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# TRABALHO FINAL
# MESTRADO INTEGRADO EM MEDICINA

Clínica Universitária de Pediatria

## Growth after Pediatric Kidney Transplantation

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# RESUMO

**Introdução**: O atraso estaturo-ponderal é umas das principais complicações da doença renal crónica em idade pediátrica. Contudo, mesmo após o transplante renal, cerca de 50% das crianças não atingem a estatura esperada na idade adulta. Os objetivos deste estudo foram avaliar o crescimento após transplante e identificar fatores que o possam influenciar.

**Métodos**: Foi realizado um estudo observacional retrospetivo. Foram analisados os processos clínicos de todos os doentes submetidos a transplante renal nos últimos 25 anos (n=149) e foram realizadas chamadas telefónicas para obtenção de dados em falta. Os z-scores de estatura e índice de massa corporal (IMC) foram examinados à altura do transplante, 3 meses, 6 meses, 1 ano e 5 anos após o transplante renal e a estatura final na idade adulta, através das curvas e tabelas de crescimento da OMS. Ademais, dados relativos à duração da doença previamente ao transplante, técnica de substituição da função renal, administração de hormona de crescimento, suporte nutricional, estatura alvo, função renal e dose cumulativa de corticosteroides foram obtidos.

**Resultados:** A análise dos z-scores revelou uma recuperação da estatura estatisticamente significativa aos 6 meses (p=0,006), 1 ano (p<0,001), 5 anos após transplante (p<0,001) e na idade adulta (p=0,012). Houve também uma recuperação significativa do IMC em todos os momentos avaliados (p<0,001). A taxa de filtração glomerular correlacionou-se de forma positiva e significativa com a estatura (p=0,006) e o IMC (p=0,006). O tratamento com hormona do crescimento não teve impacto na estatura à data do transplante (p=0,182). A utilização de gastrostomia não teve impacto significativo na estatura (p=0,167) nem no IMC (p=0,086) à data do transplante. A duração da doença renal até ao transplante não demonstrou influenciar a estatura (r=-0,087, p=0,464) e o IMC (r=-0,144, p=0,225) na idade adulta. Ademais, a dose cumulativa de corticosteroides a que são sujeitos não demonstrou impacto na estatura (r=-0,080, p=0,538) e IMC (r=-0,155, p=0,229) na idade adulta. A evidenciar, temos o facto de que, em média, a estatura destas crianças na idade adulta foi 8,82 cm mais baixa do que a estatura-alvo.

**Conclusão:** Apesar dos resultados encorajadores do nosso trabalho relativamente à recuperação da estatura após o transplante renal, os resultados permanecem longe do que seria desejável. Desta forma, estratégias devem ser estudadas e aplicadas, nomeadamente, a utilização sistemática de gastrostomia. Ademais, deve ser feito um controlo regrado do IMC de modo a evitar um excessivo ganho ponderal, que se associa a um aumento do risco cardiovascular.

Palavras-chave: Crescimento; Doença Renal Crónica; Transplante.

# ABSTRACT

**Background**: Growth failure is one of the major complications of pediatric chronic kidney disease (CKD). However, even after KT, up to 50% of patients fail to attain expected final height by the time they transition to adult services. The aims of this project were to assess longitudinal growth after KT and to identify factors that influence it.

**Methods**: A retrospective observational study was performed. We reviewed the clinical records of all patients who underwent KT in the last 25 years in a single center (n=149) and performed phone interviews in order to obtain further data. Height-for-age and sex and BMI-for-age and sex were examined at transplant, 3 months, 6 months, 1 year and 5 years post-transplant and at final adult height, using WHO growth standards. Data regarding duration of disease prior to transplant, type of dialysis, administration of pretransplant recombinant human growth hormone (rhGH), nutritional support, target height, glomerular filtration rate (GFR) and cumulative corticosteroid dose were obtained as well.

**Results**: Height z-scores showed catch-up growth at 6 months (p=.006), 1 year (p<.001), 5 years after transplantation (p<.001) and on transition to adult care (p=.012). Regarding BMI z-scores, a significant increase was also detected at all time-point assessments (p<.001). GFR was significantly associated with height z-score (p=.006) and BMI z-score (p=.006). In our cohort, treatment with rhGH had no impact on height z-score at transplant (p=.182). Use of gastrostomy feeding tube had no statistically significant impact on height z-score (p=.167) and BMI z-score (p=.086) at transplantation, although only 6% (n=6) of our patients used gastrostomy feeding tube. Disease duration until transplantation had, also, no influence on height z-score (r=-.087, p=.464) or BMI z-score (r=-.144, p=.225) at adult care transition. Furthermore, cumulative corticosteroid dose had no influence on height z-score (r=-.080, p=.538) or BMI z-score (r=-.155, p=.229) at transition to adult care. Importantly, in our cohort height in adulthood was 8.82 cm lower, on average, than the target height.

**Conclusion**: Although the encouraging results regarding catch-up growth after KT presented in this cohort, results remain far from optimum. Therefore, strategies must be thought, including systematic use of gastrostomy tube feeding. Furthermore, closely monitoring of BMI is important in order to avoid excessive weight gain as it is associated with a greater cardiovascular risk.

Keywords: Growth; Chronic Kidney Disease; Transplantation.

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# ABBREVIATIONS

BMI – Body Mass Index
CKD – Chronic Kidney Disease
CKD 5 – Chronic Kidney Disease Stage 5
CKD-MBD – CKD-Metabolic Bone Disease
ESPN – European Society for Pediatric Nephrology
FGF23 – Fibroblast Growth Factor 23
GH – Growth Hormone
GnRH – Gonadotropin-release Hormone
GFR – Glomerular Filtration Rate
G-tube – Gastrostomy tube
HD – Hemodialysis
HRQoL – Health-related Quality of Life
IL-1 – Interleukin 1
IL-6 – Interleukin 6
IGF1 – Insulin-like growth factor 1
IGFBPs – IGF-binding proteins
JAK 2 – Janus kinase 2
KRT – Kidney Replacement Therapy
KT – Kidney Transplant
LH – Luteinizing Hormone
LVH – Left Ventricular Hypertrophy
MBD – Metabolic Bone Disease
MMF – Mycophenolate Mofetil
NG – Nasogastric tube
NODAT – New Onset Diabetes after Transplantation
PD – Peritoneal Dialysis
PKD – Primary Kidney Disease
PTH – Parathyroid Hormone
RAAS – Renin Angiotensin Aldosterone System
SDS – Standard Deviation Score or z-score
rhGH - Recombinant Human Growth Hormone
SOCS – Suppressor of cytokine signaling
STAT – Signal transducer and activator of transcription
TNF-α – Tumor Necrosis Factor α
WHO – World Health Organization

# 1. INTRODUCTION

Growth failure is one of the major complications of children with chronic kidney disease (CKD). Despite kidney transplantation (KT) being the optimal treatment for CKD stage 5 (CKD 5), catch-up growth after transplantation is usually insufficient to compensate the growth failure that has been acquired before KT [1,2]. Growth failure after KT is multifactorial and influenced by age at KT, the degree of pre-transplantation growth deficit, nutritional status, presence of comorbidities, administration of recombinant human growth hormone (rhGH), graft function and exposure to steroids, which interfere with the growth hormone (GH)/ insulin-like growth factor axis [2,3].

Children with CKD rarely achieve the daily energy and protein needs required for their age. Anorexia, increased energy expenditure despite adequate caloric intake and muscle wasting are three major pathophysiologic features [1]. Anorexia is caused by a combination of factors, including altered taste sensation, gastroesophageal reflux, delayed gastric emptying, excessive fluid intake, and elevated levels of pro-inflammatory cytokines such as Interleukin (IL) -1, IL-6 and tumor necrosis factor (TNF)-α [3]. Perturbations in appetite-regulating hormones, such as leptin and ghrelin may also contribute to reduced appetite. In fact, CKD leads to the accumulation of the anorexigenic hormones but does not lead to a compensatory increase in orexigenic hormones thus favoring the development of cachexia and protein energy wasting [5]. Inflammation is also an important cause of muscle wasting in CKD. Additionally, metabolic acidosis, a common comorbidity of CKD, also contributes to growth impairment since it induces degradation of proteins and resistance to GH [4,6].

Anemia, a major comorbidity in CKD, may also contribute to CKD-related growth failure [7].

Endocrine disorders such as secondary hyperparathyroidism and metabolic bone disease (MBD) have harmful effects on bone integrity and growth. CKD-MBD is caused by the inability of the kidneys to excrete phosphate and synthesize active 1,25-dihydroxyvitamin D (1,25[OH]2 D). In order to increase phosphate excretion, early in

CKD, there is an increase in circulating fibroblast growth factor 23 (FGF23) levels and its co-receptor Klotho, which further suppresses 1,25(OH)2 D formation by the kidney. Parathyroid glands are stimulated with calcium, phosphate and vitamin D dysregulation and secondary hyperparathyroidism occurs. Increased parathyroid hormone (PTH) activity on bone results in increased bone turnover and resorption, which contributes to the weakness of the bones and increases both calcium and phosphate, which may promote vascular calcification [1,4,8].

Children with CKD also have delayed puberty with hypogonadotrophic hypogonadism caused by dysregulation of the hypothalamic-pituitary-gonadal axis, displayed by impaired sensitivity to gonadotrophins and luteinizing hormone (LH) pulsatility and bioactivity [4]. In fact, reduced release of hypothalamic gonadotropin-release hormone (GnRH) due to uremia-related inhibitory factors (such as angiotensin II) and steroid treatment result in decreased circulating levels of bioactive LH, hypogonadism and reduced pubertal growth spurt. The pubertal growth spurt is delayed, shortened and associated with a reduced growth velocity. The pubertal height gain in children with CKD is about 65% of that seen in healthy children [9,10].

Furthermore, CKD is a state of GH insensitivity characterized by deficiency of functional insulin-like growth factor 1 (IGF-1) due to reduced density of GH receptors in target organs (such as the liver), impaired GH activated post-receptor Janus kinase 2 (JAK2)/signal transducer and activator of transcription JAK/STAT pathway in uremia. An intact JAK2-STAT signaling pathway is crucial for GH stimulation of IGF-1 gene expression. Additionally, the JAK2/STAT pathway is also regulated by suppressor of cytokine signaling (SOCS). These proteins bind to JAK2 and inhibit STAT phosphorylation. Up-regulation of SOCS has been associated to inflammatory states and may play a similar role in CKD.

IGF-1 is the main IGF during the rapid growth period of puberty. In CKD, IGF-1 levels are decreased due to excess of IGF-binding proteins (IGFBPs), resulting in a net decrease in IGF bioactivity [9,10].

Children treated with rhGH demonstrated sustained catch-up growth. In children treated with rhGH, height velocity increases by 3.88 cm/year and height velocity z-score increases by 6 SDS above that of non-treated controls [11]. Members of European Society for Pediatric Nephrology (ESPN) CKD-MBD, Dialysis and Transplantation working group presented clinical practice recommendations for the use of rhGH in children with CKD on dialysis and after KT. They recommend that children with CKD stage 3-5 or on dialysis should be candidates for rhGH therapy if they have persistent growth failure, defined as a height below the third percentile for age and sex and a height velocity below the twenty-fifth percentile, once other potentially treatable risk factors for growth failure have been adequately addressed and provided the child has growth potential. Children who underwent KT and fulfil the above growth criteria are allowed to initiate rhGH therapy 1 year after KT if spontaneous catch-up growth does not occur and steroid-free immunosuppression is not a feasible option. Treatment with rhGH should not be started in patients with closed epiphyses, hypersensitivity to the active substance or to any of the excipients, in the case of unwillingness of the patient or their family, in patients with severe hyperparathyroidism, diabetic retinopathy, acute critical illness or active malignancy. Nevertheless, pros and cons of rhGH treatment should be discussed with individual patients and their families before treatment is initiated [10]. In Portugal, there are criteria for the use of rhGH, in children with CKD according to *Comissão Nacional para a Normalização da Hormona do Crescimento (CNNHC, Portugal)*. Therapy should be considered for patients older than 12 months old, creatinine clearance < 75 mL/min/1.73 $m^2$, normal thyroid function, height < -2SD, on conservative treatment modality with or without dialysis (hemodialysis or peritoneal dialysis) or after one year of KT and one year of stable kidney function. Children with severe cardiovascular disease, severe osteopathy, diabetes mellitus, active malignancy and bone age > 12 years should not start treatment with rhGH.

Growth failure may have a major impact on psychological and social development, self-esteem and quality of life. For adults transplanted in childhood, the final height was directly related to educational level, employment, marital life and independent housing [12]. Furthermore, it has been reported that one third of adults who had CKD diagnosis

during childhood is dissatisfied with their height[13]. Thus, achieving a normal final height should represent a crucial issue in the management of these children.

Regarding weight, an excessive weight gain after KT is not rare and it is most commonly due to the use of high dose of corticosteroids, improvement of the nausea and loss of appetite associated with uremia and removing of previous dietary restrictions [14,15,16]. There is a significant U-shaped association between Body Mass Index (BMI) and pediatric CKD 5 death [17] .

The prevention of growth failure pre-transplant remains inadequate in Europe, despite correction of metabolic acidosis and hyperparathyroidism and the availability of rhGH therapy in most European countries. One major difficulty is guarantying an adequate nutritional intake in the pre-transplant period [1,18]. To achieve a better nutritional status at transplant time, enteral nutrition (gastrostomy or nasogastric tube feeding) is a widely and effective method [19].

The aims of this project were to evaluate longitudinal growth after KT and to identify factors that influence it in a Pediatric Kidney Transplantation Center in Portugal.

# 2. MATERIALS AND METHODS

## 2.1 Data collection

A retrospective, observational, descriptive study was performed, through clinical records consultation and phone interviews to patients who underwent KT between September 1995 and November 2020 (n=149).

Height-for-age and BMI-for-age z-scores were examined in defined timepoints: at transplant, 3 months, 6 months, 1 year and 5 years post-transplant and at transition to adult care, using World Health Organization (WHO) child growth standards.

Clinical and demographic data were collected such as date of birth, age at transplant, time since transplant and etiology of CKD. Data regarding duration of disease prior to transplant, type and time on dialysis (hemodialysis or peritoneal dialysis), administration of pretransplant rhGH, nutritional support (gastrostomy feeding tube or nasogastric tube), target height, glomerular filtration rate (GFR) and cumulative corticosteroid dose were obtained.

The research was approved by the Ethics Committee of CAML (*Centro Académico de Medicina de Lisboa*) and CHLN (*Centro Hospitalar Universitário Lisboa Norte*).

## 2.2 Definition of Variables

Height percentile for age was calculated based on WHO growth charts. Growth deficit was defined as a height z-score < -1,88.

GFR was calculated using Schwartz bedside formula. GFR = (0.413 x height (cm))/ serum creatinine (mg/dL) [20]. Chronic Kidney Disease Epidemiology Collaboration formula (CKD-EPI) was used when participants were 18 years old or older.

Target height (TH) was calculated using Tanner's method, based on mid-parental height (girls = $[H_{mother_{cm}} + H_{father_{cm}} - 13]/2$; boys = $[H_{mother_{cm}} + H_{father_{cm}} + 13]/2$) [2].

**2.3 Statistics**

Data analysis was performed with SPSS, version 22®.

Descriptive statistics were presented as frequencies (n) and percentages (%) for categorical variables and means (M) and standard deviations (SD) for continuous variables. Having multiple standardized height (height z-scores) and BMI (BMI z-score) measurements per patient along with time dependent covariates like GFR, we applied linear mixed model regression analyses (LMM) with both a random intercept and a random slope to correct for correlation of measurements within patients. Besides GFR, we also included sex as a covariate.

On dealing with missing values, we extended the number of patients included in each time point by using Full Information Maximum Likelihood (FIML). Unadjusted height z-score and BMI z-score variation along time were presented as 3-degree polynomial smooth spline function. LMM was also used to study the interaction of height z-score time points assessment with rhGH treatment. T-tests and correlations were used to assess bivariate associations.

Significance was established with $p<.05$.

# 3. RESULTS

Out of a total of 149 patients enrolled in this study, 40 were excluded due to incomplete data in the medical records and one was excluded due to death in the first three months after transplant.

Table 1 presents baseline characteristics. Total females were 51 (47.2%) and males were 57 (52.8%). Distribution of age at KT was 12 (11.1%) patients had less than 5 years, 35 (32.4%) 5 to 10 years, 39 (36.1%) 11 to 15 years and 22 (20.4%) more than 15 years.

The most prevalent primary kidney disease (PKD) were congenital anomalies of kidney and urinary tract (CAKUT) (n=57, 52.8%) followed by primary glomerular disease (n=21, 19.4%).

Twenty patients (18.5%) underwent preemptive KT. The most prevalent Kidney Replacement Therapy (KRT) was peritoneal dialysis (n=72, 66.7%); 7 (6.5%) patients were treated with hemodialysis, nine (8.3%) patients underwent peritoneal dialysis and hemodialysis.

A total of 35 (32.4%) patients were treated with rhGH and six (5.6%) had gastrostomy feeding tube as nutritional support.

Data for GFR at adult care transition was available for 73 patients. Levels ≥ 90 mL/min/1.73m$^2$ were obtained in 32 patients (43.8%) and 60 to 89 mL/min/1.73m$^2$ in 29 patients (39.7%).

### 3.1 Baseline characteristics of the population

Table 1. Baseline characteristics of the population (n=108).

| *Baseline characteristics* | *n* | *%* |
|---|---|---|
| **Sex** | | |
| Female | 51 | 47.2% |
| Male | 57 | 52.8% |
| **Age at KT** | | |
| < 5 years | 12 | 11.1% |
| 5-10 years | 35 | 32.4% |
| 11-15 years | 39 | 36.1% |
| > 15 years | 22 | 20.4% |
| **Primary Kidney Disease (PKD)** | | |
| CAKUT | 57 | 52.8% |
| Primary Glomerular Disease | 21 | 19.4% |
| Not identified | 12 | 11.1% |
| Secondary Glomerular Disease/Vasculitis | 9 | 8.3% |
| Tubulointerstitial nephritis | 6 | 5.6% |
| Congenital Cystic Kidney Disease | 2 | 1.9% |
| Miscellaneous | 1 | 0.9% |
| **Kidney replacement therapy (KRT)** | | |
| Peritoneal dialysis | 72 | 66.7% |
| Hemodialysis | 7 | 6.5% |
| Peritoneal Dialysis + Hemodialysis | 9 | 8.3% |
| Preemptive | 20 | 18.5% |
| **Use of rhGH** | | |
| No | 73 | 67.6% |
| Yes | 35 | 32.4% |
| **Gastrostomy feeding tube** | | |
| No | 102 | 94.4% |
| Yes | 6 | 5.6% |
| **GFR at adult care transition (n=73)** | | |
| ≥ 90 mL/min/1.73m$^2$ | 32 | 43.9% |
| 60 to 89 mL/min/1.73m$^2$ | 29 | 39.7% |
| 45 to 59 mL/min/1.73m$^2$ | 6 | 8.2% |
| 30 to 44 mL/min/1.73m$^2$ | 3 | 4.1% |
| 15 to 30 mL/min/1.73m$^2$ | 1 | 1.4% |
| < 15 ml/min/1.73 m$^2$ | 2 | 2.7% |

### 3.2 Height z-score after Kidney Transplantation

At transplant, the average height z-score was -1.38. At three months, six months, one year and five years after transplant, the average height z-score was -1.33, -1.26, -1.15, -1.08 respectively. At transition to adult care, the average height z-score was -1.22.

Next, we present results for LMM for predicting height z-score and BMI z-score accounting for time, sex and GFR, a time depending covariate (Tables 2 and 3).

Unadjusted mean height z-score showed a growth tendency, significant for baseline (at transplant) comparisons 6 months after ($p=.006$), 1 year after ($p<.001$), 5 years after ($p<.001$) and on adult care transition ($p=.012$).

GFR was positively and significantly associated with height z-score, with an estimated effect of 0.001 height z-score increase for each GFR unit increase ($p=.006$). Sex was not significantly associated with height z-score and therefore not included in the adjustments.

When adjusting for both time and GFR results showed the same growth tendency for height z-score, significant estimated effects were found for baseline (at transplant) comparisons with 1 year after ($\beta=0.13$, $p=.042$) and 5 years after ($\beta=0.20$, $p=.004$). Adjusted estimated effect for GFR was $\beta=0.001$, $p=.032$.

Of those who transitioned to adult care (n=73), 38% (n=28) were at or below height z-score -1,88.

Table 2. LMM unadjusted and adjusted models for height z-score.

| | *Unadjusted (n=44)* | | | *Adjusted for time and GFR (n=44)* | | |
|---|---|---|---|---|---|---|
| | Mean height SDS (95% CI) | EFE (SE) | p-value | Mean height SDS (95% CI) | Combined EFE (SE) | p-value |
| Time | | | | | | |
| At transplant | -1.38 (-1.57; -1.19) | Ref. | - | -1.30 (-1.45; -1.15) | Ref. | - |
| 3 months after | -1.33 (-1.52; -1.14) | 0.05 (0.04) | p=.154 | -1.35 (-1.48; -1.23) | -0.05 (0.07) | p=.372 |
| 6 months after | -1.26 (-1.45; -1.07) | 0.12 (0.04) | p=.006 | -1.28 (-1.41; -1.16) | 0.02 (0.06) | p=.746 |
| 1 year after | -1.15 (-1.34; -0.96) | 0.23 (0.05) | p<.001 | -1.17 (-1.30; -1.04) | 0.13 (0.06) | p=.042 |
| 5 years after | -1.08 (-1.28; -0.88) | 0.30 (0.06) | p<.001 | -1.10 (-1.24; -0.96) | 0.20 (0.07) | p=.004 |
| ACT | -1.22 (-1.42; -1.02) | 0.17 (0.06) | p=.012 | -1.25 (-1.38; -1.11) | 0.05 (0.07) | p=.474 |
| Sex | | | | - | - | - |
| Male | -1.29 (-1.54; -1.04) | Ref. | - | - | - | - |
| Female | -1.49 (-1.76; -1.23) | -0.20 (0.18) | p=.263 | - | - | - |
| GFR | -1.34* (-1.52; -1.15) | 0.001 (≈0.00) | p=.006 | - | 0.001 (≈0.00) | p=.032 |

EFE= estimated fixed effect; SE=Standard error; * intercept estimate

### 3.3. BMI z-score after Kidney Transplantation

At transplant, the average BMI z-score was -0.27. At three months, six months, one year and five years after transplant, the average height z-score was 0.28, 0.25, 0.24, 0.32 respectively. At transition to adult care, the average BMI z-score was 0.16.

For unadjusted BMI z-score, a growth pattern was also detected, significant for baseline (at transplant) comparisons with all other time-point assessments (p<.001). Females BMI z-score was lower than males, considering the average across all time

points, with and estimated effect of β=-0.45 (p=.042), but after 5 years this tendency is reverted (Figure 1), and females start having higher BMI than males (p<.001).

GFR was positively and significantly associated with BMI z-score, with an estimated effect of 0.006 BMI z-score increase for each GFR unit increase (p=.006).

Adjusted BMI z-score results for time, sex and GFR showed significant results for the baseline comparison vs 3 months after transplant (p=.043). No other significant comparisons with baseline were found. The adjusted model found a negative significant estimated effect (β=-0.47, p=.038), suggesting that females have lower BMI than males considering the average across all time points. Interaction results showed that girls BMI start being higher than the one of the boys, from the 5th year after transplant (p<.001).

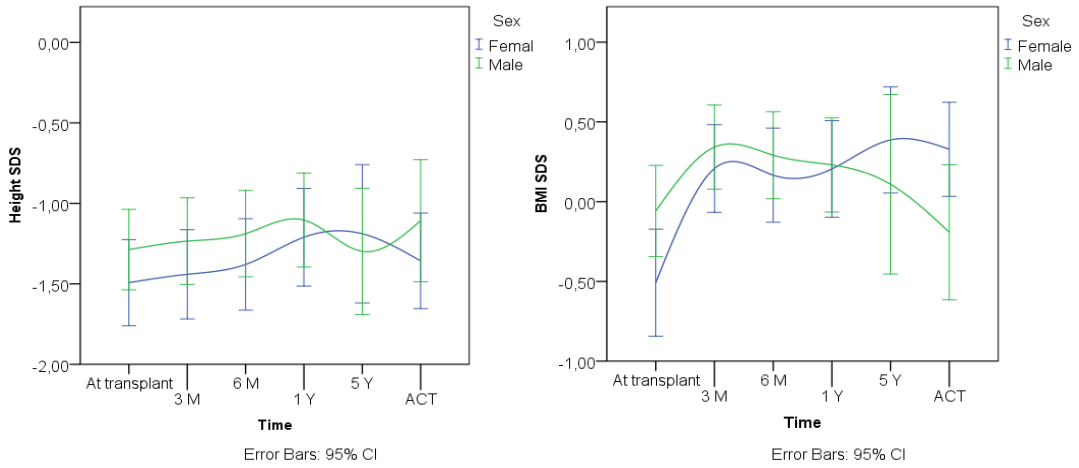
Table 3. LMM unadjusted and adjusted models for BMI z-score.

| | Unadjusted (n=44) | | | Adjusted for time, sex and GFR (n=44) | | |
|---|---|---|---|---|---|---|
| | Mean BMI SDS (95% CI) | EFE (SE) | p-value | Mean BMI SDS (95% CI) | Combined EFE (SE) | p-value |
| Time | | | | | | |
| At transplant | -0.27 (-0.48; -0.07) | Ref. | - | -0.21 (-0.49; -0.06) | Ref. | - |
| 3 months after | 0.28 (0.08; 0.48) | 0.55 (0.07) | p<.001 | 0.26 (0.06; 0.45) | 0.38 (0.19) | p=.043 |
| 6 months after | 0.25 (0.05; 0.46) | 0.52 (0.09) | p<.001 | 0.23 (0.04; 0.43) | 0.37 (0.19) | p=.055 |
| 1 year after | 0.24 (0.04; 0.45) | 0.51 (0.10) | p<.001 | 0.23 (0.03; 0.42) | 0.32 (0.28) | p=.132 |
| 5 years after | 0.32 (0.09; 0.56) | 0.59 (0.12) | p<.001 | 0.32 (0.07; 0.57) | 0.28 (0.25) | p=.152 |
| ACT | 0.16 (-0.07; 0.39) | 0.43 (0.12) | p<.001 | 0.10 (-0.49; 0.32) | -0.05 (0.25) | p=.830 |
| Sex | | | | | | |
| Male | -0.06 (-0.36; 0.24) | Ref. | - | 0.18 (0.12) | Ref. | - |
| Female | -0.51 (-0.82; -0.19) | -0.45 (0.22) | p=.042 | 0.13 (0.12) | -0.47 (0.23) | p=.038 |
| GFR | -0.24* (-0.44; -0.05) | 0.006 (≈0.00) | p<.001 | - | 0.001 (≈0.00) | p=.901 |

EFE= estimated fixed effect; SE=Standard error; * intercept estimate

Figure 1 shows unadjusted height z-score and BMI z-score. For height z-scores, males results are higher than the ones of females, except from the 5th year post-transplant time point. For BMI, results showed a significant interaction with sex, with higher BMI for females since the 5th year post-transplant.

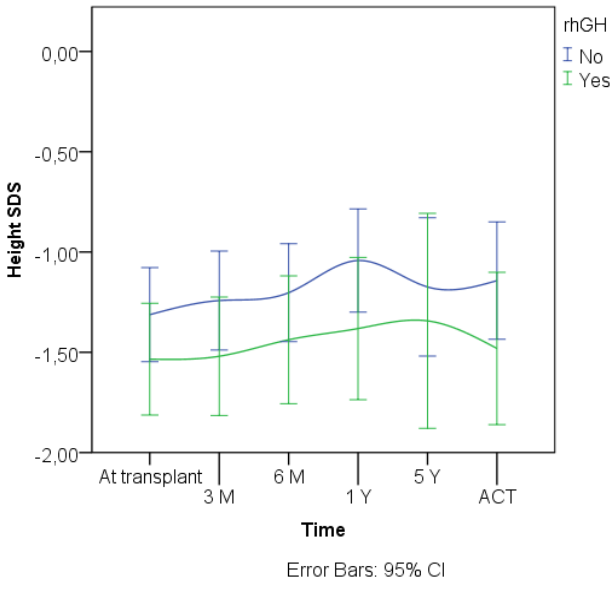
Figure 1. Unadjusted height z-score and BMI z-score stratified by sex.




### 3.4. Treatment with rhGH on Height z-score

Next, we present LMM results for the effect of rhGH on height z-score along time. No interaction was found for the effect of rhGH on height z-score along time (p=.146). Specifically, this was not observed at transplant (p=.182).

Figure 2. Unadjusted height z-score stratified by rhGH.




### 3.5. Impact of gastrostomy tube feeding on nutritional status at transplantation

No statistically significant associations were found regarding height z-score at transplantation (p=.167) and BMI z-score at transplantation (p=.086) with gastrostomy tube feeding use, although only 6% (n=6) of our cohort used gastrostomy feeding tube.

Table 4. Transplant Height z-score and BMI z-score associations with gastrostomy

| | Gastrostomy = no (n=102) | Gastrostomy = yes (n=6) | t-test |
|---|---|---|---|
| Height SDS | -1.35 (0.96) | -1.91 (0.69) | p=.167 |
| BMI SDS | -0.32 (1.14) | 0.51 (1.17) | p=.086 |

### 3.6. Disease duration until transplantation

No significant associations were found for disease duration until transplant with height z-score (r=-.087, p=.464) and BMI z-score (r=-.144, p=.225) at adult care transition (n=73).

### 3.7. Cumulative corticosteroid dose

No significant associations were found for cumulative corticosteroid dose with height z-score (r=-.080, p=.538) and BMI z-score (r=-.155, p=.229) at adult care transition (n=62).

### 3.8. Comparison between height at adult care transition and target height

Out of a total of 73 patients who transited to adult care services, we were not able to collect data regarding parents' height of 38 patients.

We present, therefore, results regarding the height difference between the target height and the height at transition to adult care of 35 patients.

Mean difference was 8.82 cm (SD=8.38), which means that in average terms, height in adulthood is 8.82 cm less than the target height, in our cohort. The patient who displayed the highest difference between target and final height was 32.90 cm shorter than expected. On the opposite hand, the patient with the slightest difference between target and final height was 4.00 cm higher than expected.

# 4. DISCUSSION

The present study evaluated the height and BMI of children and adolescents at KT and their development up to transition to adult care services.

## 4.1. Height after Kidney Transplantation

There was significant growth at 6 months, 1 year, 5 years after KT and at transition to adult care. Of those who transition to adult care (n=73), 62% were at or above height SDS -1,88.

Nevertheless, despite successful KT, the height at transition to adult services still falls below the calculated target height. In fact, in our cohort, height in transition to adult care is 8.82 cm less than the target height, calculated according to Tanner method [2].

Growth retardation is one of the major complications of a child with CKD. In fact, a height z-score decline in children with CKD is associated with a 14% increase in mortality, which denotes that short stature has implications that surpass the aesthetic issue [17]. Furthermore, The North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) data shows that growth deficit is associated with poor survival [21].

## 4.2. Factors influencing height after Kidney Transplantation

### 4.2.1. Treatment with growth hormone

The use of rhGH has been demonstrated to produce some catch-up growth, and many patients who have CKD reach a final height considered normal for their age range [15,19]. In fact, rhGH treatment can stimulate growth in children with CKD, but the prevention of growth failure pre-transplant remains inadequate, although the availability of rhGH therapy in most European countries [18,22].

In our cohort, treatment with rhGH was not related to a better outcome regarding height at transplant. In fact, as demonstrated by Figure 2, people who underwent rhGH treatment had lower height z-score (although not statistically significant) that those who were not. Children who had the most growth deficit were the ones who obtained the

treatment might be a possible explanation for this result. It would be interesting to obtain data regarding height before and after treatment initiation in order to better assess the effect of rhGH in these children.

4.2.2. Corticosteroids

After transplant, corticosteroids are known to interfere with the GH/ IGF axis by inducing down-regulation of GH receptors and inhibition of IGF-1 synthesis, which main job is to manage the effects of GH. Moreover, glucocorticoid treatment directly affects growth plate function by suppressing chondrocyte proliferation, reducing bone formation and altering endochondral ossification [2].

However, a given cumulative dose of corticosteroids has a lower inhibitory effect on growth velocity, without compromising graft function, when given on alternate days. Alternate day corticosteroids may not adversely affect final height potential, but it may still delay puberty and be associated with a delayed growth spurt. The effect of newer agents on growth and bone health, while reducing the need of corticosteroids are still not clear. Alternative forms of corticosteroids, such as deflazacort, an oxazoline derivative of prednisolone, appear to have fewer effects on growth and osteoporosis induced by corticosteroids, but are not used in clinical practice and therefore there is not enough data [23].

A multicenter trial (The TWIST study) assessed the impact of early steroid withdrawal on growth at 6 months after transplantation and on other steroid-related metabolic complications such as lipid and glucose metabolism. The experimental regimen consisted of two doses of IL-2R antagonist induction (daclizumab) administrated in combination with tacrolimus and mycophenolate mofetil (MMF), with steroids discontinued at day 4. In fact, the results demonstrated that early corticosteroid withdrawal resulted in a favorable linear growth without increasing the risk of acute rejection or graft loss at 6 months. Furthermore, both lipid and glucose metabolism profiles were significantly better with this regimen [24]. In order to determine whether the improved growth observed at 6 months was sustained at 1 and 2 years after KT, a two year follow-up study was conducted. Early corticosteroid withdrawal improves

growth up to 2 years after transplantation, most prominently in prepubertal subjects, although differences in metabolic profiles observed at 6 months were lost with increased follow-up [25]. Despite the considerable advantages of this regimen, it is important to mention that bacterial respiratory tract infection, febrile infection and blood system disorders occurred with a significantly higher frequency at 6 months and then at follow-up [24,25].

In our cohort, the correlation between cumulative corticosteroid dose and height in the transition to adult services was not statistically significant. Children with acute rejection episodes requiring pulses of corticosteroid were not sufficient to make a comparison statistically significant.

#### 4.2.3. Glomerular Filtration Rate

In our cohort, the correlation between GFR and heigh percentile was positive, meaning that higher the GFR, higher the height and BMI z-scores. So, it is important to achieve a good graft function in order to achieve better nutritional outcomes. *Nissel et al*. showed that prepubertal catch-up growth and total pubertal height gain correlated positively with GFR [26]. In fact, growth failure is generally more pronounced in children on CKD stages above 3 and in children on dialysis [27].

#### 4.2.4. Enteral Nutrition

Enteral nutrition is widely used to improve nutritional status in children with CKD. However, only 6% of our patients were gastrostomy tube (G-tube) fed.

Nasogastric (NG) and G-tube are beneficial in providing nutritional support to children on chronic dialysis. Disadvantages to NG feeding include increased gag reflux, frequent emesis, irritation to throat and nose and associated aversions to future oral intake. Besides that, there is a significant risk of being pulled out and the perception of NG tubes being unattractive and, naturally, uncomfortable. G-tube is associated with a more secure mode of feeding, without the need for frequent tube replacement and potential improvement of gastrointestinal symptoms [29]. G-tube feeding is an effective method

for achieving catch-up weight and moderate height gain in pediatric CKD patients, and does not apparently predispose patients to obesity after removal. Children with gastrostomy buttons on dialysis received an average of 61% of their caloric needs, thus contributing to catch-up growth [30]. In fact, the use of G-tube, without rhGH, maintained growth parameters in most children while on KRT and a significant improvement in growth occurred even after the KT [19,28].

An adequate nutrition, including the application of G-tube feeding, is fundamental to maximize the growth potential and general physical development and is one of the main factors for most growth-retarded children with CKD be able to achieve an adequate height in adult age [28].

#### 4.2.5. Nutritional status before and after Kidney Transplantation

The management of nutritional deficit in CKD plays a major role in children before transplantation. Caloric and energetic diets, modality of feeding, strict management of protein intake, electrolytes imbalance, iron and vitamins deficit should be monitored closely in order to reduce nutritional related comorbidities [4].

During peritoneal dialysis, intake of <75% of energy needs is common as a result of feeling of fulness from peritoneal dialysis fluid, gastric emptying delays, variation in toxin removal and uremia [29].

After transplant, dietitian support is also important because nutrition influences allograft function and cardiovascular risk factors such as blood pressure, dyslipidemia, weight gain and NODAT (new onset diabetes after transplantation). Furthermore, many dietary recommendations and modifiable lifestyle changes should be adapted for specific complications of KT such as immunosuppression side effects and electrolyte imbalances [31].

### 4.3. BMI after Kidney Transplantation

There was a significant increase in BMI percentile in the first year after transplantation. Children with CKD have nutritional deficiencies for a variety of reasons, including anorexia, nausea, vomiting and abnormal sense of taste due to uremia [15].

After transplant, the absence of uremia caused by an improvement in kidney function can mitigate this anorexia and gastrointestinal discomfort, resulting in an increased caloric intake. Furthermore, the high steroid exposure during this time period and the cessation of dietary restrictions that they were under during dialysis contribute significantly for this weight gain [16]. Obesity is induced by an excessive steroid exposure through multiple mechanisms. For instance, corticosteroid tend to increase appetite, they stimulate adipogenesis through preadipocyte differentiation and hypertrophy, particularly in central fat, and they also negatively affect brown adipose tissue, which is thought to decrease energy consumption [31]. Following transplantation, weight gain control can be challenging and requires a complex and a multimodal approach allowing parents support and cooperation [33].

*Ladhani et al*. found, over 10 years of follow-up, that pediatric KT recipients with obesity have a substantially increased risk of allograft failure [34]. Weight gain should be monitored closely after transplantation to identify early children who are at risk, as increases in BMI in the first 6 months after transplant are likely to be persistent [14]. Long-term cardiovascular morbidity in children with KT is a major issue and obesity does contribute to known risk factors such as hypertension, hyperlipidemia and NODAT [16]. Childhood obesity is associated with a higher chance of premature death and disability in adulthood [35].

### 4.4. Impact in Health-Related Quality of Life (HRQoL)

Health-related quality of life (HRQoL) is a multidimensional concept used to describe physical, mental, emotional and social functioning and generally focuses on an individual's perception of his or her own health status [26].

Preventing growth retardation should be a major concern as it is highly related to these children perception of their quality of life since it is more difficult to obtain a paid activity or a marital life and become independent with a short stature [12]. In fact, in our own experience through phone interviews, adults who are now under z-score -1,88 are highly dissatisfied with their social and professional life. Their height is clearly an obstacle to finding a good job and a normal social life in comparison to their peers. They

also related the perception that medical doctors are more focused on graft function and BMI rather than concerns regarding their stature.

On the other hand, a higher BMI is also related to a lower health-related quality of life. Their increased disease risk, negative perceptions of their body, physical impairments related to obesity and peers' and society stigmatization contribute to their distress regarding their body weight [37].

### 4.5. Strategies for Optimizing Growth in children with CKD

Strategies for prevention and treatment of growth failure should be established in order to achieve better outcomes. Thus, growth charts should be closely monitored by the assistant physician with regular intervals depending on previous growth, age and stage of CKD once height in these children may rapidly descend across the percentiles, especially during periods of expected high growth rates [38].

As discussed earlier, preserving kidney function is paramount in preventing growth retardation. Strategies such as treating hypertension, reducing proteinuria (using RAAS inhibitors), avoiding nephrotoxins and expeditiously treatment of urinary tract infections are general measures that contribute to maintain an adequate kidney function [38].

Furthermore, as previous referred, enteral feeding should be considered to meet adequate energy and protein intake, in cases of ineffective oral intake so as to achieve an appropriate nutritional status at transplant.

Metabolic acidosis is associated with poor growth in children with CKD. Thus, correction of metabolic acidosis, aiming for serum bicarbonate levels equal to or above 22 mEq/L contributes to the mitigation of associated complications. Children with salt-losing nephropathies or with extensive polyuria often require water and/or electrolytes supplementations. Children on peritoneal dialysis often experience considerable losses via peritoneal ultrafiltration requiring supplementation as well [38].

In order to minimize complications to the growing skeleton and prevent the extra skeletal calcifications that define CKD-MBD, therapeutic approaches focusing on the treatment of hyperphosphatemia and secondary hyperparathyroidism should be attempted [8]. In children with CKD stages 3–5, when the serum PTH concentration is above the target range for CKD stage (in stages 2–3 target range is 35–70 pg/mL, and in CKD 4 is 70–110 pg/mL) and the serum phosphate concentration exceeds the normal reference range for age, it is suggested that dietary phosphorus intake should be reduced and then regularly monitored. Phosphate-binding agents are required in cases of persistent hyperphosphatemia despite dietary phosphorus restriction [39].

Treatment of secondary hyperparathyroidism relies on the administration of Vitamin D sterols. In pediatric patients with CKD stages 2–4, it is recommended that active vitamin D sterols be initiated when serum PTH is above the target range for CKD stage, but only if 25(OH) vitamin D (25D) levels are sufficient (>30 ng/mL), corrected total serum calcium is <10 mg/dL, and serum phosphate is within the age-appropriate range [40].

Plasma concentrations of FGF23 increase early and progressively with advancing CKD. High plasma FGF23 concentration is significantly associated with a higher prevalence of left ventricular hypertrophy (LVH) in children with mild-to-moderate CKD. Interventional studies are needed to determine whether therapeutic strategies that reduce or attenuate the increase in FGF23 can prevent or delay the onset of LVH in children with CKD [41].

Early (preemptive) KT with minimal steroid exposure might also have a role in preventing growth failure.

Finally, in case of persistent growth failure, treatment with rhGH should be considered before KT and 1 year after KT, as long as they meet the required criteria, as earlier discussed.

**Study Strengths and Limitations**

The strengths of our work include the large population assessed and the long follow-up period. The study is the first national study to assess longitudinal growth after KT and was conducted in a reference Pediatric Kidney Transplantation Center. However, there are limitations requiring acknowledgment. The data collection was mainly dependent on clinical records consultation, which may have introduced some bias due to the possible inaccuracy of data regarding height and weight measurements and omission of some interventions such as pulses of corticosteroids, rhGH treatment and use of enteral feeding. Children with acute rejection episodes requiring pulses of corticosteroid were not sufficient to make a comparison statistically significant, which interfere with our results regarding the influence of corticosteroid in growth after transplantation. In fact, the number of patients in some subgroups was rather small. Only 6% (n=6) of our patients were fed using G-tube according to clinical records, which may be not enough to draw a conclusion concerning the impact of enteral feeding on nutritional status.

# 5. CONCLUSION

Our study demonstrated encouraging results regarding catch-up growth after KT. Nevertheless, our results remain far from optimum and efforts must be done in order to achieve better outcomes. BMI increased significantly in the year after transplant, with risks regarding obesity and associated cardiovascular risk and premature death, morbidity and lower perception of their HRQoL. Strategies must be thought, including a better nutritional status at transplant time, with, for instance, systematic use of G-tube feeding in those in need. It is imperative to improve growth in children with CKD, due to the colossal impact in this children self-esteem and quality of life, which is often underrated by healthcare workers.

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Lisboa, 2 de Julho de 2021

Nossa Refª. Nº 113/21

**Assunto:** Projeto **"Crescimento após transplante renal pediátrico (Growth after Pediatric Kidney Transplantation)**

**Relator:** *Mestre Enfermeira Graça Roldão*

Pela presente se informa que o projeto citado em epígrafe, obteve, na reunião ocorrida em 4 de Junho de 2021, parecer favorável da Comissão de Ética, considerando-se observados os imperativos que fundeiam as Boas práticas clínicas, os preceitos internacionalmente reconhecidos de qualidade ética e científica que devem ser respeitados na conceção e na realização dos estudos clínicos que envolvam a participação de seres humanos.

No uso das competências próprias constantes do disposto no Decreto-Lei. N.º 97/95 de 10 de Maio, e no exercício das suas funções em observância ao deliberado na Lei n.º 21/2014 de 16 de Abril, que aprova a lei da investigação clínica, na sua atual redação alterada pela Lei n.º 73/2015 de 27/07/15, complementada pelo Decreto-Lei n.º 80/2018 (DR n.º 198-2018, Série I de 2018/10/15) que reforça o papel das comissões de ética no contexto da instituição em que se integram, na sua missão de contribuir para o cumprimento de princípios da ética e da bioética, na prestação de cuidados de saúde e na realização de investigação clínica, e ainda em harmonia com os regulamentos internos do CHULN, os códigos deontológicos, as convenções, e as recomendações constantes das declarações e diretrizes internacionais, designadamente as Declarações de Helsínquia a de Tóquio, da Organização Mundial de Saúde e da União Europeia, a Comissão de Ética avaliou o projeto, que considera obedecer aos requisitos éticos fundamentais que devem ser respeitados, refletindo o primado da dignidade e da integridade humanas.

Encontra-se assegurado o direito à integridade moral e física do participante, cumpre as precauções essenciais, cujo desígnio visa minimizar eventuais danos para os seus direitos de personalidade, bem como o direito à privacidade e à proteção dos dados pessoais que lhe dizem respeito, respeitando os imperativos refletidos no Regulamento Geral sobre a Proteção de Dados (RGPD) entrado em vigor em 25 de Maio de 2016 e plenamente aplicável a partir de 25 de Maio de 2018, (Regulamento (UE) 2016/679 do Parlamento Europeu e do Conselho de 27/04/16), de 27 de abril, publicado no Jornal Oficial da União Europeia, no dia 4 de Maio de 2016, e na Lei n.º 58/2019, de 8 de Agosto.

Mais se informa que o referido estudo foi autorizado pelo Sr. Diretor Clínico, Dr. Luis Pinheiro

Com os melhores cumprimentos

**O Presidente da Comissão de Ética do CAML**

Prof. Doutor João Forjaz Lacerda

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