Original article

Leptin in Egyptian Children with CKD: A single Center Experience.

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Abstract

Introduction: Leptin, is an anorexigenic hormone that's secreted by fat tissue, & affect appetite.
Aim of the study: The present study evaluated serum leptin level, & its relation to growth parameters in pediatric patients with different stages of CKD.
Methods: a cross-sectional study that was conducted on 87 subjects, who were divided into 3 groups equally; CKD stage 5 on regular hemodialysis (CKD5d), & CKD stage 2-4, & age & gender matched controls. Patient with diabetes, infected with hepatitis C virus, & on growth hormone therapy were excluded. Full history taking, assessment of growth parameters using gender & age specific Z-scores of heights, weight & body mass index were done. Fasting serum leptin, calcium, phosphorus, PTH, albumin, total proteins, iron & hemoglobin were measured**.**
Results: Our patients had significantly lower growth parameters compared to controls. Hypocalcemia, high PTH, iron deficiency anemia & hypoalbuminemia were significant in CKD2-4 groups compared to other groups. Serum leptin was abnormally high in 12.6% of CKD patients. The median leptin level was comparable between the groups (p=0.20). Serum leptin hadn't changed significantly as regards gender, BMI Z-scores, diagnoses, or CKD stage (p= 1.00, 0.379, 0.542, 0.171 respectively). A negative correlation was found between leptin level & CKD duration (r = -0.276, P = 0.036), otherwise, no correlations were found with clinical & laboratory variables.
Conclusion & recommendations: Leptin level was not affected by CKD stage & not a useful marker for growth in pediatric CKD patients. Large studies on relationship between leptin & growth are needed.

Keywords: BMI, CKD, Leptin, Z-scores
Running Title: Leptin; the anorexigenic hormone in pediatric CKD patients

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INTRODUCTION

Chronic kidney disease (CKD) is a major health problem associated with disturbed metabolic process, affecting the nutrition and ends by stunted growth. Faltering growth in CKD patients is multifactorial, where anorexia, inadequate intake in addition to disturbed body metabolism and hormonal factors play major roles, in the development of malnutrition, anorexia-cachexia axis [1]. Leptin is an anorexigenic hormone, that is secreted by adipose tissue, and play vital roles in the appetite, body weight regulation, carbohydrate, and lipid metabolism, where it indues wight loss via anorexia and enhancing basal metabolic rate [2]. Serum Leptin level is affected by renal clearance, in addition to chronic inflammation and nutritional status. Leptin status and relations to growth in CKD patients especially pediatric is limited and not fully understood [3].

Aims: To evaluate serum leptin level in pediatric patients with different stages of CKD and its relation to growth.

METHODS

This controlled cross-sectional analytical study was conducted on 87 children and adolescents recruited from Children's Hospital, Ain Shams University, where they were divided into 3 groups; 29 patients with stage 5 CKD on regular hemodialysis (CKD5d), and 29 predialysis patients (CKD stage 2-4) on conservative management following up at our Pediatric Dialysis and Nephrology Unit, and 29 age and gender matched controls. Predialysis group were managed by conservative treatment, while dialysis group were under regular hemodialysis for three to four hours, thrice per week using hybrid of OL-HDF and high flux HD. All CKD patients were prescribed to follow the basic nutrition recommendation as per our pediatric nephrology- dialysis and nutrition clinic. Patient with diabetes, infected with hepatitis C virus, with malignancy, recurrent hospital admissions, heart failure, and those on growth hormone therapy were excluded from this study. Most of our patients were under treatment with antihypertensive drugs and erythropoietin stimulating agents (ESA), L-carnitine, phosphate binders, calcium, and vitamin D supplementations in addition to sodium bicarbonate in predialysis group. All subjects enrolled in the study were subjected to history taking in the form of age, gender, diagnosis, duration of CKD and hemodialysis. For assessment of growth, gender- and age specific Z-scores of heights, weight and body mass index were calculated. BMI Z-scores were classified as normal, underweight (or wasted), and overweight according to WHO recommendation (**<−2.0**, **>-2** and **<2**, **>2.0** respectively); [4]. Weight was measured in the morning for all and after termination of hemodialysis session for dialysis group (dry weight). Laboratory tests were done by withdrawing 3 ml of venous blood after 12 hours of fasting for serum leptin level assessment (ng/mL), by using commercially available quantitative human enzyme linked immune sorbent assay (ELISA); (DRG International Inc., Springfield, NJ, USA). In dialysis patients, sampling was done pre-dialysis

session in the midweek one. Measurements of serum calcium, phosphorus, PTH, albumin, total proteins, iron, and hemoglobin were done. **Ethical consideration:** Both oral and written consents were obtained from patients and their caregivers according to the guidelines of Institutional Review Board (IRB) of college of medicine.

Statistical Analysis

The collected data was revised, coded, tabulated using Statistical package for Social Science (SPSS 25). Both Descriptive and Analytical statistics were done with their suitable tests.

RESULTS

All measured data of both CKD patients and controls are shown in **[Tables 1, 2** and **3]**. Our pediatric CKD patients had significantly lower weight, height Z-scores compared to controls (p <0.001, <0.001). According to BMI Z-score classification, we had 14 underweight subjects (9 CKD5d, and 5 CKD2-4), 55 normal (23 controls, 17 CKD5d, 15 CKD2-4), and 18 overweight (6 controls, 3 CKD5d, 9 CKD2-4) with statistically significant difference between them (p=0.023). Hypocalcemia, hyperparathyroidism, hypoalbuminemia, and iron deficiency were statistically significantly in CKD 2-4 group compared to controls and dialysis group (p= 0.001, <0.001, <0.001, 0.011 respectively), while anemia was significant in both CKD groups compared to controls (p<0.001); (table 3). The measured serum leptin level in our pediatric CKD patients was normal in 87.4% and abnormally high in 12.6% (2, 6.9% dialysis patients and 9, 31.03% predialysis patients). Albeit high median serum leptin level in predialysis group, it was comparable to levels in both dialysis and control subjects (p=0.20). Serum leptin level hadn't changed significantly between the studied groups as regards gender, different BMI, diagnoses, or CKD stage (p= 1.00, 0.379, 0.542, 0.171 respectively); **(Tables 3 and 4)**.

On assessing the correlations of serum leptin levels in all subjects with growth parameters by Spearman's correlation, no correlations were found with weight, height, BMI Z-scores, nevertheless, the univariate analysis in pre-dialysis group found a positive correlation with weight Z-score (r= 0.479, p=0.009), where higher leptin level was associated with higher weight Z-score **(Tables 4, 5, 6** and **Figure 1)**. Correlation analysis of serum leptin level with other variables found a significantly negative correlation with CKD duration (r = -0.276, P = 0.036), otherwise, no significant correlations were found with other demographics, and laboratory data (age, gender, primary CKD etiology, duration of hemodialysis, CKD stage, serum albumin, total proteins, calcium, Po4, PTH, iron and hemoglobin).

Table 1: Demographic and Anthropometric data of studied groups

VARIABLES		Groups			Test of significance	
		Controls	CKD 5d	CKD 2-4		
		Mean ± SD N (%) Median (IQR)	Mean ± SD N (%) Median (IQR)	Mean ± SD N (%) Median (IQR)	Value	p-Value
Age		9.03 ± 2.24	10.62 ± 2.21	9.41 ± 3.66	***F*** = 2.56	0.083
Gender	Male	15 (51.72%)	13 (44.83%)	13 (44.83%)	X^2 = 0.36	0.832
	Female	14 (48.28%)	16 (55.17%)	16 (55.17%)		
Weight Z-score		0.34 (-0.21 - 0.87)	-2.01 (-2.68 - 0.67)	-1.34 (-2.68- 1.23)	***H*** = 20.47	<0.001 (K1)
Height Z-score		-0.23 (-0.91 -0)	-2.01 (-2.68 - 0.52)	-2.68 (-2.68 - 0.31)	***H*** = 25.27	<0.001 (K1)
BMI Z-score		0.67 (0 - 1.81)	-0.82 (-2.68 - 0.5)	0.96 (-1.01 - 2.01)	***H*** = 13.23	0.001 (K2)
BMI Z-score classification	Normal	23	17	15	***H*** = ***7.55***	0.023
	Underweight	0	9	5		
	Overweight	6	3	9		

BMI: body mass index *Kruskal Wallis test of significance (H) *Chi-Square test of significance (X^2).
*One Way ANOVA test of significance (f)
*Post-hoc test was significant between: (K1) **Control group Vs. (CKD5d and CKD2-4 groups).**
(K2) **CKD5d group Vs. (Control and CKD2-4 groups).**

Table 2: Disease demographics of CKD patients

Variables		Groups	
		CKD 5d	CKD 2-4
		Median (IQR) N (%)	Median (IQR) N (%)
Duration of CKD (years)		6 (5 - 8)	3 (2 - 5)
Duration of hemodialysis (years)		3 (1 - 7)	----
Diagnosis	CAKUT (23)	16 (55.17%)	9 (31.03%)
	Podocytopathy (13)	4 (13.79%)	9 (31.03%)
	Ciliopathy (7)	7 (24.14%)	0 (0%)
	Chronic GN (6)	1 (3.45%)	5 (17.24%)
	Chronic TIN (4)	0 (0%)	4 (13.79%)
	SLE (2)	1 (3.45%)	1 (3.45%)
	TMA (1)	0 (0%)	1 (3.45%)
CKD stage	2	0 (0%)	3 (10.34%)
	3	0 (0%)	8 (27.59%)
	4	0 (0%)	18 (62.07%)
	5	29 (100%)	0 (0%)

CAKUT: Congenital anomalies of kidney and urinary tract, GN: glomerulonephritis, SLE: systemic lupus erythromatosis, TIN: Tubulointerstitial nephritis, TMA: Thrombotic microangiopathic hemolytic anemia

Table 3: Laboratory data of studied groups

Laboratory data		Groups			Test of significance	
		Controls	CKD 5d	CKD2-4		
		Mean ± SD Median (IQR)	Mean ± SD Median (IQR)	Mean ± SD Median (IQR)	Value	p-Value
Leptin Level (ng\mL)		3.40(8.7) (1.5-10.2)	2.70 (21.7) (1.1-22.8)	3.30 (48.30) (1.2- 49.5)	*H*= 3.219	0.20
Leptin Level	Normal	29 (100%)	27 (93.1%)	20 (68.97%)	Fisher's Exact test	0.001
	High	0 (0%)	2 (6.9%)	9 (31.03%)		
Calcium (mg/dL)		9.30 ±.387	8.71 ± 1.243	8.32±1.137	*f*=1.990	0.001 (A1)
Phosphorous (mg/dL)		5.31 ± 0.58	5.87 ± 1.344	5.57 ±1.52	*f*=10.038	0.222
PTH (pg/mL)		38 (13)	6.79(819.50)	90 (618.95)	*H*=58.463	<0.001
Total protein (g\dL)		6.74 ±1.358	6.44 ± 0.52	6.25 ±1.28	*f*=1.196	0.248
Albumin (g/dL)		4.01 ± 0.47884	3.90 ± 0.37	2.99±1.01063	*f*=10.439	<0.001 (A2)
Iron (mg/dL)		98.0 (115.0) (60.0-175.0)	74.0 (173.2) (39.0- 212.2)	75.8 (160.0) (16.0-176.0)	*H*=7.312	0.011(A3)
Hemoglobin (g/dL)		12.32 ± 0.923	10.06 ±1.46	10.07 (2.24)	*f*=20.913	0.000(A4)

***Kruskal Wallis test of significance (H), *One Way ANOVA test of significance (f)**
Post-hoc Bonferroni test was significant between:
(A1) Calcium : CKD2-4 and Control, (A2) Albumin: CKD2-4 vs (Control and CKD5d)
(A3) Iron: CKD2-4 vs Control, (A4) Hemoglobin: Control vs (CKD5d and CKD2-4)

Table 4: Comparison between different clinico-demographics & leptin levels in all studied groups:

Variables		Leptin Level ng\ml		Test of significance	
		Mean ± SD	Median (IQR)	Value	p-Value
Gender	Male	6.122 ± 7.03	3.20 (4.05)	*z*= -0.00	1.00
	Female	7.67 ± 1.15	3.0 (4.30)		
BMI Z-score classification	Normal	6.77± 9.36	3.20(3.90)	***H*= *1.938***	0.379
	Underweight	5.178 ±5.76	2.40(6.50)		
	Overweight	8.81±1.28	3.25 (5.58)		
Diagnosis	CAKUT	7.24 ± 10.54	2.5 (1.9 - 9.1)	***H*=** 5.013	0.542
	Chronic GN	9.68 ± 12.82	2.85 (2.4 - 14.5)		
	Chronic TIN	22 ± 13.27	27.15 (14 - 30)		
	Ciliopathy	5.06 ± 3.35	5.1 (1.8 - 8.4)		
	Podocytopathy	9.56 ± 14.35	2.7 (1.6 - 8.2)		
	SLE	3.85 ± 1.2	3.85 (3 - 4.7)		
	TMA	6	6 (6 - 6)		
CKD stage	2	2.97 ± 0.4	2.9 (2.6 - 3.4)	***H*=** 5.017	0.171
	3	7.56 ± 9.75	2.4 (2.25 - 12.9)		
	4	15.69 ± 16.44	8.75 (2.4 - 28.7)		
	5	5.13 ± 5.54	2.7 (1.7 - 7.6)		

***Chi-Square test of significance (X^2), *Kruskal Wallis test of significance (H).**

Table 5: Correlation analyses (Spearman's correlation) of Leptin Levels (ng/mL) and other demographic, clinical and laboratory data of studied groups

Leptin Level ng\ml	Spearman's rho	p-Value
Age	0.102	0.349
Gender	0.00	1.000
Duration of CKD (years)	**-0.276**	**0.036**
Duration of Hemodialysis (years)	-0.214	0.266
Diagnosis	0.074	0.582
CKD stage	-0.172	0.197
Weight Z-SCORE	0.244	0.065
Height Z-SCORE	0.016	0.906
BMI Z-SCORE	0.222	0.094
Serum albumin (g\dL)	-0.096	0.380
Total proteins (g\dL)	0.037	0.732
Iron (mg/dL)	-0.032	0.767
Hemoglobin (g/dL)	0.003	0.979
PTH (pg/mL)	-0.125	0.250
Calcium(mg/dL)	-0.098	0.367
Po4(mg/dL)	-0.116	0.285

Table 6: Univariate analysis of plasma leptin in study groups

Leptin						
Variables	**Controls**		**CKD5d**		**CKD2-4**	
	r	**p**	**r**	**p**	**r**	**p**
CKD Diagnosis	----	----	-0.006	0.974	0.072	0.711
Duration of CKD (years)	----	----	-0.184	0.339	-0.243	0.205
Duration of hemodialysis (years)	----	----	-0.214	0.266	-----	----
Weight Z-SCORE	0.152	0.431	-0.134	0.489	0.479**	0.009

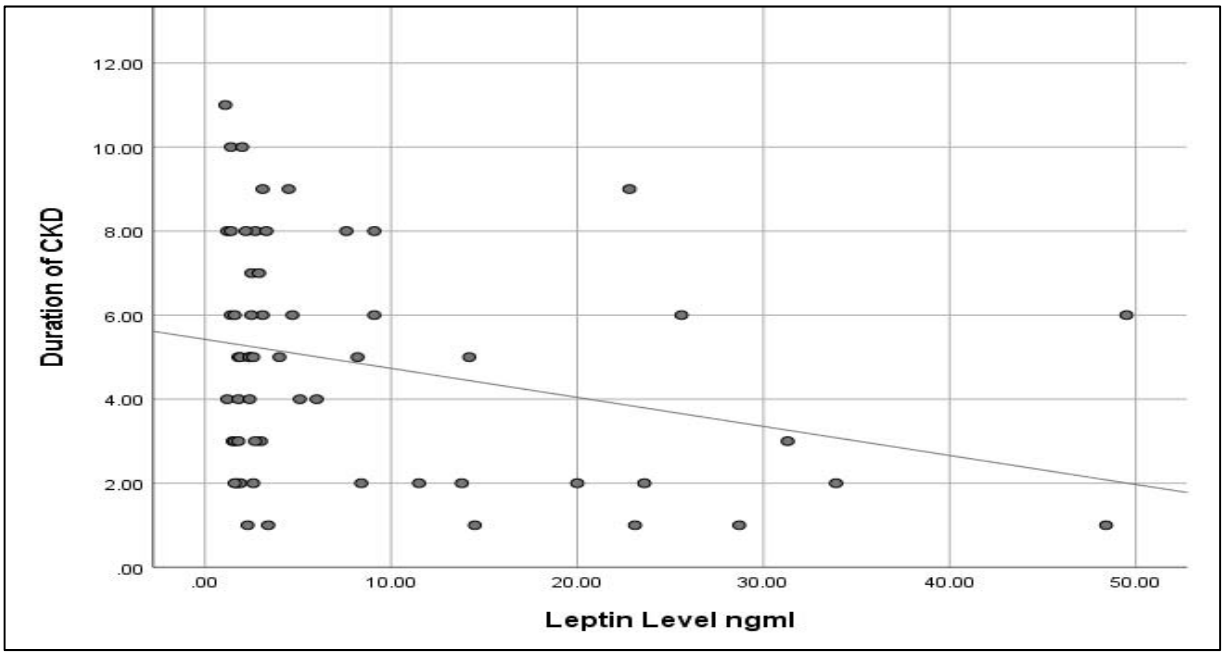

Figure 1: Correlation of Leptin Levels ng\ml and CKD duration.

DISCUSSION

In the present study, we measured the serum leptin level in different stages of CKD in pediatric patients and correlated it to the growth of the patients represented in weight, height, and BMI in Z-scores. Our pediatric CKD patients were significantly shorter and thinner compared to controls (p <0.001, <0.001). BMI Z-score was classified according to WHO recommendations as normal, over, and underweight, where a statically difference was found between all subjects (p=0.023). This agrees with previous studies, **[5, 6]** where pediatric CKD patients had significantly lower BMI than healthy controls owing to inadequate caloric intake due to anorexia, increased energy expenditure and chronic inflammatory status **[7].**

Hypocalcemia, hyperparathyroidism, hypoalbuminemia, and iron deficiency were observed in our CKD patients and was statistically significantly in CKD2-4 groups compared to controls and dialysis groups, while anemia was significantly in both CKD groups compared to controls **[Table 3]**. This agreed with data from the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) revealed the prevalence of anemia of 73 to 93%, in pediatric CKD patients, and differed according to CKD stage **[8].** The pathogenesis of anemia in CKD pediatric patients are thought to be due to a complex process, where chronic inflammatory status, lead to impaired erythropoiesis, inadequate synthesis of erythropoietin by the kidneys, and impaired iron absorption and utilization owing to altered hepcidin function, in addition to oxidative stress, and nutritional deficiencies **[9].** Previous studies **[10, 11]** had found high prevalence of hypoalbuminemia in pediatric CKD patients, as a part of protein energy wasting, with high risk of poor nutrition and chronic inflammation **[12].**

The measured serum leptin level in all our pediatric CKD patients was normal in 87.4% and abnormally high in 12.6% (2, 6.9% CKD5d patients and 9, 31.03% CKD2-4 patients). In line with numerous previous studies **[13-17]** serum leptin level was comparable in both CKD groups and control subjects (p=0.20). The exact cause for variations in serum leptin levels is unclear. Variable mechanisms were postulated, one of these mechanisms is low weight and BMI of our patients, hence the reduced production of leptin from the reduced fat mass. Thus, low leptin levels in CKD patients with low BMI **[15].** Also, the secondary hyperparathyroidism in our CKD patients, that crosstalk with adipose tissue and suppress the leptin secretion **[33].** In addition to the used erythropoietin for management of anemia in our CKD patients, induces a significant decline of leptin production **[18].** In our hemodialysis patients, normal levels are due to excess clearance by hemodialysis itself, where we use both high-flux HD and OL-HDF for all our hemodialysis patients that significantly reduce plasma leptin levels by effective clearance by convection **[19].** A Chinese study was designed to compare effect of different hemodialysis modalities on serum leptin level, where they found an effective leptin clearance

in HDF and Hemoperfusion patients was noticed more than those on conventional HD, where effective leptin elimination may improve the patients' nutritional status [20]. All these may explain the nonsignificant elevation of leptin levels in our CKD patients.

On the contrary to our findings, some pediatric and adult CKD studies [21-23] reported elevated levels of circulating leptin were due to reduced renal clearance in CKD patients, ended by leptin accumulation, also uremic serum stimulated more leptin release from adipose tissue than controls, although it was not induced by the accumulation of urea [24]. Impairment of renal degradation of leptin may play a role in hyperleptinemia in CKD patients [25, 26]. However, the results of the CKiD cohort reported by Nehus et al., [27] had suggested that the renal leptin clearance hadn't contribute to elevated levels. Serum leptin levels in CKD patients remain controversial.

Our study was exploring the link between leptin hormone level and growth parameters of our CKD pediatric patients, represented as weight, height, and BMI Z-score. It showed no significant difference with different BMI Z-scores in all studied groups (p= 1.00). Spearman's correlations of serum leptin levels revealed no significant changes with all measured
growth parameters, meanwhile the univariate analysis of plasma leptin in pre-dialysis patients found a positive correlation with weight Z-score (r= 0.479, p=0.009), where higher leptin level was associated with higher weight Z-score support the fact, that anorexigenic leptin hormone in pediatric CKD patients, not solely affects the growth, rather than it is a complex process, where increased energy expenditure, inadequate intake and increased nutritional losses during dialysis and chronic inflammation play important roles [28].

Our results depended mainly only BMI as a determinant of body composition, while other studied used the more accurately fat mass instead, which could explain this discrepancy [29]. Previous studies agreed with our results [29-32] where they found no correlation between weight, BMI, and serum leptin levels in CKD patients, though their patients were significantly thine, had bad nutritional status and low lean and fat mass and lowest serum albumin levels and had high prevalence of protein energy wasting (PEW), where CKD patients seemed to have readjusted their "leptin-state". In contrast to ours, studies [17, 26] revealed a strong positive association between plasma leptin levels and fat mass and BMI of the CKD patients, where pediatric CK5d patients with protein energy wasting had low plasma leptin levels, associated with low fat mass index and low BMI, where hyperleptinemia, induces less caloric intake, therefore low levels of leptin may be a consequence rather than a cause of PEW. The variations in the results may be attributed to conducting the studies on different population, children versus adult, and variation in the used methods to classify BMI, in addition to the use of BMI as a determinant of body composition and growth rather than considering other anthropometric measure including body fat mass. The effect of leptin in the

regulation of appetite and the development of PEW appears to be complex in uremia.

Serum leptin level hadn't changed significantly between the studied groups as regards gender, primary diagnoses, or CKD stage (p= 0.379, 0.542, 0.171 respectively). On assessing the correlations of serum leptin levels in all studied groups by Spearman's test, a statistically significantly negative correlation was found with CKD duration (r = -0.276, P = 0.036), otherwise, we couldn't establish significant correlations with age, gender, primary CKD etiology, duration of hemodialysis, CKD stage, serum albumin, total proteins, calcium, Po4, PTH, iron and hemoglobin). Like our results, Canpolat N. et al., [17] revealed no difference in leptin levels in different CKD stage, dialysis, non-dialysis, or transplant pediatric patients, when compared to the healthy controls. In contrast to our findings, previous studies, found significant differences of serum leptin levels with gender, where serum leptin, was higher in females, owing to higher adipose tissue, hence more leptin production [22, 27]. Previous studied [33, 34] revealed a negative correlation of PTH and leptin levels, where high PTH inhibits the adipocytes leptin secretion, by suppressing Akt signaling, explaining the role of adipocyte derived leptin on the crosstalk between PTH and fat status. In our study, although serum PTH was negatively correlated to serum leptin in CKD, a non-statistically significant correlation was observed (r=-0.125, p=0.25). Nasri, H. et al., [35] study contrasted to our findings, where significant positive correlations of serum leptin with duration of hemodialysis and with the ages of the patients were found, where hyperleptinemia was common in older age groups and patients with longer hemodialysis duration.

Our study has important strength points, where we included pediatric patients with different CKD stages, in addition to having a control group to evaluated leptin hormones level. Also, unlike others, we used age and gender related Z-scores of weights, height, and BMI for the assessment of nutritional status. WHO recommendation for BMI Z-score classification was used.

Our study limitations were, the relatively small sample size, representing the pediatric CKD patients, which made it difficult for definite conclusions. Also, we analyzed plasma leptin levels, not corrected for Bioimpedance Analysis based fat mass, which make a where leptin is mainly secreted into the blood stream from the adipose tissue, and body fat mass is the main determinant of plasma leptin concentrations, Finally, the cross-sectional nature of the study does not allow us to safely determine the cause-effect relationships of the on-study associations.

CONCLUSION AND RECOMMENDATIONS

Leptin level is not affected by CKD stage and not a useful marker for growth and nutritional assessment in pediatric CKD patients. Longitudinal studies are needed to elaborate this complex relationship between leptin and growth in pediatric CKD patients.

ABBREVIATIONS

BMI	Body mass index	**IQR**	Interquartile range
CAKUT	Congenital anomalies of kidney and urinary tract,	**IRB**	Institutional Review Board
		PEW	protein energy wasting
CKD	Chronic kidney disease	**PTH**	Parathyroid Hormone
CKD5d:	Chronic kidney disease stage 5 on dialysis	**SLE**	systemic lupus erythematosus
ELISA	Human enzyme linked immune sorbent assay	**SPSS**	Statistical package for Social Science
		TIN	Tubulointerstitial nephritis,
ESA	Erythropoietin stimulating agents	**TMA**	Thrombotic microangiopathic hemolytic anemia
GN	Glomerulonephritis,	**WHO**	World Health Organization**.**

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AUTHORS' CONTRIBUTIONS

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Conception and design of study:
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STATEMENTS

Ethics approval and consent to participate
This study protocol and the consents were approved and deemed sufficient by the Ethical Committee of Institutional Review Board (IRB) of college of medicine and informed written consent was obtained in every case from their legal guardians.

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