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CASE SERIES

Somatotropic axis and molecular markers of mineral metabolism in children undergoing chronic peritoneal dialysis

Eje somatotrópico y marcadores moleculares del metabolismo mineral en niños en diálisis

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Abstract

Growth failure is one of the most relevant complications in children with chronic kidney disease (CKD). Among others, growth hormone (GH) resistance and bone mineral disorders have been identified as the most important causes of growth retardation. **Objectives:** 1. To characterize bone mineral metabolism and growth hormone bio-markers in CKD children treated with chronic peritoneal dialysis (PD). 2. To evaluate height change with rhGH treatment. **Patients and Method**: A longitudinal 12-month follow-up in prepuberal PD children. Exclusion criteria: Tanner stage > 1, nephrotic syndrome, genetic disorders, steroids, intestinal absorption disorders, endocrine disturbances, treatment with GH to the entry of the study. Demographic and anthropometric data were registered. FGF23, Klotho, VitD, IGF-1, IGFBP3, and GHBP were measured to evaluate mineral and growth metabolism. **Results:** 15 patients, 7 male, age 6.9 ± 3.0 y were included. Time on PD was 14.33 ± 12.26 months. Height/age Z score at month 1 was –1.69 ± 1.03. FGF23 and Klotho: 131.7 ± 279.4 y 125.9 ± 24.2 pg/ml, respectively. 8 patients were treated with GH during 6-12 months, showing a non-significant increase in height/age Z-score during the treatment period. Bivariate analysis showed a positive correlation between Klotho and delta ZT/E, and between GHBP vs growth velocity index ($p < .05$). **Conclusions:** FGF23 values were high and Klotho values were reduced in children with CKD in PD, comparing to healthy children. Somatotropic axis variables were normal or elevated. rhGH tends to improve height and there is a positive correlation of GHBP and growth velocity in these children.

Keywords:
Growth;
GH;
FGF23;
Klotho.

Growth is a complex process that involves sequential changes in the morphology and function of cells. Particularly in bone growth, these changes occur in chondrocytes and osteocytes, therefore, any condition that blocks this process may cause bone deformities or a reduction in growth potential. Studies have shown that chronic kidney disease (CKD) and secondary hyperparathyroidism can significantly affect growth progression[1].

Growth in childhood can be divided into 3 sta-

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ges. During lactation, the phase of the fastest increase in height, dependent on nutrient intake, occurs. In mid-childhood, the growth rate remains constant at 5-7 cm/year, controlled by growth (GH) and thyroid hormones. Finally, during puberty, through the GH/insulin-like growth factor1 axis, IGF1, and initiated by sex hormones, the puberty growth spurt is stimulated[2], but delayed in CKD due to a pulsatile secretion loss of the hypothalamic gonadotrophin hormone (GnRH)[2,3].

CKD is characterized by delayed growth not being able to reach the final adult size estimated by genetics[4]. According to data from the North American Pediatric Renal Trials and Collaborative Studies in 2011, 36.9% of children with CKD have a delayed growth, and the extent correlates with the deterioration of kidney function, with an average height of -1.85 SD. In Chile, according to the 2007 National Registry of the disease, 50% of patients with CKD have a delayed growth[4].

The etiology of under height for age in CKD is multifactorial. Primary kidney disease, nutritional deficit, metabolic acidosis, hydroelectrolytic disorders, anemia, alterations of mineral metabolism, age at onset of CKD, chronic steroid treatments, and alterations of the GH/IGF1 axis are among the key associated factors[3,5].

GH in CKD is found in either normal or increased values and its half-life is extended due to resistance to its action. The binding of GH to its receptor in tissues stimulates receptor dimerization and autophosphorylation of tyrosinkinases, Janus kinase 2, phosphorylating the transcription signal proteins, STAT (1, 3 and 5). The phosphorylated STAT (STATp) are translocated to the nucleus, activating the gene expression regulated by GH[1,2,6,7].

GH has an effect through IGF-1 produced in the liver. However, IGF-1 is also secreted locally in the growth plate, acting as a paracrine/autocrine factor[6,7]. In CKD, plasma IGF-1 levels may be normal or decreased, but its bioactivity is low[6,7]. This protein is carried through plasma by binding proteins, IGF -BPs (1 to 6), which prevent rapid metabolism. 99% of IGF-1 is bound to IGFBP-3[8] and to acid-labile subunit (ALS) 7[7], forming a ternary complex. In CKD, these IGF-BPs are increased due to a decreased clearance. On the other hand, the expression of the GH receptor in white cells and the hormone-carrying protein GHBP are decreased[2,3,5].

Recombinant GH (rhGH) is an effective and safe therapy for the treatment of short stature in CKD. However, despite its use, a final height close to -2 SD is still observed in all populations studied[1].

According to an international consensus published in 2006[9], a treatment with rhGH should be considered in all patients with glomerular filtration rate < 75 ml/min/1.73 m^2, undergoing medical or dialytic treatment or kidney transplant recipients the year following the intervention, with a ZT/E score of <-1, 88 (<p3) or growth rate (GR) SD <-2[7]. The greatest effect on GR is achieved at the first year of therapy, to decline thereafter[10].

Chronic kidney disease (CKD) and secondary hyperparathyroidism can significantly affect bone growth. Alterations in mineral metabolism occur in the early stages of CKD and progress as kidney function deteriorates. These alterations are attributed to changes in the parathyroid hormone (PTH) and to the vitamin D axis that subsequently lead to disorders in the metabolism of calcium and phosphorus[11]. Fibroblast growth factor 23 (FGF23) is a key regulator[12,13]. FGF23 is synthesized by osteocytes of mineralized bone[13], which under mechanical stress, generate transduction signals regulated by endocrine signals, modifying bone architecture and mineral homeostasis[14]. FGF23 reduces plasma phosphate levels, inducing phosphaturia and suppressing the synthesis of 1.25 OH-vitamin D[15]. In addition, it decreases the transcription and secretion of PTH[16].

FGF23 requires Klotho, a single-pass transmembrane to cativate its receptor (FGF-Rs)[14,17,18]. Klotho deficiency has been described in CKD as resistance to FGF[19].

As FGF23 production occurs in osteocytes and its main renal feedback is 1.25 OH-vit D, it is important to know how phosphatonin affects osteocyte metabolism and its impact on bone growth. The relationship among growth, GH-IGF1 axis and mineral metabolism markers, FGF23-Klotho, in children with CKD, has not been yet clarified.

The primary objective of this study was to characterize markers of mineral metabolism: FGF23-Klotho and the somatotropic axis: IGF1, IGFBP3 and GHBP in pediatric patients on chronic peritoneal dialysis (PD), and the secondary objective was to evaluate the change in height of patients treated with rhGH.

Patients and Method

Design

A prospective descriptive study in children with CKD on PD at the Infant Nephrology Unit of Luis Calvo Mackenna and Roberto del Río hospitals, plus a 12-month followed up.

Inclusion criteria

Newborn > 33 weeks gestational age, Tanner stage 1, stable biochemical parameters and informed consent. Stable patient was defined according to KDOQI guidelines[20-22].

Exclusion criteria

Tanner ≥ 2; use of steroids, gastrointestinal malabsorption; endocrine diseases; genetic syndromes; ac-

tive nephrotic syndrome; use of recombinant growth hormone at the start of the study; without consent to participation in the study.

The protocol was approved by the Ethics Committee of each hospital, the Ethics Committee of the Faculty of Medicine of Universidad de Chile and by the Ethics Committee of Fondecyt.

Variables evaluated

1. *Demographic variables:* age, sex, CKD etiology, age of onset of PD and time on PD.

2. *Anthropometric variables:* At the start of the study, at 6 and 12 months, and based on Z-scores, the following information was registered: weight, age (ZW/A) and height/age (ZH/ A), body mass index (ZBMI) and Growth rate (GR). The weight was determined using a scale (Seca Corporation, Hamburg, Germany) with 0.1 kg accuracy and 150 kg maximum weight. Height was measured using a 1 mm precision stadiometer. At the time of enrollment, all patients had carpal radiography to estimate bone age (BA).

Patients were evaluated at the start and during the follow-up by a child nutritionist to ensure caloric and protein intake according to the K-DOQI 2008 nutrition guidelines[22].

At follow-up at 6 and 12 months, there were two groups: treatment with rhGH (rGH +) and treatment without rhGH (rGH-).

To analyze the change in ZH/A during the 12-month follow-up in rGH + and rGH-, delta ZH/A (ZH/A month 12-ZT/A month one) was estimated for both bone chronological and bone corrected age. GR (cm / year) was expressed as a categorical variable according to percentile (p) of GR curves published in 1985 by Tanner et al[23]. It was defined as category 1: GR> p10; Category 2: GR <p10 (short stature).

3. *Biochemical variables:* creatininemia (mg/dl) (isotope dilution mass spectrometry, IDMS, VITROSÒ 4600 Chemistry System), urea nitrogen (mg/dl), venous gases, plasma electrolytes, albumin, calcemia, phosphemia, hemoglobin, hematocrit, ferritin, and intact PTH (immunoradiometric assay, CMIA, Immunotopics, San Clemente, CA) were obtained monthly through blood samples.

4. *Variables of mineral metabolism:* at the start of the protocol, levels of 25 (OH) vit D3 and 1.25 (OH) vit D3 (RIA), FGF23 (pg/ml, ELISA two sites, Immunotopics, San Clemente, CA) and Klotho (pg/ml, ELISA, Cusabio, China) were identified. The levels of FGF23 and Klotho were also identified at months 6 and 12 of the follow-up.

5. *Somatropic axis variables:* GHBP (ELISA kit CSB-E09149 h, Gentaur, detection range: 10 to 200 ng/mL), IGF-1 (ng/mL, RIA) and IGFBP-3 (mg/mL, IRMA) were identified in the plasma.

6. *Dialytic variables:* all children were treated with automated cyclic dialysis using the Baxter Home Choice PD System, with an exchange volume of 1.100 ml/m2 and concentrations of 1.5-4.25% Dextrose of Dianeal® according to the specific requirements of each patient. A total Kt/V urea of 2.1 was considered.

Statistical Analysis

Variables of normal distribution are expressed in averages and standard deviations. Those with non-normal distribution are expressed in medians and ranges. Differences among normal distribution groups were evaluating by the *t* test, and those with non-normal distribution by the Wilcoxon sign-rank test. Pearson's correlation coefficient was used to determine the association among the variables. $p < 0,05$ was considered significant. Data were analyzed using the SPSS program (SPSS Inc, Chicago, USA).

Table 1.

Parámetro	Mes 1 (promedio y DE)	Mes 12 (promedio y DE)
Calcemia (mg/dl)	9,8 ± 1,1	9,86 ± 1,04
Fosfemia (mg/dl)	5,4 ± 1,1	5,52 ± 1,06
PTH (pg/ml)	309,4 ± 271	392,4 ± 218,6
25 OH vit D (pg/ml)	32,1 ± 7,1	-
1,25 OH vit D (pg/ml)	22,8 ± 25,9	-
FGF23 (pg/ml)	131,7 ± 279,4	143,5 ± 324
Klotho (pg/ml)	125,9 ± 24,2	128,4 ± 36,3

PTH: hormona paratiroídea; FGF23: Factor de Crecimiento Fibroblástico 23.

Results

Fifteen patients aged 6.9 ± 3.0 years old (7 males) were enrolled. The age of onset of PD was 6.4 ± 3.7 years old, time in PD: 14.3 ± 12.3 months. Etiologies of CKD were kidney dysplasia in 6 patients, obstructive uropathy in 2, hereditary nephropathies in one, hemolytic uremic syndrome in 3, vasculitis in one and unknown in 2 patients.

Bone age in children on PD was delayed compared to chronological age (5.6 ± 2.9 versus 6.9 ± 3.0 years). Biochemical and mineral metabolic variables at the starting month in the study are shown in table 1. No significant differences in the variables were observed during the 12-month follow-up.

Biochemical parameters of the somatotropic axis at month one were expressed as a Z score for chronological age and adjusted for bone age. Z IGF-1: 0.72 ±

3.53 and Z IGF-1 EO 2.72 ± 4.88, and Z IGFBP-3 1.35 ± 1.63 and Z IGFBP-3 EO 2.32 ± 2, 15, respectively[24]. Quantification of GHBP resulted in an average value of 30.8 ± 35.8 ng/ml.

Anthropometric data at the start and end of the follow-up are shown in table 2. A ZW/A score of -1.41 ± 1, 11, ZT / E -1.69 ± 1.03, and Z BMI of -0.36 ± 1.14 was observed at admission. After adjusting the Z H/A score by bone age, the value was -0.12 ± 1.81. Table 2 also shows the anthropometric characteristics differentiating patients according to the use of rGH. An increase in the number of children receiving this therapy throughout the study period was observed, with 7/14 patients at month 6 and 8/12 at month 12. ZH/A score in the rGH + group did not show significant differences during the follow-up period (-1.7 ± 1.17 vs. -1.41 ± 0.84, p = ns). After adjusting the Z H/A BA score there were also no significant differences. In rGH + and rGH- patients, both groups had similar mineral and somatotropic axis metabolic markers, except for PTH at month 6, which was found to be significantly higher in rGH- children (p = 0.035) (table 3).

Table 2.

	Mes 1	Mes 6	Mes 12
n pacientes (hombres)	15 (7)	14 (7)	12 (6)
Z P/E	–1,41 ± 1,11	–1,43 ± 1,36	–1,25 ± 0,83
Z T/E	–1,69 ± 1,03	–1,65 ± 0,96	–1,32 ± 0,79
(n) rGH+	(0)	(7) –1,7 ± 1,17	(8) –1,41 ± 0,84
(n) rGH-	(15)	(7) –1,59 ± 0,79	(4) –1,14 ± 0,76
Z T/E EO	–0,12 ± 1,81	–0,22 ± 1,54	0,1 ± 1,83
(n) rGH+	(0)	(7) 0,28 ± 1,39	(8) 0,05 ± 1,51
(n) rGH-	(15)	(7) –0,71 ± 1,63	(4) 0,2 ± 2,64
Z IMC	–0,36 ± 1,14	–0,53 ± 1,11	–0,41 ± 1,01

P/E: peso/edad; GH: hormona de crecimiento; EO: edad ósea; IMC: índice de masa corporal.

Table 3.

	Mes 1	Mes 6	Mes 12
rGH+			
n (hombres)		7 (3)	8 (4)
Edad, años		7,3 ± 2,9	7,2 ± 2,1
PTH, pg/ml		178,5 ± 61,6	320,1 ± 204,3
FGF23, pg/ml		141,13 ± 248,6	10,68 ± 7,71
Klotho, pg/ml		138 ± 38,01	128,8 ± 32,24
Z IGF1	–0,16 ± 2,18		
Z IGF1 EO	1,84 ± 2,06		
Z IGFBP3	1,7 ± 1,67		
Z IGFBP3 EO	2,48 ± 1,71		
GHBP ng/ml	29,8 ± 32,9		
rGH–			
n (hombres)		7 (4)	4 (2)
Edad, años		6,8 ± 3,1	6,3 ± 3,2
PTH, pg/ml		483,3 ± 223,6[a]	363,9 ± 206,9
FGF23, pg/ml		130,07 ± 154,33	320,48 ± 482,29
Klotho, pg/ml		152,95 ± 15,72	127,7 ± 48,81
Z lFG1	1,34 ± 4,36		
Z IGF1 EO	3,61 ± 6,61		
Z IGFBP3	1,33 ± 1,06		
Z IGFBP3 EO	2,16 ± 2,72		
GHBP ng/ml	30,4 ± 46,9		

rGH: hormona de crecimiento; PTH: hormona paratiroídea; FGF23: Factor de Crecimiento Fibroblástico 23; IGF1: factor de crecimiento insulino-símil 1; EO: edad ósea; IGFBP3: Proteína fijadora 3 del factor de crecimiento insulino-símil; mGHBP: proteina fijadora de hormona de crecimiento. [a]diferencia significativa p 0,035.

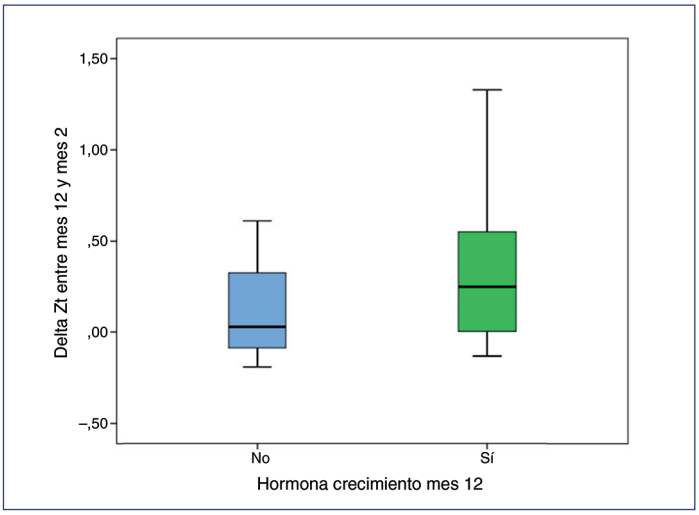

Figure 1.

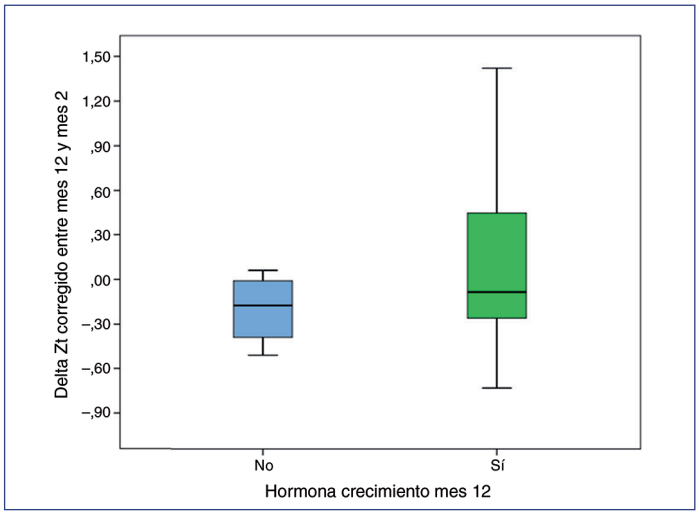

Figure 2.

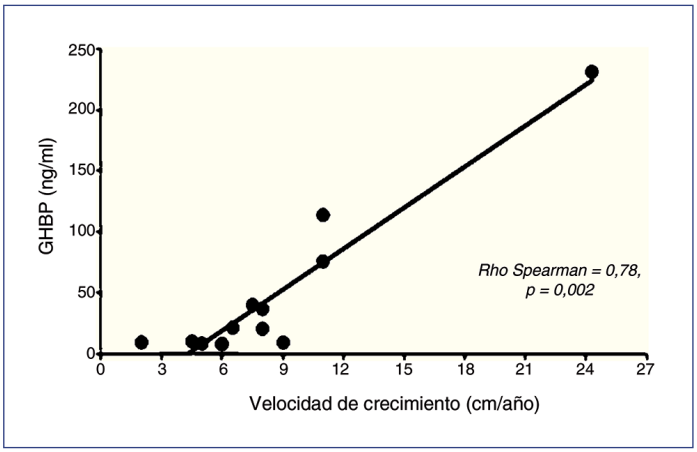

Figure 3.

Delta ZH/A (ZH/A month 12-ZH/A month one) for both chronological age and corrected bone age, showed no significant differences between rGH + and rGH- groups during the analyzed period (figures 1 and 2). At six-month follow-up, the GR of 7 rGH + patients was as follows: 5 in GR category 2 (short stature) and 2 in category 1; same scenario when adjusted by GR BA. At month 12, out of the 8 rGH + patients: only 2 were in category 2 and 3 grew below p10 when adjusted by GR BA.

A positive correlation was observed between BMI at month 12 and delta ZH/A ($p = 0.015$, coefficient of Pearson correlation: 0.68) and between Klotho and delta ZH/A BA levels ($p = 0.045$, Pearson correlation coefficient: 0.725) during the bivariated analysis. GHBP showed a negative correlation with chronological age, bone age, weight, height and BMI, and a positive one with GR ($p = 0.002$, correlation coefficient = 0.78) (figure 3).

The loss of patients during the study occurred at month 6 due to: kidney transplant from a living donor; and at month 12: 2 children due to kidney transplant from a deceased donor and another due to transfer to hemodialysis.

Discussion

Growth delay remains a major problem in children with CKD. Despite advances in medical management and kidney replacement therapies, 30-60% of children experience short stature in adulthood[25].

In this study, children on stable PD (according to K-DOQI guidelines) showed a significant height deficit, therefore, it is important to know the pathophysiological mechanisms that lead to this disorder.

Secondary hyperparathyroidism of CKD interferes with longitudinal growth, leading to destruction of growth plate. However, slight elevations of PTH are considered necessary to stimulate the expression of vitamin D receptors in growth plate and local synthesis of IGF-1[26]. The discovery of the FGF23 proteins and their cofactor Klotho represents an important advance in dealing with this pathology. FGF23 decreases phosphate reabsorption in the proximal tubule by reducing the expression of sodium-phosphate cotransporter 2a (NaPi-2a) in the apical membrane, generating phosphaturia and suppressing the Cyp27b1 gene encoding 1 a-hydroxylase enzyme, responsible for the second hydroxylation and activation of 25 (OH) vit D3. Igualmente, aumenta la expresión del gen Cyp24 que codifica para 24-hidroxilasa, enzima que inactiva la vitamina D[27,28]. In a previous study of the research team as well as in the patients of this study, FGF23 values in children with CKD on PD were found to be significantly higher than the mean value observed in

the control group of healthy children. The Klotho cofactor analysis showed lower values than the control group, and no association with FGF23 or with other biochemical variables studied were found[28]. Sugiura et al., measured the expression of soluble Klotho using an ELISA kit in patients with CKD and in controls, confirming that this protein has decreased levels in uremic patients[29].

Wesseling-Perry et al., reported results in 52 patients with grade 2-4 CKD, aged between 2 and 21 years. Plasma FGF23 levels were related to bone mineralization defects, suggesting that this hormone could be associated with height retardation in children with CKD[30]. In this study, the bivariate analysis did not confirm these results and only showed a significant correlation between Klotho levels and delta Z H/A BA, something that should be verified with other studies and whose possible association need further analysis.

The IGF network is composed of 2 types of ligands: cell surface membrane receptors and 6 soluble binding proteins, IGF-BP. This is fundamental for embryonic and postnatal growth and plays an important role in immune system function, lymphopoiesis, myogenesis and bone growth. The binding of IGF to its receptor, IGF-1R, activates intrinsic protein tyrosine-kinase activity, resulting in intracellular signals that regulate various biological responses[8].

Osteocytes are the largest cell subtype at bone level (90-95% of bone cells). Their star shape and dendritic projections allow close intercellular exchange with the pericellular matrix, converting mechanical stimuli into biochemical and electromechanical signals. These cells respond to hormonal stimuli such as: PTH, 1.25 (OH) vit D3, calcitonin, glucocorticoids, estrogens and testosterone, and have their own endocrine properties synthetizing sclerostin, matrix extracellular phosphoglycoproteins (PHEX, DMP1 , MEPE), FGF-23, etc., among others[14].

IGF-1 is synthesized in the liver and locally in the growth plate. It circulates in the blood along with IGFBP and ALS. In CKD, IGFBP has been reported to be 1.5 times higher than IGF-1, reducing the biologically active free IGF-1[2]. It has recently been reported that local bone production of IGF-1 by osteocytes, osteoblasts and chondrocytes has been observed. Therefore, the local IGF-1 production is involved in bone turnover, modeling, and remodeling. Transgenic mice studies with conditional knockout of Igf1 in osteocytes show a malfunction of postnatal periosteal longitudinal and bone growth, whereas a reduction of hepatic IGF-1 of more than 75% does not have a significant impact on growth[31]. This may partly explain the results of this study, since although children on PD have adequate levels of IGF-1, they have a significant stature retardation.

Somatotropic axis disorders in children with CKD occur at different levels of the signal pathway. GH levels vary considerably at different stages of development. In the prepubertal stage, its secretion is either normal or increased through a negative feedback of IGF-1 decrease, but during puberty, it decreases by inhibition mediated by sex hormones. GHBP and the GH receptor are decreased and at the post-receptor level, there are defects in the JAK2/STAT signals[32,33].

Studies in children with CKD have demonstrated normal or increased baseline levels of GH, therefore, a resistance to growth hormone[2]. Some of the mechanisms that explain this phenomenon include: decreased expression of the GH receptor gene[34,35], decreased IGF-1 gene expression[35], increased binding of IGF-1 to transport proteins[36] and post-receptor defects of IGF-1[37]. Our biochemical parameters of somatotropic axis at month one, revealed that IGF-1 is in the normal-high range, although with a great deviation. As for IGFBP-3, it is increased as described by other authors.

GHBP is produced by the proteolytic cleavage of the GH receptor, releasing the extracellular domain into circulation. This is why some authors consider GHBP as a marker of GH receptor abundance in tissues[38]. However, there is great controversy regarding the interpretation of the values found[6,39,40]. In our study, a great variation in GHBP levels was observed, similar to that reported by Toenshoff, assuming a non-normal distribution. In addition, GHBP values correlated with BMI (expressed in SD) and proved to be the best predictor of GR in the cohort of patients studied[41].

We observed a significant correlation between GHBP levels and GR in our patients, but not with the other growth parameters or BMI. However, the patients of the studies discussed were in the predialysis phase and the method of measurement of GHBP was based on an assay on an immune-functional ligand vs. the enzymatic assay used in our study[41].

Our research group published an in vitro study of intracellular GH axis in children with CKD. The results showed a significant decreased JAK-2 phosphorylation and a decreased STAT-5b translocation to the nucleus, resulting in a decreased expression of target proteins such as IGFBP3[42]. These defects are consistent with Schaefer et al findings in experimental models in uremic rats, observing a decreased phosphorylation of JAK-2 and STAT-5; decreased translocation of phosphorylated STAT proteins to the nucleus and increased SOCS inhibitory proteins compared to healthy rats[43].

RhGH treatment has shown to significantly improve stature in these patients, with an increase of 0.73 SD in children under 5 years old and 0.26 SD in those older than 6 years old, after a year of treatment[4,7]; however, this treatment does not completely reverse the growth deficit, resulting in a final stature shorter

than the expected by genetics. This was corroborated in our study, as the children treated with rhGH did not present a significant increase of the Z H/A score. This could have been influenced by the duration of therapy (less than one year) and the genetic potential of the parents, something not considered in the analysis of our results.

All the above shows that growth retardation in children with CKD is even more complex than what is known so far, and understanding the mechanisms that determine growth will allow new therapies under study such as recombinant IGF-1, recombinant IGFBP3 and IGFBP blockers can improve GH resistance to better manage these patients.

Ethical Responsibilities

Protection of People and animals: The authors reported that no experiments on either people or animals have been performed.

Confidentiality of personal data: The authors reported that no patient data is contained in this article.

Privacy Right and informed consent: The authors have obtained the informed consent from patients and/or subjects referred to in the article. These documents are in the possession of the corresponding author.

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Conflict of interests

The authors declare no conflict of interest.

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