT, mean height SDS and mean final height SDS

Country	N	Mean height SDS* start RRT[a] (SE#)	Mean height SDS* (SE#)	Mean final height SDS (SE#)	% boys	Mean age at start RRT	Mean duration dialysis (years)	Mean duration Tx (years)
Albania	6	-1.41 (0.82)	-1.67 (0.60)		66.7	10.9 (1.8)	0.0 (0)[c]	0.0 (0)[c]
Belarus	65	-2.18 (0.29)	-2.54 (0.20)		56.1	9.7 (0.2)	1.5 (0.8)	0.2 (0.03)
Belgium	134	-2.47 (0.31)	-1.60 (0.16)	-1.48 (0.41)	57.9	7.7 (0.3)	1.4 (0.1)	4.1 (0.3)
Bulgaria	26	-1.18 (0.42)	-1.18 (0.30)		55.6	11.2 (0.6)	0.0 (0)[c]	0.0 (0)[c]
Czech Republic	76	-1.53 (0.33)	-1.66 (0.20)	-1.54 (0.41)	55.6	8.0 (0.5)	0.8 (0.1)	2.3 (0.3)
Estonia	4	-1.99 (0.99)	-2.44 (0.70)		50.0	7.7 (0.6)	1.9 (0.4)	0.5 (0.07)
Finland	165	-1.44 (0.24)	-1.77 (0.16)	-1.70 (0.26)	54.6	3.7 (0.2)	1.1 (0.04)	6.0 (0.2)
Greece	75	-0.18 (0.30)	-2.09 (0.20)	-2.56 (0.50)	58.1	6.1 (0.3)	2.2 (0.3)	1.9 (0.3)
Italy[b]	312	-1.64 (0.21)	-2.16 (0.13)	-2.95 (0.28)	55.0	8.1 (0.1)	1.7 (0.06)	0.3 (0.04)
Lithuania	36	-2.33 (0.82)	-1.50 (0.26)		55.6	10.2 (0.5)	1.8 (0.2)	1.2 (0.2)
FYR of Macedonia	11	-1.87 (0.64)	-1.97 (0.43)		72.7	7.1 (0.4)	3.2 (0.6)	0.01 (0.004)
Montenegro	3	-1.47 (1.14)	-1.38 (0.83)		75.0	3.2 (0.3)	0.3 (0.3)	0.0 (0)[c]
The Netherlands	174	-0.93 (0.16)	-1.54 (0.10)	-1.92 (0.19)	58.6	8.3 (0.2)	1.8 (0.09)	0.4 (0.02)
Norway	80		-1.80 (0.20)	-1.58 (0.33)	61.3	6.5 (0.4)	0.4 (0.04)	4.9 (0.3)
Portugal	141	-1.68 (0.24)	-1.78 (0.16)	-1.90 (0.40)	55.6	7.9 (0.2)	1.9 (0.09)	1.1 (0.07)
Russia	458	-1.84 (0.21)	-2.31 (0.12)		56.3	9.4 (0.1)	1.1 (0.05)	0.8 (0.05)
Serbia	85	-1.63 (0.34)	-1.77 (0.19)	-1.69 (0.32)	57.5	8.1 (0.3)	2.0 (0.1)	2.6 (0.2)
Slovenia	16	-0.85 (0.57)	-1.58 (0.36)		68.8	8.8 (0.6)	1.8 (0.2)	0.5 (0.1)
Slovakia	31	-1.70 (0.39)	-1.78 (0.28)		62.5	10.6 (0.4)	1.1 (0.2)	1.1 (0.2)
Spain	704	-1.35 (0.18)	-1.42 (0.12)	-1.40 (0.21)	61.9	8.9 (0.09)	0.8 (0.02)	3.4 (0.07)
Turkey	275	-1.99 (0.22)	-2.42 (0.14)	-3.00 (0.38)	55.1	8.8 (0.2)	1.5 (0.1)	0.7 (0.08)
United Kingdom	1304	-1.96 (0.17)	-2.00 (0.11)	-1.98 (0.21)	59.5	8.9 (0.07)	1.3 (0.03)	3.1 (0.06)

* Standard Deviation Score; # Standard Error; a Renal Replacement Therapy; b Only dialysis patients; c No follow up

Differences between policies in relation to height SDS and economic indicators

Policies and outcomes are shown in Table 2. GDP was significantly higher in countries in which rGH was reimbursed (31.8) as compared to countries in which rGH was not reimbursed (17.0, *P*=0.01). GDP was positively associated with mean height SDS during RRT (beta=0.013), height SDS at start of RRT (beta=0.003) and final height SDS (beta=0.009). This association was only statistically significant for mean height SDS during RRT (*P*<0.001).

Mean height SDS [95%CI] was significantly higher in countries where rGH was reimbursed (-1.80 [95%CI -2.06 to -1.53]) compared with countries where rGH was not reimbursed (-2.34 [95%CI: -2.49 to -2.18], *P*<0.001). Similar results were obtained when comparing mean height SDS at the start of RRT and final height SDS. There was no difference between countries that were allowed to prescribe rGH among CKD and dialysis only and among CKD, dialysis and Tx patients (Table 2).

Table 2. Policies and outcome parameters

	Mean height SDS[4]	Mean height SDS[4] at start of RRT[5]	Mean final height SDS[4]
rGH[1] prescription			
No	-2.34 (-2.49; -2.18)[7]	-2.19 (-2.49; -1.88)[7]	-2.27 (-2.75; -1.78)[7]
CKD[2] and dialysis	-1.82 (-2.33; -1.30)	-1.85 (-2.58; -1.11)	-2.09 (-3.29; -0.90)
CKD[2], dialysis, Tx[0]	-1.80 (-2.06; -1.53)	-1.58 (-2.12; -1.05)	-1.77 (-2.33; -1.21)
Minimum age rGH[1] prescription#			
0 < 12 months	-1.98 (-2.08; -1.88)[7]	-1.92 (-2.08; -1.74)[7]	-2.12 (-2.34; -1.91)[7]
12 ≤ months < 24	-1.93 (-2.14; -1.73)[7]	-1.26(-1.61; -0.91)	-2.14 (-2.67; -1.61)[7]
≥ 24 months[0]	-1.52 (-1.82; -1.22)	-1.30 (-1.98; -0.61)	-1.49 (-2.07; -0.91)
Maximum age rGH[1] prescription#			
< 18 years[0]			-1.39 (-1.93; -0.84)
≥ 18 years			-2.02 (-2.27; -1.78)[7]
rGH[1] prescription in CKD[2] stages#			
CKD[2] stage IV-V	-1.78 (-2.00; -1.55)	-1.48 (-1.85; -1.10)[7]	-1.68 (-2.06; -1.31)
CKD[2] stage III-V	-1.55 (-1.66; -1.45)[7]	-1.33 (-1.51; -1.14)[7]	-1.50 (-1.74; -1.27)[7]
CKD[2] stage II-V	-2.16 (-2.33; -1.99)[7]	-1.64 (-1.95; -1.34)	-2.95 (-3.38; -2.52)[7]
CKD[2] stage I-V[0]	-1.98 (-2.26; -1.70)	-1.94 (-2.58; -1.29)	-1.95 (-2.50; -1.40)
Height criteria for rGH[1] prescription#			
Height SDS[4] /or growth velocity[0]	-1.79 (-2.08; -1.50)	-1.75 (-2.44; -1.06)	-1.67 (-2.22; -1.11)
Height SDS[4]	-1.88 (-2.15 -1.61)	-0.93 (-1.37; -0.49)[6,7]	-2.34 (-3.07; -1.61)
Height SDS[4] and growth velocity	-1.88 (-2.00; -1.76)	-1.34 (-1.55; -1.13)[7]	-2.10 (-2.36; -1.84)[7]
Minimum duration of growth retardation #			
< 12 months[0]	-1.81 (-2.08; -1.54)	-1.67 (-2.32; -1.02)	-1.78 (-2.33; -1.23)
≥ 12 months	-1.82 (-1.95; -1.68)	-1.41 (-1.66; -1.15)[7]	-1.74 (-2.02; -1.47)

[0] reference group; [1] growth hormone; [2] chronic kidney disease; [3] transplantation; [4] standard deviation score; [5] renal replacement therapy; [6] only data of Bulgaria and Greece; [7] significant difference from reference group

Age range of rGH prescription

When categorizing the minimum age at start of rGH, mean height SDS was significantly lower in countries who were allowed to prescribe rGH under the age of 12 months (mean height SDS: -1.98) versus those allowed to prescribe from 12-24 months (mean height SDS:- 1.93) and from 24 months and older (-1.52 SDS, *P*<0.001).

When looking at the upper age limits, mean final height SDS was 0.63 SDS lower (*P*<0.001) in countries who were allowed to prescribe rGH in children over 18 years, as compared to countries who were not allowed to prescribe rGH in children over 18 years of age.

Height criteria

Mean height SDS tended to be lower in countries who were allowed to prescribe rGH based on height SDS alone or based on height SDS and growth velocity as compared to countries who were allowed to prescribe rGH based on either height SDS or a stable/decrease in growth velocity (*P*>0.05) (Table 2).

CKD stage

Countries were allowed to prescribe rGH at different stages of CKD, varying from CKD stage 1-5 to CKD stage 4-5. There were very small differences in mean height SDS at start of RRT by CKD stage, but there was an inverse relationship between CKD stage and height at start of RRT; height SDS was significantly higher in countries who were allowed to prescribe rGH in CKD stage 4-5 (-1.48, 95%CI: -1.85 to -1.10) or stage 3-5 (-1.33, 95%CI: -1.51 to -1.14) as compared to countries where physicians were allowed to prescribe rGH from CKD stage 1 onwards (-1.94, 95%CI: -2.58 to -1.29).

Actual provided care

We were able to retrieve the percentage of rGH use between 2007 and 2011 in 13 out of the 28 countries. We calculated the percentage of children who were eligible for rGH use. Overall rGH use between 2007 and 2011 in dialysis and transplantation was 21.7% and 5.5%, respectively, and major country differences were observed (Table 3A and 3B).

45.9% of dialysis and 38.9% of transplantation patients had a short stature (height SDS < -2) and would be therefore be eligible for receiving rGH. In all countries the actual use of rGH was lower than the number of children eligible for rGH: only 26.0% of short dialysis and 8.9% of short transplantation patients actually received rGH. When applying country specific criteria to define short stature, similar figures were observed (Table 3A and 3B).

Table 3A. Actual use of rGH and patients with short stature on dialysis

Country		Eligibility according to short stature (height SDS<-2)		Eligibility according to national criteria	
	% of rGH use	% of patients eligible for rGH	% of eligible patients receiving rGH	% of patients eligible for rGH	% of eligible patients receiving rGH
Belgium	40.2	33.5	49.7	38.0	39.8
Czech Republic	22.2	42.0	16.7	42.0	16.7
Estonia	50.0	83.3	50.0	83.3	50.0
Greece	18.8	56.3	26.3	56.3	26.3
Italy	20.5	52.8	21.5	15.9	16.5
Lithuania[1]	6.8	40.2	9.1	40.2	9.1
The Netherlands	31.0	26.4	41.9	33.1	33.1
Portugal	22.6	49.7	29.5	33.5	23.2
FYR of Macedonia	33.3	44.4	50.0	15.6	0.0
Serbia	34.9	54.3	42.4	32.7	38.3
Slovenia	43.6	38.1	51.4	44.1	51.4
Spain	24.8	39.2	33.6	47.1	29.1
United Kingdom	11.6	53.8	15.9	47.0	15.5
Overall	*21.7*	*45.9*	*26.0*	*30.1*	*24.1*

[1]Although rGH is not reimbursed in Lithuania, a limited number of patients might receive reimbursement from a patient fund and are actually treated with rGH

Table 3B. Actual use of rGH and patients with short stature on transplantation

Country		Eligibility according to short stature (height SDS<-2)		Eligibility according to national criteria	
	% of rGH use	% of patients eligible for rGH	% of eligible patients receiving rGH	% of patients eligible for rGH	% of eligible patients receiving rGH
Belgium	19.9	51.9	29.3	38.9	22.8
Czech Republic	7.7	30.7	10.0	35.7	8.3
Estonia	0.0	20.0	0.0	38.9	0.0
Greece	6.5	48.4	13.3	48.7	11.1
Lithuania[1]	2.1	57.3	2.8	50.6	8.3
The Netherlands	4.0	25.6	6.0	28.8	10.4
Portugal	0.0	34.3	0.0	26.5	3.8
Serbia	4.6	40.8	9.6	35.4	9.5
Slovenia	0.0	53.6	0.0	46.5	0.0
Spain	8.3	29.4	13.7	39.8	9.2
United Kingdom	3.9	45.4	6.6	47.5	5.3
Overall	*5.5*	*38.9*	*8.9*	*42.3*	*7.6*

[1]Although rGH is not reimbursed in Lithuania, a limited number of patients might receive reimbursement from a patient fund and are actually treated with rGH

Physicians stated that the difference between actual rGH use and percentage of children eligible for rGH was due to several factors: patients refused treatment, improving nutritional intake and metabolic bone disease had priority over starting rGH, dialysis adequacy was sub-optimal, and patients were suffering from severe uncontrolled hyperparathyroidism. In addition, physicians stated that delayed prescription could occur when the responsibility for prescribing rGH was under control of the endocrinologist. There was no association between the percentage of rGH use and mean height SDS during RRT (Figure 1 A and 1B) or percentage of rGH use and final height in both dialysis (beta=0.02, *P*=0.28; Figure 1C) and transplantation (beta=0.03, *P*=0.25; Figure 1D).

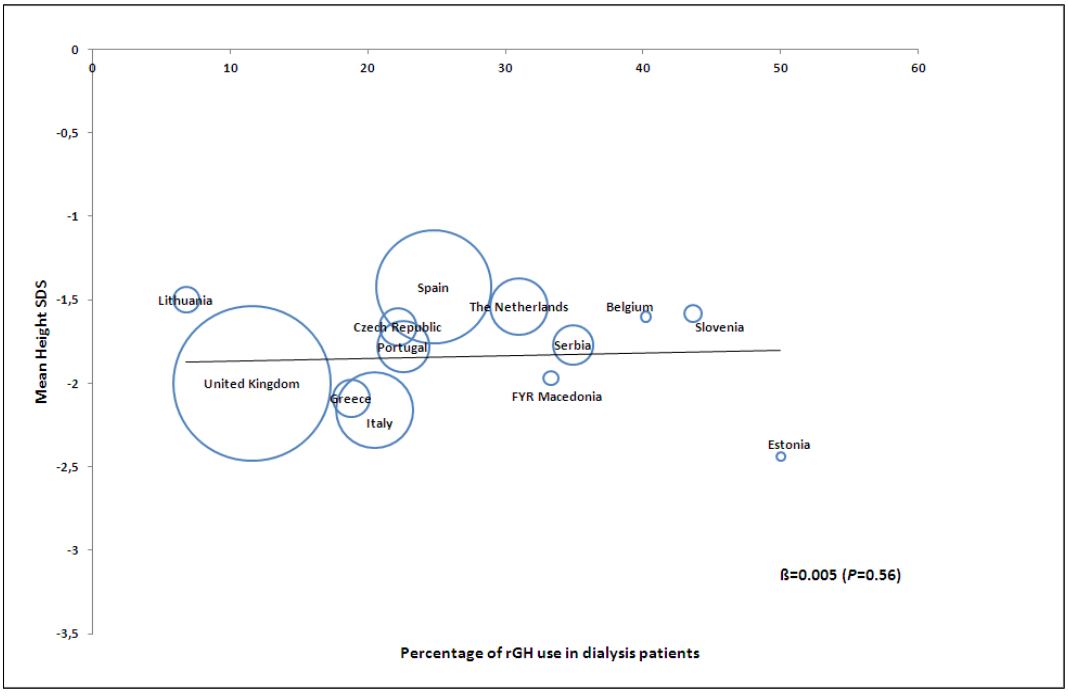

Figure 1A. Percentage of rGH use in dialysis patients and mean height SDS

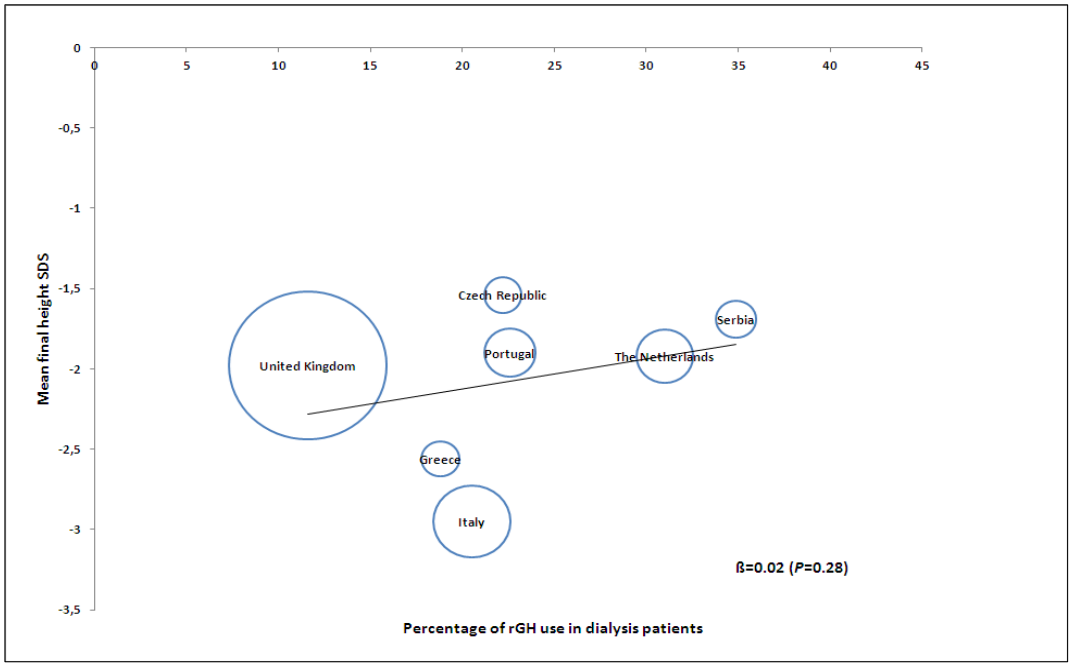

Figure 1B. Percentage of rGH use in dialysis patients and mean final height SDS

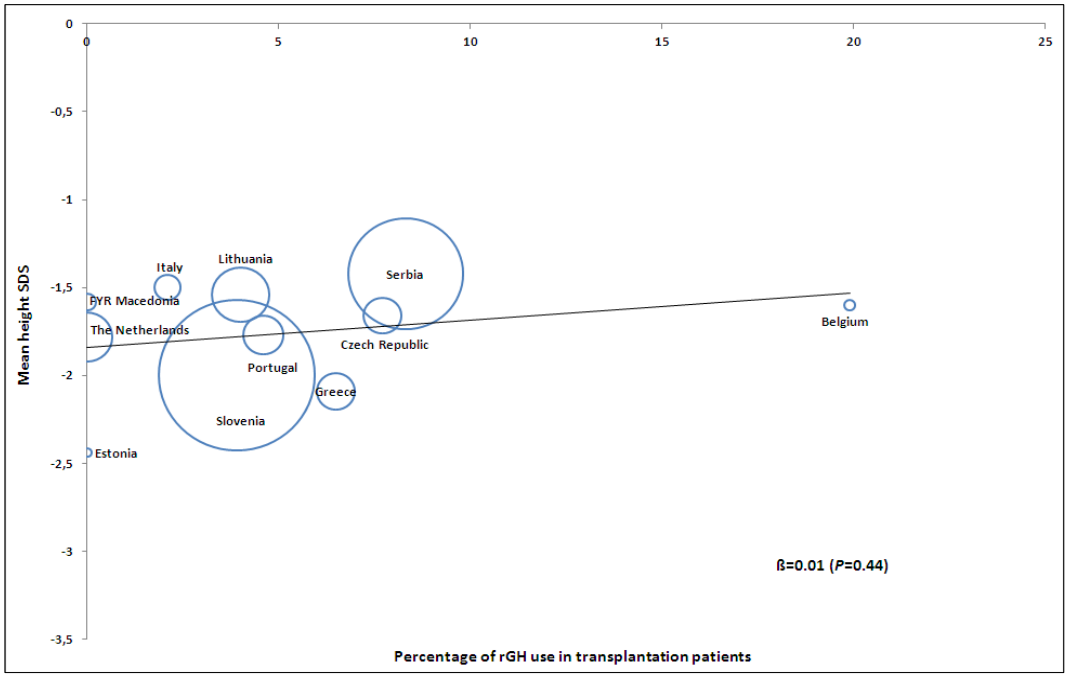

Figure 1C. Percentage of rGH use in transplantation patients and mean height SDS

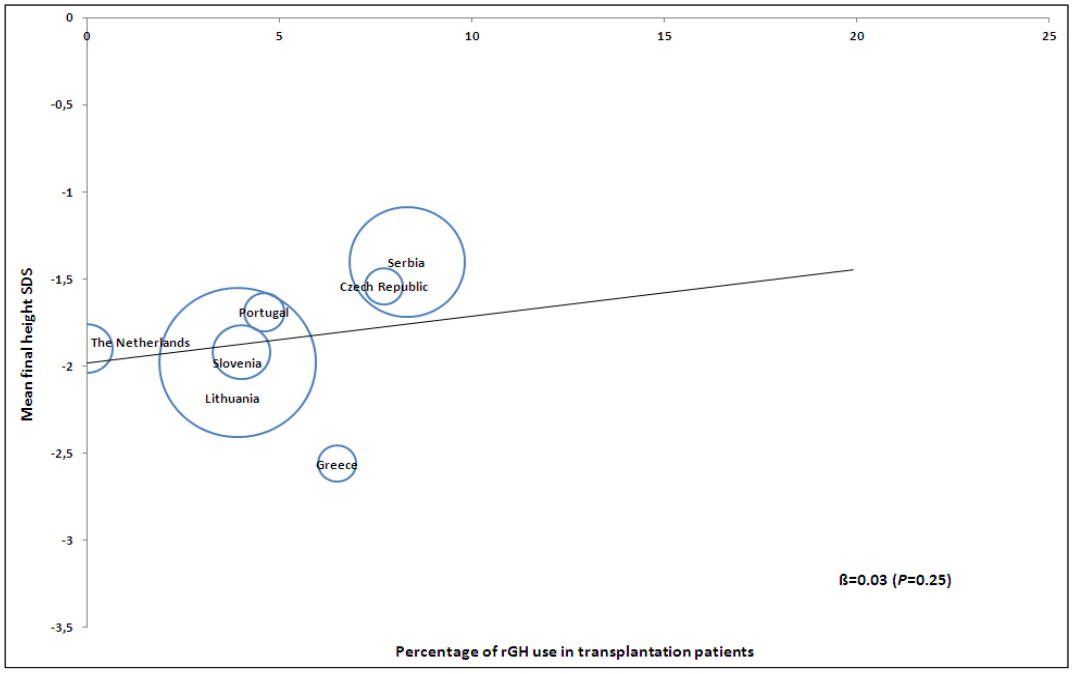

Figure 1D. Percentage of rGH use transplantation patients and mean final height SDS

DISCUSSION

In this paper, we demonstrated a considerable variation in growth hormone policies across 28 countries in Europe. Policy variation results in differences in care for growth retarded children with ESRD. These differences might affect health and health related outcome, such as quality of life, in childhood but also in adulthood.

In 22 out of 28 countries the use of growth hormone was reimbursed. In six countries its use was allowed, but not reimbursed, showing that in specific countries in Europe, children with ESRD cannot be treated with rGH due to financial constraints. Another constraint for not routinely prescribing rGH, mentioned by two countries, was that there should be strict endocrinological indications, whereas in CKD GH levels are usually normal and GH stimulation tests are often positive [10,20]. Two countries stated not being allowed to prescribe rGH in transplanted children. For one country, this was due a fear of graft loss in rGH treatment in transplanted children with already a shortage in available donor kidneys. Although older studies indeed suggest rGH treatment in transplanted children is associated with an increased risk of allograft loss [21,22], more recent studies did not show an increased risk of allograft loss or adverse events in children treated with rGH after renal transplantation

[23–28]. Therefore, the policies in which rGH is not allowed in transplanted children might need to be reconsidered.

We found a large variation in the minimum age for prescribing rGH, which was associated with mean (final) height SDS; mean height SDS was lowest in the countries who were allowed to prescribe rGH before 24 months of age. This is surprising, unless the policy is adapted to the mean (final) height SDS in those countries, where the policy is to treat children at a younger age in order to achieve a better final height. Data from Mencarelli et al. [29] and a study by Fine at al. [9] showed a significant improvement in height SDS in growth retarded children with chronic kidney failure when treated with rGH at a young age. Nevertheless, other studies [30,31] hypothesized that growth failure at a young age is mainly a reflection of nutritional influences and could be treated conservatively. The Kidney Disease Outcomes Quality Initiative (KDOQI) [7] recommends frequent monitoring of nutritional deficiencies and adequate caloric intake before starting rGH therapy in children aged under 3 years. Although most nephrologists probably follow the KDOQI guidelines on adequate caloric intake, there is still much debate about the definition of 'optimal feeding' and hence on the exact indication for growth hormone therapy. Data on supplemental feeding are not available from the registry. Therefore, we were not able to investigate this subject.

Height criteria for initiating rGH therapy also vary between different guidelines. The KDOQI guidelines [7] recommend considering rGH in children with a height SDS <-1.88 or height-for-age <3rd percentile and a growth velocity-for-age SDS <-1.88 or growth velocity-for-age <3rd percentile. The CARI guidelines [32] recommend offering rGH therapy to all children with a height <25th percentile and a growth velocity <25th percentile. Within our study height criteria for prescribing rGH varied considerably across countries, with the policy based on height SDS or growth velocity showing higher mean (final) height SDS. Children with a functioning graft have a more favourable outcome as compared to children who are on dialysis for a longer time period. Since Italy provided only data of children on dialysis, the same analyses were performed excluding the data from Italy. This sensitivity analyses showed no significant differences in the results. Therefore, we believe that the results of this study are not distorted to a large extent by data of children on dialysis.
Whether the differences in outcome are merely the effect of differences in policies remains unclear, since we had limited data on actual rGH use. In keeping with previous studies, we did show that the majority of children with a short stature did not use growth hormone in the preceding period. In the UK it has been estimated that although 29% of the children on a renal transplant with chronic renal failure and 41% of the children on dialysis suffered from growth retardation, less than 5% of the children receive rGH treatment. Also, the NAPRTCS study found that rGH is used in only a minority (33% and 3% of children on dialysis and on a renal transplant, respectively) [33]. Recently, the CKiD study group showed that only 23% of

children with severe growth retardation (height SDS < -1.88) receive growth hormone therapy [34]. These findings correspond with the results of our study.
There were differences between policies and actual provided care, possibly explained by both doctor and patient related factors, such as patients refusing rGH therapy. Improving nutritional intake and treatment of metabolic bone disease sometimes were prioritized over starting rGH. Also, non-adherence might be an obstacle in prescribing rGH, as demonstrated in an earlier study by the CKiD group where self-reported non-adherence to rGH, defined by missing at least one dose within 7 days, was 25% [34]. Another study by Greenbaum et al. [35] explored the obstacles to prescribing rGH in children with CKD. They found several reasons why children did not receive growth hormone, such as psychosocial reasons (family refusal, non-adherence and 'overwhelmed' family) in 30% of the cases, whereas in 25% of cases no reason could be identified.

The extremely low use of rGH after renal transplantation might be caused by the fear of triggering rejection episodes. Studies in transplant recipients did, however, not show an association between the use of rGH and rejection episodes [24–26,28,36]. Finally, under-reporting of rGH use in the registry might at least partly explain the difference between rGH use and percentage of children on rGH.
The reimbursement of rGH affected height outcome, whereas differences between policies in the countries in which rGH was reimbursed, did not seem to lead to a difference in height outcome parameters. Furthermore, the actual care provided by the doctors and their attitudes towards growth hormone therapy also affects height outcome, although data on growth hormone use are limited and no data are available on the duration of rGH treatment.
We found that in a few countries outdated growth charts are applied, possibly leading to an underestimation of the growth retardation of individual children. Nevertheless, when using the outdated growth charts, still a minority of children eligible for receiving rGH, actually are receiving rGH.
The percentage of children receiving rGH in dialysis and transplantation showed a weak positive association with mean final height SDS, although this did not reach statistical significance.
Nevertheless, this is clinically relevant, as it seems likely to assume that more children achieve a better final height when rGH is adequately prescribed. Furthermore, it suggests that when rGH is not prescribed when actually indicated, other interventions to achieve an adult height within the normal range, such as optimal caloric intake, seem to fail.

CONCLUSION

In this study we aimed to quantify the variation in growth hormone policies in paediatric ESRD across European countries and their effect on height. We found considerable variation in policies regarding growth hormone within 28 European countries. Furthermore, rGH was significantly less often prescribed than would be expected, suggesting that outcome is not only affected by growth hormone policy, but also by a reluctance of local physicians to prescribe rGH and because of psychosocial reasons. Both doctors and patient related obstacles to prescribe rGH are amenable for interventions in order to improve the use of rGH in children with ESRD and offer those children more beneficial health outcomes.

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APPENDIX 1 QUESTIONNAIRE

1. Which country are you representing?
2. Is it allowed to prescribe Recombinant Human Growth Hormone (rGH) in your country?
3. Is there a national policy on rGH prescription?
4. Is there a written policy on rGH?
5. Upon which of the following is your policy based? (multiple answers possible)
6. How is your (national) policy regarding the reimbursement of rGH?
7. At what minimum age (in months) are you allowed to start rGH?
8. At what maximum age (in years) do you have to stop rGH?
9. When do you have to stop rGH? (multiple answers possible)
10. Are you allowed to prescribe rGH among non-dialysis patients?
11. Are the criteria for rGH prescription different for dialysis, CKD and transplantation (Tx) patients?
12. At what CKD stage is it allowed to start rGH?
13. At what time (in months) after Tx are you allowed to (re)start rGH?
14. In some countries multiple criteria exist for prescribing rGH for example: height SDS <-2 OR height SDS < -1.88 and stable or decrease in height SDS over the previous year). Which criteria need to be met in your country, in order to permit prescribing of rGH? (please specify all possible criteria)
15. How long should the growth retardation at least be present before starting rGH?
16. At what time (in months) after Tx are you allowed to (re)start rGH?
17. You have completed the questionnaire. We highly appreciate any additional comments or questions:

APPENDIX 2 OVERVIEW POLICIES

	Albania	Belarus	Belgium	Bulgaria	Croatia	Czech Republic	Denmark	Estonia	Finland	France	FYR of Macedonia	Germany	Greece	Italy	Lithuania	Moldova	Montenegro	the Netherlands	Norway	Portugal	Russia	Serbia	Slovakia	Slovenia	Spain	Sweden	Turkey	United Kingdom	Total	
rGH allowed	-	-	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	-	-	+	+	+	+	-	+	22	
Yes	+	+	-	-	-	-	-	-	-	-	-	-	-	-	+	+	-	-	-	-	+	+	-	-	-	-	+	-	5	
No	-	-	+	+	+	+	-	+	+	+	-	+	+	-	-	-	-	-	+	+	-	-	+	+	+	+	-	+	16	
National policy	-	-	+	+	+	-	-	+	+	+	-	-	+	-	-	-	+	+	+	+	-	-	+	+	+	+	-	+	15	
Written policy																														
Patients in whom rGH is allowed																-														
Dialysis only	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	
CKD5 and dialysis	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	2	
CKD5, dialysis, Tx[a]	-	-	+	+	-	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	-	-	-	+	+	+	-	+	20	
Minimum allowed age																-														
< 12 months	-	-	+	+	-	-	+	+	-	+	-	+	-	+	-	-	+	+	-	+	-	-	-	-	-	-	-	+	7	
> 12 months	-	-	-	-	+	+	-	-	+	-	+	-	+	-	-	-	+	+	+	+	-	-	+	+	+	+	-	-	16	
Maximum allowed age																-														
< 18 years	-	-	-	+	+	-	-	-	-	+	-	+	+	-	-	-	+	+	-	+	+	-	-	+	+	-	-	-	10	
> 18 years	-	-	+	-	-	+	+	+	+	-	+	+	-	+	-	-	-	+	+	-	-	+	+	-	-	+	-	+	13	
CKD5 stage allowed																-														
I-V	-	-	-	-	-	+	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	3	
II-V	-	-	-	-	-	-	-	-	-	+	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3	
III-V	-	-	+	+	-	-	-	-	-	-	-	+	+	-	-	-	-	+	+	+	-	-	+	-	+	-	-	-	10	
IV-V	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-	3	
V without dialysis	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	