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Perceived Appetite and Clinical Outcomes in Children with Chronic Kidney Disease

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Abstract

Background—Children with chronic kidney disease (CKD) may have impaired caloric intake through a variety of mechanisms, with decreased appetite as a putative contributor. In adult CKD, decreased appetite has been associated with poor clinical outcomes. There is limited information about this relationship in pediatric CKD.

Methods—879 participants of the Chronic Kidney Disease in Children (CKiD) study were studied. Self-reported appetite was assessed annually and categorized as very good, good, fair, or poor/very poor. The relationship between appetite and iothexol or estimated glomerular filtration rate (ieGFR), annual changes in anthropometrics z-scores, hospitalizations, emergency room visits, and quality of life were assessed.

Results—An ieGFR < 30 ml/min per 1.73m² was associated with a 4.46 greater odds (95% confidence interval: 2.80, 7.09) of having a worse appetite than those with ieGFR >90. Appetite did not predict changes in height, weight, or BMI z-scores. Patients not reporting a very good appetite had more hospitalizations over the next year than those with a very good appetite. Worse appetite was significantly associated with lower parental and patient reported quality of life.

Conclusions—Self-reported appetite in children with CKD worsens with lower ieGFR and is correlated with clinical outcomes, including hospitalizations and quality of life.

Keywords

Nutrition; pediatric; ER visits; quality of life; hospitalization; renal function

Introduction

Inadequate nutritional intake is a classic manifestation of chronic kidney disease (CKD) in adults and children.[1–3] Decreased caloric intake in CKD is believed to be secondary to a variety of mechanisms, including nausea, early satiety due to delayed gastric emptying, altered taste, and, in some patients, the need to drink large volumes of fluid to keep up with high urine output.[4,3] Poor nutritional intake is believed to have a role in the poor linear growth in children with CKD.[5,2,3] This is especially true for infants, who seem to experience the greatest benefit from aggressive nutritional intervention.[5,6,3]

A number of studies have shown a positive relationship between glomerular filtration rate (GFR) and nutritional intake.[2,1,3] In adults with CKD, self-reported decreased appetite is associated with a variety of poor outcomes, including decreased quality of life,[7] and increased hospitalizations and mortality in hemodialysis patients.[8] However, the relationship between self-reported appetite and GFR is poorly defined in children with CKD and there is limited information on the relationship between self-reported appetite and clinical outcomes in children with CKD.

Methods

Study Population and Design

From January 2005 through March 2014, 891 children with CKD were enrolled in the Chronic Kidney Disease in Children (CKiD) study, a prospective cohort study conducted at 54 pediatric nephrology centers across North America. The study design and conduct were approved by an external study monitoring board appointed by the National Institute of Diabetes and Digestive and Kidney Diseases and by the institutional review boards of each participating center. Details of the CKiD study have been previously published.[9] Clinical and demographic information were collected at annual visits. A total of 879 participants contributed data to at least one of the current analyses and served as our study population.

GFR Measurement

Glomerular filtration rate was determined from plasma iohexol disappearance curves at study entry, one year later and every other year thereafter using methods that have been detailed previously.[10] Briefly, to measure GFR, an intravenous line or butterfly needle was

used to administer 5 ml of iohexol. A second intravenous line was saline locked and used for obtaining blood samples for measurement of serum creatinine (SCr) and blood urea nitrogen (BUN); an aliquot was also obtained for HPLC determination of an iohexol blank. Serum creatinine (enzymatic) and BUN were analyzed centrally at the CKiD laboratory at the University of Rochester (G. Schwartz) on a Bayer Advia 2400 analyzer (Siemens Diagnostics, Tarrytown NY). Blood samples were collected at either four time points (10, 30, 120 and 300 min) or more recently from two or three time points after the infusion of iohexol, and serum iohexol concentrations were used to calculate iGFR. The validity of two and three point iGFR determinations have previously been described. [11] GFR values were subsequently scaled to body surface area (BSA), using the formula of Haycock et al.[12] When GFR was not directly measured (at odd-numbered study visits after the baseline visit), it was estimated (eGFR) using published equations.[13] For our analyses, ieGFR was defined as the iGFR value when available and the eGFR value during alternate years when iGFR was not measured.

Assessment of Appetite

As part of each annual visit, study participants were asked the first question of the Appetite and Diet Assessment Tool (ADAT), “During the past week, how would you rate your appetite?” Response options were on a 5-point scale: very good, good, fair, poor and very poor. It has been previously shown that responses to this question were associated with decreased dietary energy and protein intake and with other measures of nutritional status. [14] Because less than 1% of responses indicated a very poor appetite, we combined the poor and very poor responses into one category.

Primary Outcomes

Appetite during the past week ascertained at each visit served as the ordinal categorical outcome in our first set of analyses. Next, we examined the change in age-sex-specific height, weight, and body mass index (BMI) z-scores [15] between two consecutive visits; we also examined whether or not there were differences in age-sex-specific height, weight, and BMI z-scores at the first visit (index visit) in the pair of visits. The number of hospitalizations and the number of emergency room (ER) visits in the year following self-reported appetite were analyzed. Finally, parent and patient assessment of overall, physical, emotional, social and school quality of life were evaluated using the Pediatric Quality of Life Inventory (PedsQL) survey. This instrument has been validated to measure health related quality of life in children and adolescents [16]. Results from this survey are scored in a 0–100 scale, so that higher scores indicate better health related quality of life.

Covariates

ieGFR was grouped into four categories: ≥ 90 ml/min per 1.73m^2 , 60 to <90 , 30 to <60 , and <30 . CKD diagnoses were categorized as glomerular and non-glomerular. Age was treated continuously and to give the intercepts of the regression models (described below) some meaning we centered age at 12 years. Participants were categorized as white or non-white, and income was dichotomized into $>\$36,000$ and $\leq \$36,000$. Maternal education was classified as at most a high school graduate, some college, or college graduate.

Statistical Analyses

Mixed effects ordinal logistic regression models were used to quantify the degree of association that ieGFR and other covariates had with appetite. Linear mixed models were applied to pairs of consecutive study visits and used to quantify the degree of association that appetite and other covariates had with age-sex-specific height, weight, and BMI z-scores at both the first visit in the pair of visits (index visit) and the change between visits (standardized to a year). Mixed effects Poisson regression models were used to quantify the degree of association that appetite and other covariates had with both the number of hospitalizations and the number of emergency room visits in the following year. Linear mixed models were used to quantify the concomitant relationship between appetite and both parent- and patient-reported quality of life. A random subject effect was included in all regression models to account for repeated assessments of study outcomes on the same study participant over time. All statistical significance was evaluated at $\alpha = 0.05$.

Results

Eight-hundred-and-seventy-nine participants enrolled in the CKiD cohort who contributed a total of 2777 person-years of follow-up (median= 2.9 years, IQR=1.1, 5.8) were included in at least one of our analyses. Table 1 shows the characteristics of these 879 children at the baseline visit. In summary, 62% were male, the median age was 11.1 years (IQR= 7.6, 14.7), 66% were white, 31% had a glomerular CKD etiology, and the median ieGFR was 51.7 ml/min per 1.73m² (IQR= 38.2, 71.0). A very good appetite was reported 43% of the time; a good appetite was reported at 38% of all person-visits, a fair appetite at 15% of all person-visits, and a poor/very poor appetite at 4% of person-visits.

Table 2 illustrates the distribution of self-reported appetite first by different levels of ieGFR, and then by categories of CKD etiology, age, sex, race, family income, and maternal education. For example, at the 219 study visits conducted in which the participant had a ieGFR > 90 ml/min per 1.73m², 60% of the responses indicated that the participant had a very good appetite, 31% of the responses indicated the participant had a good appetite, 7% of the responses a fair appetite was reported, and only 2% of the responses was of a poor or very poor appetite. It is clear from the distribution of appetite for each ieGFR category that ieGFR was associated with appetite; whereby reports of poor or very poor appetite were more likely to be reported as ieGFR decreased. Moreover, after adjusting for all of the variables included in Table 2, lower ieGFR was the strongest correlate of poorer appetite. Specifically, compared to participants with a ieGFR > 90 ml/min per 1.73m² and with similar CKD etiology, age, sex, race, family income, and maternal education, a ieGFR between 60 to <90 was associated with a 1.63 (95% confidence interval [CI]: 1.07, 2.47) greater odds of poorer appetite, a ieGFR 30 to <60 was associated with a 2.25 (95% CI: 1.47, 3.44) greater odds of poorer appetite, and a ieGFR < 30 was associated with a 4.46 (95% CI: 2.80, 7.09) greater odds of poorer appetite. Other characteristics significantly associated with poorer appetite were age ≥ 5 years and White race.

We compared the mean index values of age-sex-specific height, weight, and BMI z-scores as well as the annualized changes in each z-score between children with different levels of appetite but with similar ieGFR, age, CKD diagnoses, sex, race, income and maternal

education (Table 3). Compared to those who reported a very good appetite, those who reported poor or very poor appetite had significantly lower height, weight, and BMI age-sex-specific z-scores. Specifically, those reporting a very good appetite had on average an age-sex-specific height z-score of -0.98 (95% CI: $-1.20, -0.76$), a weight z-score of 0.03 (95% CI: $-0.21, 0.27$), and a BMI z-score of 0.61 (95% CI: $0.40, 0.83$). Individuals with similar ieGFR, CKD diagnosis, age, sex, race, family income, and maternal education as those with a very good appetite, but with poor or very poor appetite, had a mean age-sex-specific height that was 0.19 standard deviations lower (95% CI: $-0.29, -0.08$), a mean weight that was 0.39 standard deviations lower (95% CI: $-0.51, -0.27$), and a mean BMI that was 0.35 standard deviations lower (95% CI: $-0.47, -0.23$). Participants with a good or fair appetite had average z-scores that were between those with poor/very poor and very good appetites.

After adjusting for index height, weight, and BMI, ieGFR and age, CKD diagnosis, sex, race, income, and maternal education, those with a poor or very poor appetite had greater mean annualized changes in their height z-score (0.00 vs. -0.06 [$p=0.066$]), weight z-score (0.14 vs. 0.00 [$p=0.001$]), and BMI z-score (0.15 vs. 0.03 [$p=0.021$]) than those reporting a very good appetite (Table 3).

In multivariate analyses, after adjusting for ieGFR, age, CKD diagnosis, sex, race, income, and maternal education, patients with very good appetites were hospitalized less often (0.09 times, 95% CI: $0.06, 0.15$) and had fewer emergency room visits (0.46 visits, 95% CI: $0.33, 0.65$) in the subsequent year than patients with poorer appetites (Table 4). Specifically, patients with good, fair, or poor/very poor appetites had 1.42 (95% CI: $1.09, 1.85$), 2.13 (95% CI: $1.54, 2.94$), or 1.69 (95% CI: $0.98, 2.91$) times as many hospitalizations, respectively as those who reported a very good appetite. Patients with only a fair appetite had 1.32 (95% CI: $1.06, 1.65$) times as many emergency room visits as those who reported a very good appetite.

Finally, self-reported appetite was significantly associated with quality of life in multivariate analyses. In parent reported (top of Table 5) and patient reported (bottom of Table 5) quality of life data, there was a consistent and significant decrease in overall quality of life and all subscales as self-reported appetite worsened after adjustment for ieGFR, age, CKD diagnosis, sex, race, income, and maternal education. For example, children who reported a good, fair, or a poor/very poor appetite had parents who rated their child's overall quality of life on average 2.4 units lower (95% CI: $-3.6, -1.3$), 4.4 units lower (95% CI: $-6.1, -2.7$), or 7.1 units lower (95% CI: $-10.0, -4.2$), respectively, than parents with children who reported a very good appetite (mean quality of life = 70.6 , 95% CI: $67.9, 73.3$). Even patients with a good appetite had a significantly lower quality of life than patients with a very good appetite in overall and all subscales of parent reported and patient reported quality of life (Table 5).

Discussion

Even though self-reported appetite is a subjective assessment of nutritional intake, we have described a relationship between self-reported appetite and clinical outcomes in a large prospective cohort of children with CKD. Self-reported appetite worsens as ieGFR declines. Children with worse self-reported appetite had lower BMI, height, and weight z-scores at the

time of the assessment, but then had a greater improvement in these z-scores over the subsequent year. In multivariate analysis, all domains of quality of life, both by parent and child report, worsened as self-reported appetite worsened. We also observed an increased number of hospitalizations and ER visits over the subsequent year as self-reported appetite worsened.

The mechanism of the relationship between decreased GFR and decreased appetite is poorly understood. In one study, children with CKD had decreased taste function compared to controls and there was a significant relationship between decreased GFR and decreased taste, although there was no association with decreased odor identification.[4] CKD leads to accumulation of the anorexigenic hormones des-acyl ghrelin, obestatin and leptin, but does not lead to compensatory increase in orexigenic hormones such as acyl ghrelin.[17,18]

Worse appetite, as might be expected, was associated with lower BMI, height, and weight z-scores at the time of the assessment. Interestingly, there was more improvement in these growth parameters over the subsequent year in patients with worse appetite, which indicated a tendency towards “catching up” to those with a very good appetite. It is possible that a combination of poor appetite and decreased height or BMI led to interventions such as high calorie foods or supplements, appetite stimulants or tube feedings. Overweight and obesity are not uncommon in patients with CKD [19] with 34% of patients from the CKiD cohort having BMI above the 85th percentile for age and gender at their first visit. We could speculate that some patients with good appetites may have been trying to lose weight. Other factors that could affect assessment of anthropometric measurements in our pediatric CKD population include edema, protein-energy wasting and growth hormone therapy.

We have identified that self-reported appetite has a unique association with poor clinical outcomes. Children with very good appetites were less likely to be hospitalized or make an emergency room visit over the subsequent year. There are limited predictors of morbidity in children with pre-dialysis CKD. In children receiving dialysis, hypoalbuminemia, short stature, poor linear growth, and low BMI are associated with increased mortality.[20,21] Similarly, a variety of indicators of nutritional status are associated with increased morbidity and mortality in adults receiving dialysis[22] and with pre-dialysis CKD.[23,24] Moreover, decreased self-reported appetite is associated with morbidity and mortality in adult hemodialysis patients.[8]

The dramatic association of small changes in self-reported appetite with all domains of quality of life was surprising in this population of children with CKD, although a previous study demonstrated an association between quality of life and self-reported appetite in adult hemodialysis patients.[7] The mechanism of this association cannot be discerned from this analysis, although it seems most likely that self-reported appetite is a general indicator of overall well-being.

Our results suggest that asking about appetite at routine clinic visits could be used to identify patients who may warrant intervention. Additional research is needed to determine how to optimize the use of this information in clinical practice.

One limitation of this study is that self-reported appetite is only recorded once a year and focuses only on the week preceding the study visit. It is possible that more frequent recording would increase the predictive value of this question. In addition, self-reported appetite was asked in the context of a clinical study and thus further research is needed to determine its utility in the context of clinical care.

Conclusions

Self-reported appetite worsens as ieGFR declines in children with CKD. Worse self-reported appetite is associated with increased emergency room visits and hospitalizations over the subsequent year. Moreover, worse self-reported appetite is associated with decreased quality of life, both by patient and parent report. Self-reported appetite may be a useful, simple indicator of overall well-being in children with CKD.

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Table 1

Baseline Characteristics of 879 participants of the Chronic Kidney Disease in Children (CKiD) cohort study.

Characteristics	Median (Inter-quartile range) or % (n)
Age, years	11.1 (7.6, 14.7)
Male Sex	62% (545)
White Race	66% (577)
Family Income > \$36,000	59% (517)
Maternal Education	
College Graduate	32% (282)
Some College	28% (242)
High School Graduate	40% (355)
Glomerular Filtration Rate, ml/min per 1.73m ²	51.7 (38.2, 71.0)
Glomerular CKD etiology	31% (271)

The relationship of glomerular filtration rate and other patient characteristics with concomitant self-reported appetite among 879 participants over a total of 3473 CKiD study visits.

Table 2

Variable	No. person-visits	% of responses with indicated appetite				Multivariate Odds Ratio ^a (95% Confidence Interval)
		Very Good	Good	Fair	Poor/ Very Poor	
ieGFR, ml/min per 1.73m ²						
90	219	60%	31%	7%	2%	1 (reference)
60 to <90	868	49%	37%	11%	3%	1.63 (1.07, 2.47)
30 to <60	1800	42%	39%	15%	4%	2.25 (1.47, 3.44)
<30	586	33%	37%	23%	8%	4.46 (2.80, 7.09)
CKD etiology						
Non-glomerular	2686	42%	37%	16%	4%	1 (reference)
Glomerular	787	47%	40%	11%	3%	0.96 (0.71, 1.31)
Age, years						
5	231	31%	41%	22%	7%	1 (reference)
5 to 10	845	40%	37%	18%	5%	0.73 (0.52, 1.02)
10 to 15	1229	49%	34%	14%	3%	0.48 (0.33, 0.69)
>15	1168	42%	41%	13%	3%	0.61 (0.41, 0.90)
Sex						
Female	1342	43%	41%	14%	3%	1 (reference)
Male	2131	44%	36%	16%	5%	1.11 (0.85, 1.44)
Race						
Non-White	1116	49%	36%	11%	4%	1 (reference)
White	2357	41%	39%	17%	4%	1.56 (1.17, 2.07)
Family Income (baseline)						
>\$36,000	2076	45%	37%	14%	4%	1 (reference)
\$36,000	1397	41%	38%	16%	5%	1.31 (0.98, 1.77)
Maternal Education (baseline)						
College Graduate	1085	47%	35%	14%	4%	1 (reference)

Variable	No. person-visits	% of responses with indicated appetite				Multivariate Odds Ratio ^f (95% Confidence Interval)
		Very Good	Good	Fair	Poor/ Very Poor	
Some College	990	41%	39%	16%	4%	1.17 (0.84, 1.64)
High School Graduate	1398	42%	39%	15%	4%	1.25 (0.89, 1.75)

ieGFR, glomerular filtration rate; CKD, chronic kidney disease.

^f The odds ratio represents the odds of reporting a worse appetite in the given group compared to the reference group.

Table 3

Relationship between self-reported appetite and both index-visit values and annualized changes in age-sex-specific height, weight, and body mass index z-scores^a; N=735 study participants contributing a total of 2286 visit pairs to each analysis.

	Age-Sex-Specific Height Z-score		Age-Sex-Specific Weight Z-score		Age-Sex-Specific Body Mass Index Z-score	
	Mean Index Value (95% CI)	Mean Annualized Change (95% CI)	Mean Index Value (95% CI)	Mean Annualized Change (95% CI)	Mean Index Value (95% CI)	Mean Annualized Change (95% CI)
Self-Reported Appetite						
Very Good	-0.98 (-1.20, -0.76)	-0.06 (-0.10, -0.02)	0.03 (-0.21, 0.27)	0.00 (-0.05, 0.04)	0.61 (0.40, 0.83)	0.03 (-0.02, 0.09)
Good	-0.99 (-1.21, -0.77)	-0.08 (-0.12, -0.04)	-0.05 (-0.30, 0.19)	-0.03 (-0.07, 0.02)	0.52 (0.31, 0.73)	0.01 (-0.04, 0.07)
Fair	-1.05 (-1.27, -0.83)	-0.08 (-0.13, -0.03)	-0.14 (-0.39, 0.11)	-0.04 (-0.10, 0.02)	0.42 (0.20, 0.63)	-0.01 (-0.08, 0.06)
Poor or Very Poor	-1.17 (-1.41, -0.93)	0.00 (-0.07, 0.07)	-0.36 (-0.62, -0.09)	0.14 (0.05, 0.24)	0.26 (0.02, 0.50)	0.15 (0.05, 0.26)

CI, confidence interval

^aRegression models in which the index values were modeled were adjusted for ieGFR at index, age at index (centered at 12 years), CKD diagnosis, sex, race, income, and maternal education. Regression models in which the annualized change was modeled were also adjusted for the corresponding height, weight, body mass index z-scores at the index visit.

Table 4

Hospitalizations and emergency room visits in the year following documentation of self-reported appetite, N=2039 pairs of visits contributed by 725 participants of the CKiD cohort.

Appetite	Hospitalizations in the following year ^J				Emergency Room Visits in the following year ^J			
	Average Number	95% Confidence Interval	Relative Number	95% Confidence Interval	Average Number	95% Confidence Interval	Relative Number	95% Confidence Interval
Very Good	0.09	(0.06, 0.15)	1	(reference)	0.46	(0.33, 0.65)	1	(reference)
Good	0.13	(0.08, 0.22)	1.42	(1.09, 1.85)	0.52	(0.37, 0.73)	1.12	(0.94, 1.32)
Fair	0.20	(0.12, 0.33)	2.13	(1.54, 2.94)	0.61	(0.42, 0.89)	1.32	(1.06, 1.65)
Poor or Very Poor	0.16	(0.08, 0.31)	1.69	(0.98, 2.91)	0.59	(0.38, 0.93)	1.28	(0.91, 1.80)

^JOne mixed effects Poisson regression model was used to estimate the average number and relative number of hospitalizations and a second regression model was used to estimate the average number and relative number of Emergency Room visits. Both models were adjusted for ieGFR at index, age at index (centered at 12 years), CKD diagnosis, sex, race, income, and maternal education.

Self-reported appetite in the CKiD cohort and parent, and patient reported quality of life using the Pediatric Quality of Life Inventory (PEDSQL).

Table 5

	Parent report of child's quality of life (N=2259 observations from 738 unique parents) [/]			
	Difference in Mean Overall (95% CI)	Difference in Mean Physical (95% CI)	Difference in Mean Emotion (95% CI)	Difference in Mean Social (95% CI)
Appetite				
Very Good	70.6 (reference)	71.1 (reference)	73.6 (reference)	74.6 (reference)
Good	-2.4 (-3.6, -1.3)	-2.7 (-4.3, -1.1)	-2.5 (-4.0, -1.1)	-2.2 (-3.7, -0.7)
Fair	-4.4 (-6.1, -2.7)	-4.1 (-6.4, -1.8)	-5.9 (-7.9, -3.8)	-4.3 (-6.5, -2.1)
Poor or Very Poor	-7.1 (-10.0, -4.2)	-7.9 (-11.8, -3.9)	-8.2 (-11.7, -4.6)	-7.1 (-10.8, -3.4)
	Participant self-report of quality of life (N=1875 observations from 662 unique participants) [/]			
	Difference in Mean Overall (95% CI)	Difference in Mean Physical (95% CI)	Difference in Mean Emotion (95% CI)	Difference in Mean Social (95% CI)
Appetite				
Very Good	73.1 (reference)	76.3 (reference)	72.6 (reference)	78.7 (reference)
Good	-2.1 (-3.3, -1.0)	-1.7 (-3.0, -0.5)	-2.3 (-3.9, -0.7)	-2.4 (-3.8, -0.9)
Fair	-4.2 (-5.8, -2.6)	-4.5 (-6.4, -2.6)	-4.7 (-7.0, -2.3)	-5.2 (-7.6, -2.9)
Poor or Very Poor	-5.9 (-8.8, -3.0)	-5.0 (-8.3, -1.7)	-5.6 (-9.8, -1.4)	-8.1 (-11.9, -4.3)

PEDSQL scores are reported in a 0–100 scale, so that higher scores indicate better health related QoL.

CI, confidence interval

[/] Analyses adjusted for concomitant values of ieGFR and age, CKD diagnosis, sex, race, income, and maternal education.