Original Article

Influence of Cinacalcet on Insulin-like Growth Factor-1 in Children on Regular Hemodialysis for End-stage kidney disease.

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ABSTRACT

Introduction: End-stage kidney disease (ESKD) in children is associated with multifactorial growth failure. Control of patients' parathyroid hormone level (PTH) may improve their growth.
Aim of the study: The study aimed to assess the relationship between PTH and IGF-1 levels in the blood and the impact of Cinacalcet on IGF-1 levels in children with ESKD on regular hemodialysis.
Methods: Thirty-five children with ESKD, aged eight to eighteen, on regular hemodialysis with uncontrolled hyperparathyroidism (HPT), were included in this prospective analysis. Cinacalcet was given to every child for three months. Blood IGF-1, parathyroid hormone (PTH), serum calcium, phosphorus, and alkaline phosphatase (ALP) were measured before and after three months following the administration of Cinacalcet.
Results: Serum IGF-1 levels were increased by 37.01 (± 22.07) % after cinacalcet therapy. Cinacalcet effectively lowered PTH levels by 58.3 (± 17.65) %. The mean value (± SD) of the percentage of change in Ca^{2+}, phosphorus, and ALP were -2.3 (± 1.78) %, -8.1 (± 12.27) %, and 72 (± 5.24) %, respectively, which was a statistically significant change. Serum IGF-1 and serum PTH (r=-0.465 and P= 0.001), Ca2+ (r= -0.399 and P= 0.001), and serum phosphorus (r= -0.342 and P= 0.003) all showed a significant negative correlation.
Conclusions: For children with ESKD, cinacalcet controls sHPT and increases blood IGF-1 levels.
Keywords: Cinacalcet, Insulin-Like Growth Factor-1, Pediatric, ESKD, Hemodialysis.

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INTRODUCTION

The CKD burden in Egypt increased by 36 % from 2009 to 2019, matching the worldwide trend. CKD is ranked the fifth main reason for pediatric mortality [1]. Growth retardation is a prevalent occurrence in children with ESKD, a condition that is multifactorial [2]. Secondary hyperparathyroidism (sHPT) is one of these factors. Standard of care therapy (SOC) for sHPT in children with ESKD consists of dietary calcium supplements, phosphate-binding agents, and calcitriol; however, they are frequently inadequate to permit patients to reach their targeted blood Ca2+, PTH, and calcium-phosphorus product (Ca x P) objectives [3].

The calcimimetic "cinacalcet" is an allosteric calcium-sensing receptor (CaR) modulator that enhances calcium receptor affinity and, thus, boosts calcium's extracellular strength, leading to reductions in PTH secretion and synthesis [4]. In Europe, cinacalcet is recommended for patients aged 3 and above with ESKD who receive regular dialysis and whose SOC treatment does not properly control sHPT [5, 6]. Treatment with calcimimetics restores the sHPT-associated changes in vitamin D and CaR expression and proliferation of parathyroid cells [7].

Growth hormone (GH) indirectly stimulates a child's growth by boosting insulin-like growth factor 1 (IGF-1) synthesis. Several children with kidney failure have normal or increased GH levels in their blood. At the same time, IGF-1concentrations are decreased since approximately 98% of IGF-1 is bound to one of the binding proteins (BP) that accumulated in the circulation due to a decrease in their clearance by the kidney, so this accumulated protein will reduce the binding of IGF-1 to its receptors and decrease its function [8, 9].

Monitoring growth velocity in children with ESKD requires a long follow-up period to notice small differences in growth velocity; however, the evaluation of IGF-1 level is an earlier marker for evaluating growth potentials [10].

Although the correlation between cinacalcet administration and reductions in PTH level was previously studied [11-13], to the best of our knowledge, no data has demonstrated the effect of cinacalcet on IGF-1. We hypothesized that using cinacalcet in controlling hyperparathyroidism in children with uncontrolled sHPT may improve growth in children with ESKD on regular hemodialysis.

METHODS

This prospective study involved 35 pediatric ESKD patients aged 8 to 18 on regular hemodialysis with uncontrolled sHPT. The Tanta University Hospitals (TUH) Ethical Committee cleared the research (approval code: 36264PR295/8/23).Written informed consent was obtained from the patient's family guardians. The study was conducted from August 2023 to February 2024 at TUH in the pediatric nephrology unit.

Patient selection

If the glomerular filtration rate (GFR) was ≤15 ml/min/1.73 m2 and hemodialysis was necessary for more than three months, a pediatric nephrologist diagnosed ESKD. All patients were on regular hemodialysis three times a week.

Children with PTH > 300 pg/ml, despite high doses of active vitamin D (alfacalcidol) that cannot be further

increased for fear of hypercalcemia, were included. A comprehensive evaluation was performed on all children: history taking with details on dialysis duration and medications taken, clinical examination as heart rate, blood pressure monitoring, and anthropometric measurements.

Patients were receiving supportive treatment, including a low phosphate diet, 100 mg/kg BW/month of intravenously administered iron dextran, 50 IU/kg BW/session of erythropoietin, 1 mg/day of oral folic acid, 1000 mg/day of oral calcium, and 0.01-0.05 μg/day of oral vitamin D (calcitriol). In addition, hypertensive patients were given antihypertensive medication.

Exclusion criteria

Patients with prior parathyroidectomy, serum calcium level <8.4 mg/dL, seizure disorder on anti-convulsant medication should be cautious when using cinacalcet due to its potential to exacerbate hypocalcemia and lower seizure threshold, hepatic dysfunction as cinacalcet is metabolized by the liver, allergic reactions, and ongoing growth hormone therapy.

Laboratory investigations

Serum creatinine, blood urea, ionized calcium, serum phosphorus, iPTH, and alkaline phosphatase were assessed in patients within three hours of dialysis. The assay of serum IGF-1 levels was performed after centrifugation of the clotted samples at 1500 xg for 15 minutes and then stored in an alicot at -20°C then subsequent assay of IGF-1 serum level by enzyme amplified sensitivity immunoassay (EASIA) technique (DIA source Immunoassays SA, Nivelles, Belgium; KAP1581). The interassay coefficient of variation was 11.5% and 5.2% at 193.3 and 466.15 ng/mL, respectively.

Dialysis description

The Fresenius 4008-S dialysis machine (Germany) was used to dialyze patients at a blood flow rate of 5ml/kg/minute. High flux hollow-fiber dialyzers were employed, which were calibrated to the body surface area (BSA) of the patients (Fresenius, Fx40 = 0.7 m2, Fx50 = 1.0 m2, and Fx60 = 1.2 m2). The dialysate temperature was maintained at 37°C, and bicarbonate dialysis solutions were employed (Na 140 mEq/L, K 2 mEq/L, Ca 1.25 mmol/L, bicarbonate 32 mEq/L).

Treatment Received

In addition to receiving supportive care, all children were given cinacalcet for three months. Starting at 0.5 mg/kg/d, the dosage was titrated every two weeks until a maximum of 1.5 mg/kg/d was reached or until iPTH was less than 300 pg/mL. Serum IGF-1, PTH, serum Ca2+, phosphorous, and ALP were measured before and 3 months after Cinacalcet administration. The primary outcome was the alteration in serum IGF-1 following a three-month course of cinacalcet treatment. The secondary outcomes were the alteration in blood PTH, Ca 2+, phosphorus, alkaline phosphatase, and the relationship between serum IGF-1 and PTH, Ca 2+, and phosphorus.

Sample Size Calculation

Universität Kiel, Germany's G*Power 3.1.9.2 performed the sample size computation. After conducting pilot research with five patients, we discovered that the mean difference in IGF-1 levels before and after cinacalcet treatment was 11 ng/ml, with a common standard deviation of 9.6. The sample size was determined based on the 0.961 effect size, 95% confidence limit, 95% research power, and the addition of five cases to

overcome dropout. As a result, 35 patients were recruited.

Statistical analysis

IBM Inc., Chicago, IL, USA's SPSS v27 was utilized for statistical analysis. The quantitative data were presented as mean ± standard deviation (SD), and the paired Student's t-test was employed to compare the two measures. The data was analyzed using the Fisher's exact test or Chi-square test, and qualitative variables were reported as frequency and percentage (%) when applicable. The correlation between the variables was ascertained using the Pearson correlation for normally distributed linearly linked variables. A P-value with two tails less than 0.05 was considered statistically significant.

RESULTS

This study enrolled 35 patients (13 males and 22 females) with a mean age of 12.7 ± 3.39 years. **Table 1** displays the characteristics of the patients. Anthropometric measures did not significantly alter before and after cinacalcet treatment (P > 0.05). Serum IGF-1 levels were significantly elevated after cinacalcet therapy (P value<0.001). While serum PTH, Ca2+, phosphorus, and alkaline phosphatase (ALP) were significantly decreased after cinacalcet therapy (P value<0.001). **Table 2**

Serum PTH showed a negative correlation (r=-0.465 and P value<0.001) with serum IGF-1 and a positive correlation (P value<0.05) with serum creatinine, C reactive protein (CRP), Ca2, and alkaline phosphatase. **Figure 1A** Serum IGF-1 showed a negative correlation with Ca2+(r= -0.399 and P value<0.001), **Figure 1B** and serum phosphorus (r= -0.342 and P value = 0.003) **Figure 1C. Table 3** and Serum parathormone.

Table 1: Clinical data of the studied patients

Age (years)	12.7 ± 3.39			
Sex	Male	13 (37.14%)		
	Female	22 (62.86%)		
Clinical data	**Before (n=35)**	**After (n=35)**	**Percent of change**	**P value**
Weight Z score	0.52 ± 0.46	0.51 ± 0.46	0.005 ± 0.01	0.855
Height Z score	-2.38 ± 1.4	-2.39 ± 1.5	0.004 ± 0.01	0.94
BMI Z score	1.52 ± 1.4	1.518 ± 1.4	-0.001 ± 0	0.083
Heart rate (beats/min)	100.1 ± 10.42	99.9 ± 10.5	-0.143 ± 0.49	0.096
Systolic blood pressure (percentiles)	61.3 ± 18.96	59.1 ± 18.69	-2.143 ± 7.10	0.083
Diastolic blood pressure (percentiles)	59.4 ± 19.24	58 ± 19.9	-1.429± 5.89	0.16
Kt/V	1.5 ± 0.18	1.4 ± 0.17	-0.54 ± 1.78	0.083
IDWG	3.2 ± 0.31	3.1 ± 0.31	-0.37 ± 1.29	0.103

Data are presented as mean ± SD

Table 2: Laboratory data of the studied patients

	Before (n=35)	After (n=35)	Percent of change	P value
Hemoglobin (g/dl)	10.7 ± 0.93	10.9 ± 1.07	1.86 ± 1.61%	0.17
Serum creatinine (mg/dl)	7.3 ± 1.03	7 ± 1.52	-1.18 ± 25.85 %	0.453
Blood urea (mg/dl)	180.2 ± 19.93	177.1 ± 46.38	-28.92 ± 24.45 %	0.84
Serum CRP (mg/dl)	9.8 ± 2.62	9.6 ± 2.39	-1.61 ± 7.99 %	0.058
Serum PTH (pg/ml)	507.63 ± 138.85	211.1 ± 104.85	-58.3 ± 17.65%	<0.001*
Serum Ca^{2+} (mg/dl)	10.7 ± 0.64	10.5 ± 0.67	-2.3 ± 1.78%	<0.001*
Serum phosphorus (mg/dl)	6.8 ± 0.79	6.2 ± 1.11	-8.1 ± 12.27%	<0.001*
Serum ALP (U/l)	314.3 ± 100.26	85.5 ± 25.06	72 ± 5.24%	<0.001*
Serum IGF-1 (ng/ml)	64.46 ± 17.82	88.26 ± 28.98	37.01 ± 22.07%	<0.001*

The data is shown as mean ± SD. * P values ≤0.05 are considered significant

Table 3: Correlation between PTH, IGF–1 and other laboratory data of the studied patients(n=35)

Serum PTH (pg/ml)		
Serum creatinine (mg/dl)	**R**	0.239
	P value	0.045*
Serum CRP (mg/dl)	**R**	0.397
	P value	0.005*
Serum Ca^{2+} (mg/dl)	**R**	0.430
	P value	<0.001*
Serum phosphorus (mg/dl)	**R**	0.319
	P value	0.007*
Serum ALP(U/l)	**R**	0.658
	P value	<0.001*
Serum IGF-1 (ng/ml)	**R**	-0.465
	P value	<0.001*
Serum IGF-1 (ng/ml)		
Serum calcium (mg/dl)	**R**	-0.399
	P value	<0.001*
Serum phosphorus (mg/dl)	**R**	-0.342
	P value	0.003*

r: Pearson coefficient. * Significant as P value≤0.05.

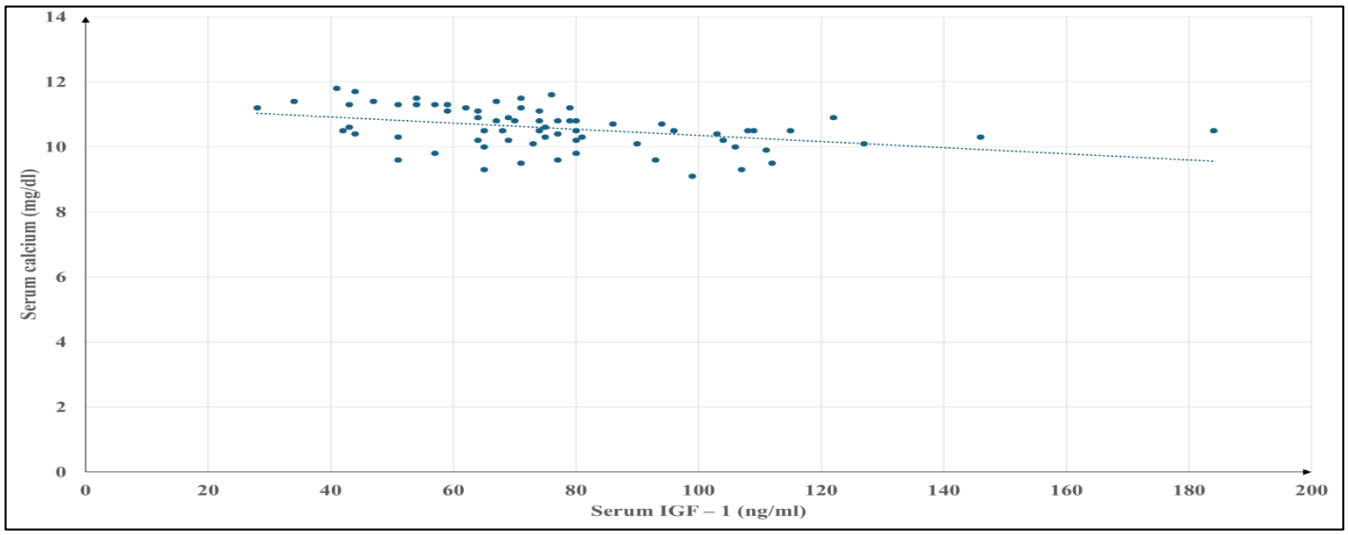

Figure 1: A: Correlation between Serum IGF-1: insulin-like growth factor 1 and serum Calcium

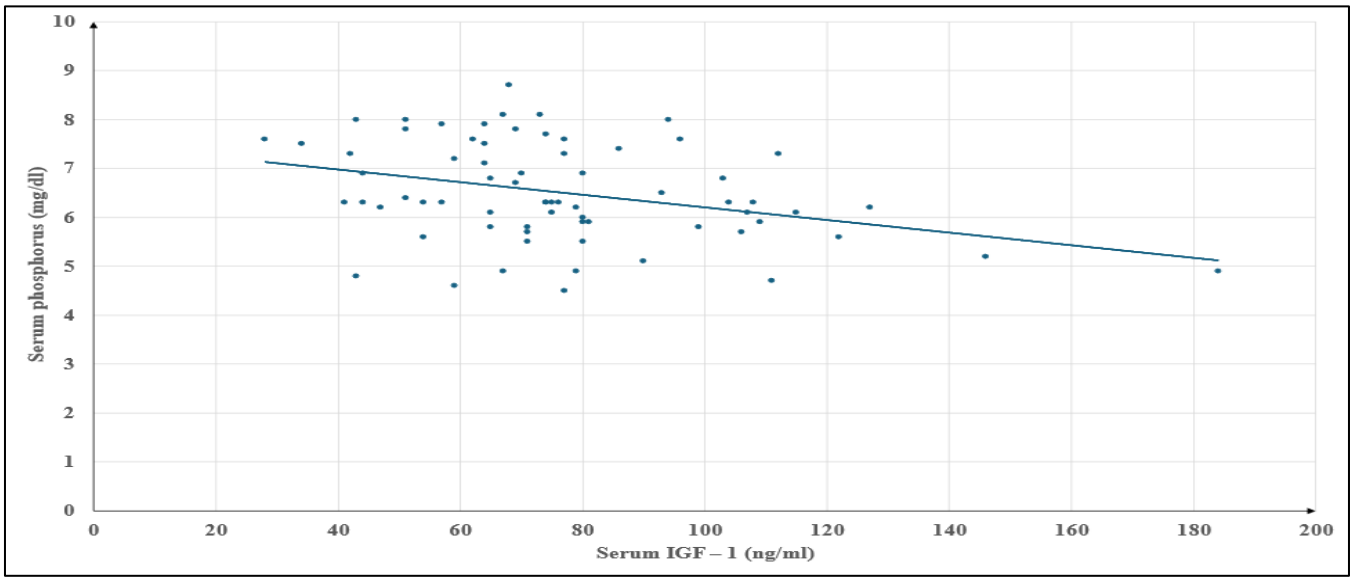

Figure 1: B: Correlation between Serum IGF-1: insulin-like growth factor 1 and serum Phosphorus

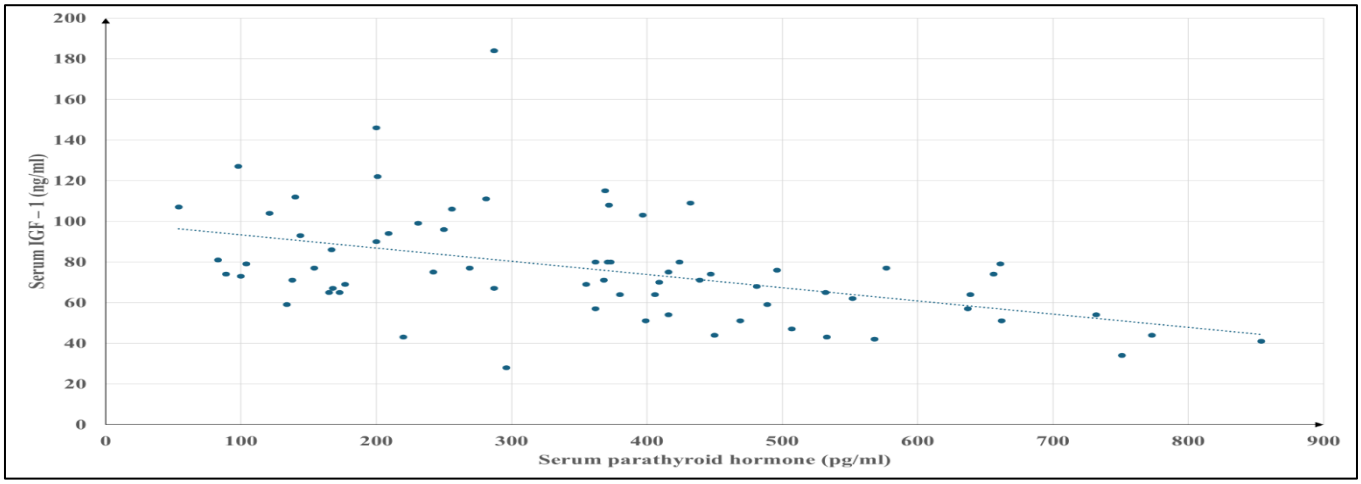

Figure 1C: Correlation between serum parathyroid hormone and serum IGF-1

DISCUSSION

Achievement of adequate growth in children with ESKD is a potential target. Without effective control of secondary HPT, this goal cannot be reached. The direct impact of PTH on growth has not been sufficiently elucidated; additionally, the absolute optimal ranges for PTH that optimize growth or minimize growth failure have not yet been determined **[14]**.

Diminished linear growth was described in children with CKD on intermittent calcitriol therapy, especially those with adynamic bone disease **[15, 16].** In the large Pediatric PD Network Registry, The clinical and radiological symptoms of sHPT were significantly apparent when PTH concentrations exceeded 300 pg/ml, and time-averaged PTH concentrations above 500 pg/ml were associated with impaired longitudinal growth **[17]**. Arenas et al.**[18]** found that The linear growth demonstrated a substantial improvement during cinacalcet therapy ($\triangle$SDS -0.62 ± 1.2 versus $+0.91 \pm 1.4$; $p < 0.005$). These previous studies suggest that reducing PTH may improve growth; however, the mechanism is unclear.

The present study demonstrated that serum IGF-1 levels significantly rose after 3 months of cinacalcet therapy. In addition, serum PTH, Ca2+, phosphorus, and ALP decreased significantly after cinacalcet therapy. The elevated level of IGF1 after Cinacalcet administration could be explained by the decline of serum PTH level **[19]**. The decrease in ALP suggests that bone turnover is decreasing. Notably, most of our patients had high turnover bone disease since their intact PTH and alkaline phosphatase were highly elevated.

The efficacy of cinacalcet in controlling sHPT is well documented. Warady et al. **[11]** reported that 7.4 to 57.1% of participants who received cinacalcet achieved PTH levels within 3 months of the suggested goal limits, while 22.2% to 70.6% reported a $\geq$ 30% drop in PTH levels, serum calcium levels decrease significantly from baseline within 3 months and serum phosphorus level showed the greatest reduction after 2 months of treatment with cinacalcet in pediatric subjects with sHPT receiving dialysis. Manaka et al. **[20]** found that the levels of corrected serum Ca2+ and intact PTH were considerably decreased by Cinacalcet therapy. Other study **[21]** compared cinacalcet with SOC showed that the PTH levels decreased in the cinacalcet group more in comparison to the control group (81.8 vs. 21.6%

respectively) with a concurrent decrease in serum calcium (-6.5 vs. +0.9%) and serum phosphorus (-3.6 vs. -1.1%).

The ability of cinacalcet to inhibit PTH production enables the reduction of Ca2+, phosphorus, and calcium-phosphorus products, giving another option for treatment for a subset of individuals for whom parathyroidectomy was the sole possibility. Our results revealed a negative correlation between serum PTH and IGF-1. Few reports in the literature are linking PTH to IGF-1. Elis et al. [22] reported that PTH has simultaneous anabolic and catabolic activities on human and animal skeletal systems. PTH initiates a signaling cascade by attaching to its osteoblast receptor, stimulating the production of phosphoinositide protein kinase C (PKC) and cAMP protein kinase A (PKA). This results in the gene transcriptional activation associated with osteoblast development and activity, like osteocalcin, or genes involved in osteoclast activity, such as RANKL. Emerging data indicate that the effects of IGF-1 and PTH on bone are synergistic and that the local synthesis of IGF-1 controls a portion of the anabolic benefits of PTH [23].

LIMITATIONS OF THE STUDY

The study's duration was short, so the effect of the treatment on growth velocity cannot be noticed. The control group (without cinacalcet treatment) is lacking due to limited patient numbers.

RECOMMENDATIONS

Further studies with more subjects and a longer treatment period have to be designed in the future for better determination of cinacalcet effect on bone metabolism and BMD in hemodialysis pediatric patients with refractory hyperparathyroidism

CONCLUSIONS

Cinacalcet effectively manages sHPT and improves serum IGF-1 levels in children with ESRD.

ABBREVIATIONS

ALP	alkaline phosphatase
CaR	calcium-sensing receptor
EASIA	enzyme amplified sensitivity immunoassay
ESKD	End-stage kidney disease
HPT	Hyperparathyroidism
IGF-1	insulin-like growth factor 1
PTH	parathyroid hormone level
sHPT	secondary hyperparathyroidism
SD	standard deviation
SOC	standard of care

REFERENCES

1. Farag YMK, El-Sayed E. Global dialysis perspective: Egypt. Kidney360. 2022;3:1263-8.
2. Haffner D. Strategies for optimizing growth in children with chronic kidney disease. Front Pediatr. 2020;8:399-412.
3. Bellorin-Font E, Vasquez-Rios G, Martin KJ. Controversies in the management of secondary hyperparathyroidism in chronic kidney disease. Curr Osteoporos Rep. 2019;17:333-42.
4. Denburg MR, Kumar J, Jemielita T, Brooks ER, Skversky A, Portale AA, et al. Fracture burden and risk factors in childhood ckd: Results from

the CKiD cohort study. J Am Soc Nephrol. 2016;27:543-50.

5. Bacchetta J, Schmitt CP, Ariceta G, Bakkaloglu SA, Groothoff J, Wan M, et al. Cinacalcet use in paediatric dialysis: A position statement from the european society for paediatric nephrology and the chronic kidney disease-mineral and bone disorders working group of the ERA-EDTA. Nephrol Dial Transplant. 2020;35:47-64.
6. Karaboyas A, Muenz D, Hwang Y, Goodman W, Cheng S, Desai P, et al. Etelcalcetide versus cinacalcet in hemodialysis patients in the united states: A facility calcimimetic approach to assess real-world effectiveness. Kidney Med. 2022;4:100-475.
7. Cianferotti L, Gomes A, Fabbri S, Tanini A, Brandi M. The calcium-sensing receptor in bone metabolism: from bench to bedside and back. OSTEOPOROSIS INT. 2015;26:2055-71.
8. Brown DD, Dauber A. Growth hormone and insulin-like growth factor dysregulation in pediatric chronic kidney disease. Horm Res Paediatr. 2021;94:105-14.
9. Haffner D, Grund A, Leifheit-Nestler M. Renal effects of growth hormone in health and in kidney disease. Pediatr Nephrol. 2021;36:2511-30.
10. Haffner D, Mahan JD. Growth and pubertal development in children and adolescents receiving chronic dialysis. Pediatric Dialysis. 2021;10:509-40.
11. Warady BA, Ng E, Bloss L, Mo M, Schaefer F, Bacchetta J. Cinacalcet studies in pediatric subjects with secondary hyperparathyroidism receiving dialysis. Pediatr Nephrol. 2020;35:1679-97.
12. Salusky IB, Goodman WG, Kuizon BD. Implications of intermittent calcitriol therapy on growth and secondary hyperparathyroidism. Pediatr Nephrol. 2000;14:641-5.
13. Cansick J, Waller S, Ridout D, Rees L. Growth and PTH in prepubertal children on long-term dialysis. Pediatr Nephrol. 2007;22:1349-54.
14. Bover J, Arana C, Ureña P, Torres A, Martín-Malo A, Fayos L, et al. Hyporesponsiveness or resistance to the action of parathyroid hormone in chronic kidney disease. Nefrologia (Engl Ed). 2021;41:514-28.
15. Kuizon BD, Goodman WG, Jüppner H, Boechat I, Nelson P, Gales B, et al. Diminished linear growth during intermittent calcitriol therapy in children undergoing CCPD. Kidney Int. 1998;53:205-11.
16. Schmitt CP, Ardissino G, Testa S, Claris-Appiani A, Mehls O. Growth in children with chronic renal failure on intermittent versus daily calcitriol. Pediatr Nephrol. 2003;18:440-4.
17. Borzych D, Rees L, Ha IS, Chua A, Valles PG, Lipka M, et al. The bone and mineral disorder of children undergoing chronic peritoneal dialysis. Kidney Int. 2010;78:1295-304.
18. Arenas Morales AJ, DeFreitas MJ, Katsoufis CP, Seeherunvong W, Chandar J, Zilleruelo G, et al. Cinacalcet as rescue therapy for refractory hyperparathyroidism in young children with advanced chronic kidney disease. Pediatr Nephrol. 2019;34:129-35.
19. Cecconi E, Gasperi M, Genovesi M, Bogazzi F, Grasso L, Procopio M, et al. Growth hormone secretion in primary and secondary hyperparathyroidism. J Endocrinol Invest. 2005;28:113-6.
20. Manaka K, Sato J, Kinoshita Y, Ito N, Fujita M, Iiri T, et al. Effectiveness and safety of cinacalcet for primary hyperparathyroidism: a single center experience. Endocr J. 2019;66:683-9.
21. Sterrett JR, Strom J, Stummvoll HK, Bahner U, Disney A, Soroka SD, et al. Cinacalcet HCI (Sensipar/Mimpara) is an effective chronic therapy for hemodialysis patients with secondary hyperparathyroidism. Clin Nephrol. 2007;68:10-7.
22. Elis S, Courtland HW, Wu Y, Fritton JC, Sun H, Rosen CJ, et al. Elevated serum IGF-1 levels synergize PTH action on the skeleton only when the tissue IGF-1 axis is intact. J Bone Miner Res. 2010;25:2051-8.
23. Chen T, Wang Y, Hao Z, Hu Y, Li J. Parathyroid hormone and its related peptides in bone metabolism. Biochem Pharmacol. 2021;192:114-669.

AUTHORS' CONTRIBUTIONS

The submitted manuscript is the work of the author & co-author.
All authors have contributed to authorship, have read, and approved the manuscript.
Conception and design of study: S.M.E
Acquisition of data: S.M.E
Analysis and/or interpretation of data: S.M.E

Drafting the manuscript: S.M.E and M.A.A
Revising the manuscript critically for important intellectual content: S.M.E and M.A.A
Approval of the version of the manuscript to be published: all authors.
All authors contributed to authorship, have read, and approved the manuscript.

STATEMENTS

Ethics approval and consent to participate
The Tanta University Hospitals Ethical Committee gave its clearance for the research (approval code: 36264PR295/8/23). Written informed consent was obtained from the patient's family guardians.
Data Materials and/or Code availability
Data is available upon reasonable request from corresponding author.
Consent for publication
The contents and material of the manuscript have not been previously reported at any length or are being considered for publishing elsewhere.
Competing interests
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