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Correlates of Leptin in Children with Chronic Kidney Disease

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Abstract

Objective—Leptin is elevated in patients with advanced chronic kidney disease (CKD).

Although leptin is excreted by the kidney, increased production in association with adiposity or inflammation may also contribute to hyperleptinemia. The objective of this study was to investigate the relative associations of renal function, obesity and inflammation with serum leptin levels in children with CKD.

Study design—This study is a cross-sectional analysis of 317 children in the Chronic Kidney Disease in Children (CKiD) cohort, a large cohort of pediatric patients with stage II-IV CKD. Linear regression modeling was used to evaluate the association of serum leptin with iothel glomerular filtration rate (iGFR), demographicss, body mass index (BMI), and cardiovascular risk factors, including inflammatory cytokines, insulin resistance, and serum lipids.

Results—In univariate analyses, elevated serum leptin was significantly associated with increased BMI, older age, and female sex (all p values < 0.001). Leptin also correlated positively with serum triglycerides and insulin resistance (p < 0.001) and negatively with serum high-density lipoprotein cholesterol (p = 0.002). Leptin was not associated with iGFR or inflammatory cytokines. In multivariate analysis, BMI, age, female sex, and serum triglycerides were significantly associated with serum leptin.

Conclusions—Increased leptin production was associated with female sex, older age, and adiposity in children with mild to moderate CKD. Renal function was not associated with serum leptin, indicating that decreased clearance does not contribute to elevated leptin.

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Keywords

obesity; inflammation; renal function; pediatrics

Leptin is a hormone produced by adipocytes that acts centrally to signal satiety and increase energy expenditure. The association of leptin with adiposity has been interpreted as a state of “leptin resistance” that may be involved in the pathogenesis of obesity.^{1–3} Furthermore, the association of leptin with inflammation, insulin resistance, and hyperlipidemia has implicated its role as a mediator of cardiovascular disease.^{4–8}

Leptin levels are elevated in patients with advanced chronic kidney disease (CKD) and may be involved in the inflammation, malnutrition, and cardiovascular disease in this population.^{9, 10} The putative cause of increased leptin levels in CKD has not been determined. Although leptin is a 16 kDa molecule that is excreted by the kidney,^{11, 12} the relative contribution of decreased renal clearance to total serum leptin is not known. Increased production in association with increased fat stores or inflammation are other potential causes of hyperleptinemia in CKD.^{13–16} The objective of this study was to investigate the relative associations of renal function, obesity, and inflammation with leptin in children with CKD. We performed a cross-sectional analysis of 317 children enrolled in the Chronic Kidney Disease in Children (CKiD) study, a prospective observational study of children with mild to moderate CKD. We hypothesized that leptin was primarily associated with body mass index (BMI) and renal function in children with CKD.

METHODS

The CKiD study is a multicenter, longitudinal, observational study of children with CKD, whose design and methods have been published previously.¹⁷ Institutional Review Board approval was obtained at each participating center. The goals of the CKiD study include the evaluation of novel and traditional risk factors for cardiovascular disease in children with CKD. Inclusion criteria were age between 1 and 16 years as well as a glomerular filtration rate (GFR) of 30 to 90 ml/min/1.73m². This study is a cross-sectional analysis of baseline serum leptin levels obtained in the initial CKiD cohort at year two of the study. The initial CKiD cohort was comprised of 586 children at 46 pediatric nephrology centers in North America. Among study participants, 317 patients had serum available for analysis of leptin levels.

Serum leptin analysis was carried out at the Metabolic Phenotyping Core, The University of Texas Southwestern Medical Center, Dallas, Texas using serum samples from the CKiD study. Original samples were collected locally, shipped, and stored at the NIH Biologic Repository at –80°C. Human Leptin ELISA Kits (Millipore, Billerica, MA) were used to determine serum leptin levels.

Fasting insulin levels (Human Insulin ELISA, Millipore, Billerica, MA), tumor necrosis factor (TNF)- α , interleukin (IL)-6, and IL-10 from the same sample were determined utilizing the same laboratory. A multiplex bead array (Bio-Rad Laboratories, Hercules, CA) using Luminex 100 system was used to determine cytokine concentrations. This assay has

been validated previously and demonstrated excellent linearity, precision, and sensitivity.^{18–20} The homeostasis model assessment of insulin resistance (HOMA-IR) was used as a measure of insulin resistance. HOMA-IR was calculated by dividing the product of serum insulin (mU/ml) and glucose (mmol/ml) by a factor of 22.5.

Other laboratory data obtained for analysis included fasting lipid profiles (high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides) and urine protein to creatinine ratios. GFR was calculated using plasma iothexol disappearance curves (iGFR) as previously described.¹⁷ Demographics were obtained at the same time that serum leptin levels and other laboratory data were collected and included age, sex, Tanner stage, casual blood pressure, and BMI. Children were classified as overweight and obese as recommended by the Centers for Disease Control and Prevention.²¹ Overweight was defined as an age- and sex-specific BMI at or above the 85th percentile and lower than the 95th percentile, and obese as an age- and sex-specific BMI at or above the 95th percentile.

Statistical Analyses

Continuous variables were reported as median and interquartile ranges (IQR), as most variables were not normally distributed. Nonparametric testing was used for categorical variables (Wilcoxon rank-sum test or Kruskal-Wallis test). Pearson's correlation coefficients were used for continuous independent variables after log transformation as needed to fulfill the assumptions of linear regression modeling. Laboratory values that were log transformed included serum leptin, HOMA-IR, serum insulin, inflammatory markers, and lipid profiles. Multivariable regression analysis was performed using all variables with a p value of < 0.10 in univariate analyses. Backward elimination selecting variables significant at the 0.05 level was then performed for the final regression model. All analyses were conducted using SAS statistical software (version 9.3 SAS Institute, Cary, NC).

RESULTS

Baseline characteristics of the cohort are shown in Table I. Fifteen percent of children were obese. About one-half were pre-pubertal, with the remainder in all four stages of pubertal development. Most children had a non-glomerular cause of CKD. The most common etiologies were obstructive uropathy, renal dysplasia, and reflux nephropathy (21%, 17%, and 16% of the entire cohort, respectively). Focal segmental glomerulosclerosis (FSGS) and hemolytic uremic syndrome (HUS) were the most prevalent glomerular etiologies, representing 7% and 4% of the cohort.

Serum leptin and patient demographics

Serum leptin levels did not differ by race. Children with a glomerular etiology of CKD had higher median levels than those with a non-glomerular cause (7.1 vs 2.9 ng/ml, $p < 0.01$). Median leptin levels were also higher in females (6.9 ng/ml) compared with males (2.4 ng/ml, $p < 0.001$). Leptin levels by Tanner stage are displayed in Table II. Leptin increased throughout puberty in females, whereas males demonstrated a mild increase in early puberty without any subsequent rise. Leptin levels were significantly increased in obese children

(Figure 1), with median leptin values of 33.2 ng/ml in obese children compared with 3.0 ng/ml in non-obese children ($p < 0.001$). Leptin levels strongly correlated with age ($r = 0.32$, $p < 0.001$) and BMI z score (Figure 2, A).

Serum leptin levels, markers of inflammation, and renal function

Serum leptin levels did not correlate with iGFR (Figure 2, B) or with urine protein to creatinine ratio. There was no association between markers of inflammation (IL-6, IL-10, and TNF- α) and serum leptin.

Serum leptin levels, insulin resistance, and dyslipidemia

Elevated serum leptin levels were significantly associated with high triglycerides ($r = 0.22$, $p < 0.001$) and low HDL cholesterol ($r = -0.18$, $p = 0.001$), but were not associated with LDL. Leptin was also significantly associated with both fasting insulin ($r = 0.23$, $p < 0.001$) and HOMA-IR ($r = 0.22$, $p < 0.001$).

Multivariate analysis

Age, sex, BMI z score, and triglycerides were independently associated with serum leptin levels in multivariate analysis. There was an increase in mean serum leptin of 64.6 % per 1 unit increase in BMI z score (95% CI: 46.0 – 85.6%), and leptin increased 10.8% per year in age (95% CI: 7.1% – 14.7%). Females had an adjusted mean increase in leptin of 96.0% compared with males (95% CI: 47.2 – 161.1%). Triglycerides had a mild independent association with leptin, increasing 3.4% per 10% increase in serum leptin (95% CI: 0.5 – 6.3%).

DISCUSSION

We demonstrated that in these children, leptin is primarily associated with age, BMI, and female sex, and renal function and inflammation did not correlate. These results suggest that in children with CKD, leptin production is increased in association with adiposity and differences related to sex and development.

Leptin levels vary with sex, development, and BMI in healthy children. In our cohort, they correlated significantly with BMI and were increased among females, findings consistent with previous studies in children without CKD.^{22–25} Leptin increased with age among both males and females in our cohort, although previous reports of leptin demonstrated sex differences throughout puberty. In healthy females, leptin continues to rise throughout puberty, whereas males demonstrate an early increase in leptin followed by a mild decline in late puberty and adolescence.^{22–25} In contrast, leptin levels did not decline in Tanner stage V children in our cohort (Table I). This finding may be secondary to 1) the relatively small percentage of male subjects in adolescence (15 % of all males were Tanner V), and 2) the confounding effect of BMI in older males. Among Tanner V males, 35% were overweight or obese, compared with only 13% of Tanner II–IV males.

Although the primary action of leptin is to reduce food consumption and body weight, the association of leptin with obesity has been interpreted as a state of ‘leptin resistance’.³

Furthermore, leptin has also demonstrated an independent association with other cardiovascular risk factors including dyslipidemia and insulin resistance.^{4–6, 26} Although we found a significant association of leptin with HDL, triglycerides, insulin, and HOMA-IR, only serum triglycerides remained significant after adjusting for sex, age, and BMI. Chu et al similarly reported that the association of BMI with cardiovascular risk factors, including total cholesterol and HDL, was not substantially changed after adjustment for plasma leptin.²⁶ These results suggest that leptin is not a direct mediator in the high prevalence of cardiovascular risk factors, including dyslipidemia and insulin resistance, reported in the CKiD cohort by Wilson et al.²⁷ Rather, leptin is likely associated with these metabolic risk factors primarily as a result of its well-known relationship with increased adiposity.

Leptin levels are elevated in children and adults with end stage renal disease (ESRD), who have demonstrated median leptin values 2 – 4 times that of healthy controls.^{14, 28–30} Previous studies in children and adults have also demonstrated a negative correlation between GFR and serum leptin after adjusting for BMI.^{13, 31} The latter studies in particular suggest that decreased clearance contributes to hyperleptinemia in patients with advanced kidney disease. However, decreased GFR per se may not be the only cause of increased leptin levels in CKD. Increased production may also contribute, and this is supported by several findings. First, increased leptin in healthy subjects is caused by increased abdominal tissue production in association with adiposity rather than alterations in leptin clearance.³² Second, BMI is the primary determinant of serum leptin levels in patients with CKD, accounting for much more variation than GFR.^{13, 31} Third, Suneja et al demonstrated increased production of leptin in response to feeding in hemodialysis patients compared with controls, although elimination half-lives were similar between the two groups.¹⁶

Leptin was not associated with GFR decline in our cohort, which is in contrast to prior reports. For example, Daschner et al reported that GFR was an independent, albeit weak ($r = -0.17$), predictor of serum leptin in a cohort of 134 children with kidney disease. This can be explained by the inclusion of patients in previous studies with much more advanced CKD and ESRD, in whom leptin values are known to be more significantly elevated. The cohort of Daschner et al included 55 patients (41%) with a GFR of $< 20 \text{ ml/min/1.73m}^2$, 26 of whom were receiving chronic dialysis. In contrast, only 11% of our cohort had a GFR of $< 20 \text{ ml/min/1.73m}^2$, and no children were receiving dialysis. It is possible that the relative contribution of renal function to increased leptin levels is more pronounced with advanced CKD and accounts for the lack of association between GFR and leptin in our cohort. Consistent with this, the median serum leptin value in our cohort was 3.4 ng/ml, which is well within the range of reported normal values in healthy subjects^{22–25, 33} and significantly less than children receiving hemodialysis, who have reported median values of 13.7 ng/ml.²⁸

Leptin is independently associated with increased risk of cardiovascular disease in adults,^{34, 35} which may be mediated by its correlation with inflammation as well as metabolic risk factors.⁸ In adults with advanced CKD and ESRD, leptin is associated with markers of inflammation,^{15, 31} although we did not demonstrate a similar relationship in our cohort of children with less severe kidney disease. This may be secondary to the absence of any significant inflammation present in our cohort, whose median levels of inflammatory

cytokines were not markedly different from those reported in healthy controls using a similar assay.³⁶

This study has several strengths, including standardized methods of data collection and accurate measure of GFR with a validated method using iohexol clearance.³⁷ Nevertheless, there are a few limitations. Although the largest to date to evaluate leptin levels in children with CKD, our cohort is still much smaller than adult cohorts that have demonstrated an association of leptin with inflammatory markers and CKD.^{8, 38} For example, a recent study of the third National Health and Nutrition Examination Survey (NHANES) reported that high plasma leptin was significantly associated CKD in a cohort of over 5000 adults.³⁸ We cannot exclude the possibility that our study was underpowered to detect a mild association of leptin with GFR. Second, we did not evaluate leptin levels in healthy children, which prevented any direct comparison of our cohort with control subjects. Although leptin was not markedly different from reported values in healthy children, variability in patient characteristics and assay techniques preclude a categorical statement that our cohort as a whole did not have a mild elevation of serum leptin. The lack of correlation of leptin with GFR, however, indicates that renal function per se is not a major contributing factor to hyperleptinemia in children with mild to moderate CKD.

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Abbreviations

CKD	chronic kidney disease
CKiD study	Chronic Kidney Disease in Children study
BMI	body mass index
GFR	glomerular filtration rate

References

1. Ahima RS. Central actions of adipocyte hormones. Trends in endocrinology and metabolism: TEM. 2005; 16:307–13. [PubMed: 16098759]
2. Ahima RS, Saper CB, Flier JS, Elmquist JK. Leptin regulation of neuroendocrine systems. Frontiers in neuroendocrinology. 2000; 21:263–307. [PubMed: 10882542]
3. Myers MG Jr, Leibel RL, Seeley RJ, Schwartz MW. Obesity and leptin resistance: distinguishing cause from effect. Trends in endocrinology and metabolism: TEM. 2010; 21:643–51. [PubMed: 20846876]
4. Considine RV, Sinha MK, Heiman ML, Kriauciunas A, Stephens TW, Nyce MR, et al. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. N Engl J Med. 1996; 334:292–5. [PubMed: 8532024]
5. Donahue RP, Prineas RJ, Donahue RD, Zimmet P, Bean JA, De Courten M, et al. Is fasting leptin associated with insulin resistance among nondiabetic individuals? The Miami Community Health Study. Diabetes care. 1999; 22:1092–6. [PubMed: 10388973]

6. Ruige JB, Dekker JM, Blum WF, Stehouwer CD, Nijpels G, Mooy J, et al. Leptin and variables of body adiposity, energy balance, and insulin resistance in a population-based study. The Hoorn Study. *Diabetes care*. 1999; 22:1097–104. [PubMed: 10388974]
7. Shamsuzzaman AS, Winnicki M, Wolk R, Svatikova A, Phillips BG, Davison DE, et al. Independent association between plasma leptin and C-reactive protein in healthy humans. *Circulation*. 2004; 109:2181–5. [PubMed: 15117839]
8. Wannamethee SG, Tchernova J, Whincup P, Lowe GD, Kelly A, Rumley A, et al. Plasma leptin: associations with metabolic, inflammatory and haemostatic risk factors for cardiovascular disease. *Atherosclerosis*. 2007; 191:418–26. [PubMed: 16712853]
9. Gunta SS, Mak RH. Ghrelin and leptin pathophysiology in chronic kidney disease. *Pediatr Nephrol*. 2013; 28:611–6. [PubMed: 23229444]
10. Mak RH, Cheung W, Cone RD, Marks DL. Leptin and inflammation-associated cachexia in chronic kidney disease. *Kidney Int*. 2006; 69:794–7. [PubMed: 16518340]
11. Cumin F, Baum HP, de Gasparo M, Levens N. Removal of endogenous leptin from the circulation by the kidney. *International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity*. 1997; 21:495–504.
12. Zeng J, Patterson BW, Klein S, Martin DR, Dagogo-Jack S, Kohrt WM, et al. Whole body leptin kinetics and renal metabolism in vivo. *The American journal of physiology*. 1997; 273:E1102–6. [PubMed: 9435524]
13. Daschner M, Tonshoff B, Blum WF, Englaro P, Wingen AM, Schaefer F, et al. Inappropriate elevation of serum leptin levels in children with chronic renal failure. European Study Group for Nutritional Treatment of Chronic Renal Failure in Childhood. *J Am Soc Nephrol*. 1998; 9:1074–9. [PubMed: 9621291]
14. Merabet E, Dagogo-Jack S, Coyne DW, Klein S, Santiago JV, Hmiel SP, et al. Increased plasma leptin concentration in end-stage renal disease. *J Clin Endocrinol Metab*. 1997; 82:847–50. [PubMed: 9062494]
15. Pecoits-Filho R, Nordfors L, Heimbürger O, Lindholm B, Anderstam B, Marchlewska A, et al. Soluble leptin receptors and serum leptin in end-stage renal disease: relationship with inflammation and body composition. *European journal of clinical investigation*. 2002; 32:811–7. [PubMed: 12423321]
16. Suneja M, Murry DJ, Stokes JB, Lim VS. Hormonal regulation of energy-protein homeostasis in hemodialysis patients: an anorexigenic profile that may predispose to adverse cardiovascular outcomes. *American journal of physiology Endocrinology and metabolism*. 2011; 300:E55–64. [PubMed: 20959536]
17. Furth SL, Cole SR, Moxey-Mims M, Kaskel F, Mak R, Schwartz G, et al. Design and methods of the Chronic Kidney Disease in Children (CKiD) prospective cohort study. *Clin J Am Soc Nephrol*. 2006; 1:1006–15. [PubMed: 17699320]
18. de Jager W, te Velthuis H, Prakken BJ, Kuis W, Rijkers GT. Simultaneous detection of 15 human cytokines in a single sample of stimulated peripheral blood mononuclear cells. *Clin Diagn Lab Immunol*. 2003; 10:133–9. [PubMed: 12522051]
19. Martins TB, Pasi BM, Pickering JW, Jaskowski TD, Litwin CM, Hill HR. Determination of cytokine responses using a multiplexed fluorescent microsphere immunoassay. *Am J Clin Pathol*. 2002; 118:346–53. [PubMed: 12219776]
20. Prabhakar U, Eirikis E, Davis HM. Simultaneous quantification of proinflammatory cytokines in human plasma using the LabMAP assay. *J Immunol Methods*. 2002; 260:207–18. [PubMed: 11792390]
21. Barlow SE. Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report. *Pediatrics*. 2007; 120 (Suppl 4):S164–92. [PubMed: 18055651]
22. Blum WF, Englaro P, Hanitsch S, Juul A, Hertel NT, Muller J, et al. Plasma leptin levels in healthy children and adolescents: dependence on body mass index, body fat mass, gender, pubertal stage, and testosterone. *J Clin Endocrinol Metab*. 1997; 82:2904–10. [PubMed: 9284717]
23. Clayton PE, Gill MS, Hall CM, Tillmann V, Whatmore AJ, Price DA. Serum leptin through childhood and adolescence. *Clin Endocrinol (Oxf)*. 1997; 46:727–33. [PubMed: 9274704]

24. Falorni A, Bini V, Molinari D, Papi F, Celi F, Di Stefano G, et al. Leptin serum levels in normal weight and obese children and adolescents: relationship with age, sex, pubertal development, body mass index and insulin. *International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity*. 1997; 21:881–90.
25. Garcia-Mayor RV, Andrade MA, Rios M, Lage M, Dieguez C, Casanueva FF. Serum leptin levels in normal children: relationship to age, gender, body mass index, pituitary-gonadal hormones, and pubertal stage. *J Clin Endocrinol Metab*. 1997; 82:2849–55. [PubMed: 9284709]
26. Chu NF, Spiegelman D, Hotamisligil GS, Rifai N, Stampfer M, Rimm EB. Plasma insulin, leptin, and soluble TNF receptors levels in relation to obesity-related atherogenic and thrombogenic cardiovascular disease risk factors among men. *Atherosclerosis*. 2001; 157:495–503. [PubMed: 11472752]
27. Wilson AC, Schneider MF, Cox C, Greenbaum LA, Saland J, White CT, et al. Prevalence and correlates of multiple cardiovascular risk factors in children with chronic kidney disease. *Clinical journal of the American Society of Nephrology : CJASN*. 2011; 6:2759–65. [PubMed: 21980183]
28. Besbas N, Ozaltin F, Coskun T, Ozalp S, Saatci U, Bakkaloglu A, et al. Relationship of leptin and insulin-like growth factor I to nutritional status in hemodialyzed children. *Pediatr Nephrol*. 2003; 18:1255–9. [PubMed: 14586683]
29. Heimbürger O, Lonnqvist F, Danielsson A, Nordenstrom J, Stenvinkel P. Serum immunoreactive leptin concentration and its relation to the body fat content in chronic renal failure. *J Am Soc Nephrol*. 1997; 8:1423–30. [PubMed: 9294834]
30. Sharma K, Considine RV, Michael B, Dunn SR, Weisberg LS, Kurnik BR, et al. Plasma leptin is partly cleared by the kidney and is elevated in hemodialysis patients. *Kidney Int*. 1997; 51:1980–5. [PubMed: 9186891]
31. Nordfors L, Lonnqvist F, Heimbürger O, Danielsson A, Schalling M, Stenvinkel P. Low leptin gene expression and hyperleptinemia in chronic renal failure. *Kidney Int*. 1998; 54:1267–75. [PubMed: 9767543]
32. Klein S, Coppack SW, Mohamed-Ali V, Landt M. Adipose tissue leptin production and plasma leptin kinetics in humans. *Diabetes*. 1996; 45:984–7. [PubMed: 8666153]
33. Hassink SG, Sheslow DV, de Lancey E, Opentanova I, Considine RV, Caro JF. Serum leptin in children with obesity: relationship to gender and development. *Pediatrics*. 1996; 98:201–3. [PubMed: 8692618]
34. Soderberg S, Stegmayr B, Stenlund H, Sjöström LG, Agren A, Johansson L, et al. Leptin, but not adiponectin, predicts stroke in males. *J Intern Med*. 2004; 256:128–36. [PubMed: 15257725]
35. Wallace AM, McMahon AD, Packard CJ, Kelly A, Shepherd J, Gaw A, et al. Plasma leptin and the risk of cardiovascular disease in the west of Scotland coronary prevention study (WOSCOPS). *Circulation*. 2001; 104:3052–6. [PubMed: 11748099]
36. Martos-Moreno GA, Burgos-Ramos E, Canelles S, Argente J, Barrios V. Analysis of insulin and cytokines during development using a multiplexed immunoassay: implications in pediatrics. *An Pediatr*. 2011; 74:356–62.
37. Schwartz GJ, Furth S, Cole SR, Warady B, Munoz A. Glomerular filtration rate via plasma iothexol disappearance: pilot study for chronic kidney disease in children. *Kidney Int*. 2006; 69:2070–7. [PubMed: 16612328]
38. Shankar A, Syamala S, Xiao J, Muntner P. Relationship between Plasma Leptin Level and Chronic Kidney Disease. *International journal of nephrology*. 2012; 2012:269532. [PubMed: 22666590]

Figure 1. Serum leptin in obese vs. non-obese children by sex and pubertal status. * indicates p value < 0.05

Figure 2. Correlation of leptin (ng/ml) with a) BMI z score ($r = 0.44$, $p < 0.001$) and b) iGFR ($r = 0.03$, $p = 0.65$) in children with CKD. Serum leptin was log transformed.

Table 1

Baseline characteristics of CKiD cohort

Characteristic	CKiD cohort (n=317)
Age (years)	12.4 (8.9, 15.6)
Sex	
Male	57%
Female	43%
Race	
Caucasian	72%
African-American	13%
Other	15%
Cause of CKD	
Glomerular	21%
Non-glomerular	79%
Tanner Stage	
I	48%
II	12%
III	9%
IV	13%
V	17%
Duration of CKD (years)	7.6 (4.3, 11.7)
iGFR (ml/min/1.73m ²)	45 (34, 58)
Height percentile	25 (8, 51)
Weight percentile	45 (21, 77)
BMI percentile	59 (33, 87)
Systolic blood pressure percentile	59 (29, 82)
Diastolic blood pressure percentile	61 (39, 85)
HDL (mg/dl)	48 (41, 56)
LDL (mg/dl)	104 (84, 121)
Triglycerides (mg/dl)	107 (74, 143)
IL-6 (pg/ml)	1.9 (1.1, 3.5)
IL-10 (pg/ml)	2.3 (1.6, 4.3)
TNF- α (pg/ml)	5.0 (3.6, 8.2)
leptin (ng/ml)	3.4 (1.5, 15.5)
Glucose (mg/dl)	89 (83, 95)
Insulin (mU/l)	7.6 (4.2, 12.2)
HOMA-IR	1.7 (0.9, 2.8)
Protein-to-creatinine ratio	0.44 (0.18, 1.1)

Continuous variables presented as median (interquartile range)

Categorical variables presented as percentages

Table 2

Serum leptin by sex and Tanner stage

Tanner stage	n	Male	n	Female
I	87	1.7 (1.0, 4.9)	58	3.8 (1.5, 17.0)
II	24	4.0 (3.0, 11.7)	14	8.9 (3.1, 17.4)
III	9	3.3 (2.2, 6.4)	19	13.3 (1.4, 60.9)
IV	28	2.7 (1.3, 4.4)	13	28.4 (4.2, 80.8)
V	26	5.2 (1.8, 25.2)	27	23.6 (5.2, 62.4)

Leptin levels (ng/ml) expressed as median (interquartile range)