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A single-center longitudinal study of factors associated with the progression of stage 3 and 4 chronic kidney dis-ease in children

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Abstract

Introduction: Chronic kidney disease (CKD) has a natural evolution toward the loss of progressive kidney function; however, there is controversy about whether the progression has a constant and predictable rhythm. The objective of the present study was to identify the risk factors associated with progression in a group of children with CKD.

Methods: This longitudinal study was carried out in a follow-up of children under 16 years of age diagnosed with CKD in stages 3 and 4 at the Hospital de Pediatría, Centro Médico Nacional Siglo XXI, from October 2014 to October 2015. Somatometry, blood pressure, creatinine, hemoglobin, cholesterol, triglycerides, phosphorus, bicarbonate, proteinuria, and CKD progression were measured. The sample is compared between those who presented progression (P-ERC) and those who did not (SP-ERC). Values with medians are presented.

Results: 35 patients were ten years old, 18 women (54.4%), and 57% had urinary tract malformations. After follow-up for 2.95 years, the glomerular filtration rate (GFR) was 31.7 ml/min/1.73 m2. In stage 3, 20 patients were 8.7 years old, and 60% were women. In stage 4, 15 patients were 11.4 years old, and 66.7% were men. The decrease in GFR was 6.7 ml/min/1.73 m2/year, 6.6 for stage 3, and 2.8 for stage 4. Cholesterol levels were associated with the progression of kidney damage (P=0.03), and other factors were not significant. In both groups, the number of patients with obesity increased (P>0.05).

Conclusion: In the first year, 50% of the patients had P-CKD. Stage 3 patients have a higher velocity P-CKD. Hypercholesterolemia is a factor in the progression of CKD in children.

Keywords:

MESH: Renal Insufficiency, Chronic; Child; Glomerular Filtration Rate; Disease Progression; Risk Factors.

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The progression of chronic kidney disease (CKD) in children is influenced by various factors, some of which may be modifiable, such as arterial hypertension, proteinuria, glycemic control, obesity, dyslipidemia, anemia, and metabolic factors [1]. Children with CKD do not have the same epidemiological profile as adults, and modifiable factors are likely to have a different pattern than adults [2].

Regarding proteinuria in the pediatric age group, the Italkid project evaluated patients with hypoplastic kidneys, dividing them into three groups: a group without proteinuria, another with mild proteinuria (protein/creatinine ratio 0.2–0.9), and the third with moderate proteinuria (protein/creatinine ratio > 0.9). CKD progression was defined as renal function deterioration > 3 ml/min/1.73 m2 per year. The patients were followed up for an average of 3 and a half years; more significant deterioration of renal function was observed in patients in the group with moderate proteinuria, with a decrease in glomerular filtration rate (GFR) of 3.61 ± 5.4 ml/min/1.73 per year, compared to the groups without proteinuria or mild proteinuria (0.16 ± 3.64 and 0.54 ± 3.67 ml/min/1.73 m2 per year, respectively) ($P < 0.0001$) [3].

On the control of hypertension in children, in the cut made in 2003 of the NAPRTCS study, Mitsnefes et al. [4] analyzed 3,834 patients between the ages of 2 and 17 years with a GFR < 75 mL/min/1.73 m2. The study's endpoint was defined as the start of substitution therapy or deterioration in GFR of 10 mL/min/1.73 m2 concerning the baseline. The results describe that the children who presented hypertension at the start of the follow-up had a higher proportion of deterioration than those with normal blood pressure (58% vs. 49%). In contrast, when performing the multivariate analysis, systolic arterial hypertension was determined to be an independent factor ($P = 0.003$) of renal function deterioration.

Few studies document the prevalence of dyslipidemia in children and adolescents with CKD. A meta-analysis by Fried et al. from a total of 362 CKD patients in clinical trials with a small number of participants suggests that dyslipidemia treatment was associated with a 1.9 mL/min improvement in GFR when compared to controls without this treatment [5], while in a study carried out in 2011 by Holl R et al. in German, Swiss and Austrian adolescent patients showed that for every 10 ml/min/1.73 m2 decrease in GFR, there was a positive correlation with the increase in cholesterol, triglycerides, and cholesterol but no HDL, as well as a negative correlation with HDL cholesterol. In particular, children with a GFR < 30 mL/min/1.73 m2 were at increased risk of developing dyslipidemia [6].

Regarding anemia as a factor of progression, a multicenter and prospective study of 23 adolescents with CKD between the ages of 11 and 18 observed every six months for three years reported a decrease in GFR of 5.6 ml/min/1.73 m2 per year. The decrease was more significant in patients with anemia (hematocrit < 36%): 7.8 ml/min/1.73 m2 (95% CI: 3.3 – 12 ml/min/1.73 m2) [7].

There is now evidence that metabolic acidosis contributes to the progression of kidney disease in adults and children [8].

Children with chronic kidney disease have a high metabolic syndrome and obesity prevalence. These children experience a more rapid decline in renal function [9] compared to children with normal BMI.

With these antecedents, the present study's objective was to identify the factors associated with the deterioration of renal function in pediatric patients with chronic kidney disease in stages 3 and 4 in a national pediatric reference center in Mexico with a minimum follow-up of 6 months.

Materials and methods

Study design

The present study is observational, descriptive, and longitudinal.

Scenery

The study was conducted in the nephrology department at the High Specialty Medical Unit, Hospital de Pediatría, Centro Médico Nacional Siglo XXI, Instituto Mexicano del Seguro Social, Mexico City, Mexico, from October 1, 2014, to October 1, 2014. October 2015.

Participants

Pediatric patients with a diagnosis of stage 3 and 4 chronic kidney disease who were evaluated in the outpatient clinic of the institution were included. Renal transplant patients were excluded. Patients who reached the age of majority and who lost continuity of control in the outpatient clinic were excluded. Cases with incomplete data for analysis, incomplete medical records, or without follow-up after admission were eliminated.

Variables

The variables were anemia, nephrotic range proteinuria, hypercholesterolemia, hypertriglyceridemia, hyperphosphatemia, systolic arterial hypertension, diastolic arterial hypertension, etiology of chronic kidney disease, obesity, age, and sex. Confusion variables were considered to be the treatment received, the time of evolution of CKD, and the stage of CKD. The dependent variable was the progression of chronic kidney disease.

Data sources/measurements

The source was indirect; the institutional electronic file, statistics registry, nephrology, and outpatient services were reviewed. The glomerular filtration rate (GFR) in this study was estimated by calculating creatinine clearance with the Schwartz update formula.

Biases

To avoid possible interviewer, information, and memory biases, the principal investigator kept the data at all times with a guide and records approved in the research protocol. Observation and selection bias was avoided by applying the participant selection criteria. All the clinical and paraclinical variables of the period above were recorded. Two researchers independently analyzed each record in duplicate, and the variables were recorded in the database once their concordance was verified.

Study size

The sample was nonprobabilistic, census-type, where all possible cases from the study period were included since there is a low prevalence of CKD in the pediatric population that attends the institution.

Quantitative variables

Descriptive and inferential statistics were used. The results were expressed on a scale of means and standard deviation. Categorical data such as sex are presented as proportions.

Statistical analysis

Noninferential and inferential statistics are used. For the descriptive analysis, measures of central tendency and dispersion were calculated according to the measurement scale of each of the variables. Qualitative variables will be presented with absolute numbers and percentages; for the quantitative variables, the median is a measure of central tendency, and the minimum and maximum values are measures of dispersion.

Inferential analysis: The comparison between two groups for the quantitative variables will be made with the Mann–Whitney U test, and the comparison of proportions will be made with the chi-square test.

The statistical significance level was $P < 0.05$. The statistical package used was SPSS 25.0 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.).

Results

Participants

Thirty-five patients were studied out of 79 (Figure 1).

Baseline characteristics of the study population

The median age at the time of the first consultation was ten years; there were 18 women (54.4%), the overall follow-up was 2.95 years, and a median GFR estimated by the height of 31.7 ml was calculated./min/1.73 m2. Urinary tract malformations were the most common etiology (57%) and included vesicoureteral reflux, neurogenic bladder, and posterior urethral valves. The study population was classified by glomerular filtration rate, placing them in stage of CKD 3 or 4. The group of patients in stage 3 was made up of 20; the median age was 8.7 years, 60% were female, and the median follow-up was 2.8 years. The group of stage 4 patients consisted of 15 patients, whose median age was 11.4 years; 66.7% were male, with a median follow-up of 3.1 years (see Table 1). For both stages, urinary tract malformations were the most frequent etiology.

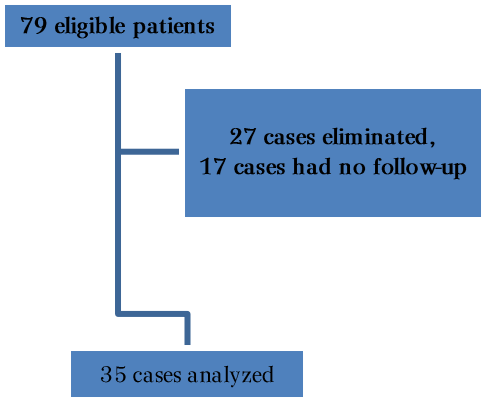

Figure 1. Participant flow chart.

Table 1. Description of the population according to the stage of CKD to the beginning of the study

	Stage 3 n = 20	Stage 4 n = 15
Age to the diagnosis of CKD (years)*	8.7 (1.4 - 16.2)	11.4 (2.5-16.1)
Sex		
Female	12 (60%)	5 (33.3%)
Male	8 (40%)	10 (66.7%)
Time waiter of tracing a starting from stages 3 & 4 (years)	3.1 (0-12)	3.1 (0.1-9)
Etiology of CKD		
Glomerulonephritis	1 (5%)	2 (13.3%)
Alport	2 (10%)	1 (6.7%)
Urinary malformations	11 (55%)	9 (60%)
Neoplasm	3 (15%)	1 (6.7%)
Other causes **	3 (15%)	2 (13.3%)

*Median (min MAX) (percentage) ** Aftermath of necrosis tubular sharp, Syndrome of Barter, Illness cystic renal

Evaluation of renal function and rate of progression

The GFR had an overall median at the beginning of the study of 31.7 ml/min/1.73 m2; for stage 3, it was 42.5 ml/min/1.73 m2, and for stage 4, it was 18 ml/min/1.73 m2. In 18 patients (54.42%), a decrease in the GFR of more than 3

ml/min/1.73m2 per year was observed, 11 (31.4%) patients had no decrease in creatinine clearance of more than 3 ml/min/1.73m2 per year, and in 6 patients (17.5%), an improvement in creatinine clearance was observed. The median global progression rate was 6.7 ml/min/1.73 m2 per year, 6.6 ml/min/1.73 m2 per year for patients in stage 3, and 2.8 ml/min/1.73 per year for those who were in stage 3.

Factors associated with the progression of kidney disease

At the beginning of the study, the variables were not different between the groups (Table 2). When classifying each factor according to the abnormality cutoff point, we observed that in the group of patients located in stage 3, the percentage of patients with both systolic and diastolic hypertension was higher for the group corresponding to stage 4; on the other hand, the percentage corresponding to nephrotic proteinuria, hypercholesterolemia, and hypertriglyceridemia was higher in this last group. The percentages corresponding to anemia, metabolic acidosis, and hyperphosphatemia were similar for both groups (see Table 3).

Analysis of CKD progression

In the group that presented progression of kidney disease, median proteinuria and triglycerides increased concerning baseline. The median percentiles for systolic blood pressure and cholesterol decreased (see Table 4). The group without chronic kidney disease progression presented a decrease in the median for triglycerides; for the rest of the identified variables, there was no significant difference (see table 4). Only elevated cholesterol levels at the start of follow-up were associated with the progression of kidney damage (P =0.03). Comparing the groups that progressed or not, according to the behavior of the factors with the cutoff point of abnormality, for the group of patients with progression, it was observed that more patients had hypertriglyceridemia, hypercholesterolemia, metabolic acidosis, and hyperphosphatemia at the end of follow-up despite the treatment established. In addition, fewer patients presented nephrotic proteinuria.

For the group without progression, the number of patients with arterial hypertension, hypertriglyceridemia, metabolic acidosis, and hyperphosphatemia decreased, and the number of patients with nephrotic proteinuria increased. In both groups, the number of patients with obesity increased (see Table 5). None of the factors studied at the beginning of the study were associated with CKD progression. Due to the sample size, it was not possible to calculate the risk of renal function progression by the factor associated with it.

Table 2. Variables studied in the population at the beginning of the study, in overall and classifying a population according to the stage of CKD*

	Total n=45	Stage 3 n=30	Stage 4 n=15
Percentile of body mass index	67 (0-98)	67 (0-98)	61.4 (8.7-98)
z score of body mass index	0.43 (-3.04 - 2.31)	0.43 (-3.04 - 2.15)	0.30 (-two - 2.31)
Percentile Arterial systolic pressure	69.1 (5.6-99.8)	64.2 (5.7-99.8)	69.1 (12.6 - 97.4)
Percentile Arterial Diastolic pressure	61.4 (5.7-99.8)	62.8 (5.7-99.8)	58.3 (30.2 - 93.4)
GFR Estimated by size (ml/min/1.73 m ^{2})	31.7 (5.2-59)	42.5 (30-59)	18 (9.3 -29.7)
Proteinuria (mg/m ^{2}/h)	17.6 (1-119)	12 (1-70.2)	36.6 (4.2 - 119)
Index UPr/UCr	0.96 (0.05-3)	0.37 (0.05 -3.6)	1.58 (0.16 -3)
Hemoglobin in serum (g/dL)	13 (5.8-15.4)	13.4 (5.9-15.4)	12.5 (9.1-13.4)
Cholesterol in serum (mg/dl)	154.5 (111-241)	158 (111-241)	151 (126-186)
Serum triglycerides (mg/dl)	104 (42-374)	96 (42-241)	130 (74-374)
HCO3 (mmol/l)	22.7 (16.6-29.7)	23.3 (16.6-29.7)	22.3 (19.1-27.4)
Phosphate (mg/dL)	5 (3.5-6)	5 (3.5-6)	4.9 (3.9 -6.9)

Table 3. Factors associated with the progression of CKD at the beginning of the study.

	Stage 3 n=30	Stage 4 n=15	P **
Obesity (IMC >PC95)	3 (10%)	3 (13.3%)	1.53
Arterial systolic hypertension (>PC95)	4 (20%)	1 (6.7%)	1.37
Arterial Diastolic hypertension (>PC95)	3 (15%)	1 (8%)	1.34
Nephrotic proteinuria(> 40 mg/m2 sc/h)	3 (10%)	3 (26.7%)	1.63
Anemia (< PC5)	5 (25%)	4 (26.7%)	1.1
Hypercholesterolemia (>P95)	3 (10%)	3 (21%)	1.63
Hypertriglyceridemia (>P95)	4 (20%)	6 (40%)	1.72
Acidosis metabolic*	6 (20%)	5 (26.7%)	1.1
Hyperphosphatemia*	3 (10%)	3 (13.3%)	1.53

Table 4. Characteristic of the population according to the progression of CKD at the beginning and finish of the study.

		Progression n=11		No progression n=17		P**	P**
		Basal	Term	Basal	Term		
Sex	Female	8 (44.4%)		11 (64.7%)		0.29	
	Male	10 (55.6%)		6 (35.3%)			
Stage	3	12 (66.7%)		8 (47.1%)		0.31	
	4	6 (33.3%)		9 (52.9%)			
z Score: Body mass index		0.49 (-1.50- 2.15)	0.34 (-1.6- 2.11)	0.44 (-3.04-2.2)	0.07 (-2.7-2.2)	0.61	0.5
Percentile: Body mass index		64.7 (6.9-98)	63.7 (5.5-98)	67 (0-98)	52 (0-96)	0.85	0.5
Percentile: Systolic blood pressure		71.3 (2.7-99.8)	49.4 (9.7-92.2)	62.9 (2.6-99.2)	53.6 (15.2-89.3)	0.61	0.6
Percentile: Diastolic blood pressure		57.3 (2.7-99)	64.4 (5.7-94.8)	62.9 (28.8-99.8)	61.8 (21.1-94.3)	0.75	1
GFR (ml/min/1.73 m)		35.7 (13.2-62.6)	29.3 (8.6-58)	29.7 (9.3-65)	29.2 (8.1-70.2)	0.48	0.6
Proteinuria (mg/m/h)		13.5 (1-109)	25.2 (4.3-134)	21 (3.5-47.2)	20.2 (0.7-73)	0.76	0.7
Index UPrlCr		0.66 (0.05-7)	1.78(0.1-8.8)	1.54 (0.1-3.6)	1.42 (0.1-4.8)	0.28	0.5
Hemoglobin (g/dL)		11.95 (9.8-14.3)	11.7 (9.4-16)	13.2 (10-15.4)	12.4(9.2-15.4)	0.13	0.6
Cholesterol (mg/dL)		175.5(101-241)	169 (101-226)	144 (104-226)	145 (103-236)	0.03	0.6
Triglycerides (mg/dL)		102 (42-282)	118 (48-219)	105.5 (69-374)	98 (50-303)	0.94	0.3
HCO3 (mmol/l)		24(16.6-28.8)	22.8 (15.4-27.2)	21.6(18.8-29.7)	22(18-35)	0.20	0.6
Phosphate (mg/dL)		4.8(3.1-6)	4.9(2.9-7.1)	5 (2.9-5.9)	4.8(3.5-6)	0.58	0.9

*Median (min MAX).** comparison of the proportion of the factors by the U-Mann–Whitney test.

Table 5. Factors identified in the population of study classified according to the progression of CKD by episodes of tracing and treatment established.

		Progression n=11			Without progression n=17			
		Basal	Mid	Ult	Basal	Mid	Ult	P*
Obesity		3 (16.7%)	2 (11.1%)	3 (16.7%)	1 (5.9%)	2 (11.8%)	2 (11.8%)	1.0
Systolic hypertension		1 (5.6%)	2 (11.1%)	1 (5.6%)	4 (23.5%)	1 (5.9%)	1 (0%)	1.14
Diastolic hypertension		1 (5.6%)	2 (11.1%)	1 (5.6%)	2 (11.8%)	1 (0%)	1 (5.9%)	1.0
AHT treatment		2 (11.1%)	3 (16.7%)	4 (22.2%)	3 (17.7%)	3 (17.6%)	2 (11.8%)	
Nephrotic proteinuria		4 (22.2%)	4 (22.2%)	3 (16.7%)	2 (11.8%)	5 (29.4%)	4 (23.5%)	1.0
AHT treatment	Enalapril	1 (5.6%)	2 (11.1%)	1 (5.6%)	2 (11.8%)	3 (17.7%)	2 (11.8%)	
	Losartan	2 (11.1%)	1 (5.6%)	2 (11.1%)	1 (0%)	2 (11.8%)	2 (11.8%)	
	Enalapril + losartan	1 (5.6%)	1 (5.6%)	1 (0%)	1 (0%)	1 (0%)	1 (0%)	
Anem ia treat-ment	None	1 (5.6%)	2 (11.1%)	1 (0%)	1 (0%)	1 (0%)	2 (11.8%)	
	Iron	2 (11.1%)	1 (5.6%)	3 (16.7%)	3 (17.7%)	1 (5.9%)	1 (5.9%)	
	Iron + EPO	2 (11.1%)	2 (11.1%)	1 (0%)	1 (5.9%)	3 (17.7%)	4 (23.5%)	
Hypercholesterolem ia		3 (16.7%)	4 (22.2%)	4 (22.2%)	2 (11.8%)	4 (23.5%)	3 (17.7%)	1.1
Treatment	Dietary	1 (5.6%)	3 (16.7%)	3 (16.7%)	1 (5.9%)	2 (11.8%)	2 (11.8%)	
	Pharmacological	2 (11.1%)	1 (5.6%)	1 (5.6%)	1 (5.9%)	2 (11.8%)	1 (5.9%)	
Hypertriglyceridem ia		6 (33.3%)	13 (72.2%)	10 (56%)	6 (35.3%)	8 (47.1%)	6 (35.4%)	1.1
Treatment	Dietary	6 (33.3%)	8 (44.4%)	9 (50.4%)	3 (17.65%)	3 (17.65%)	4 (23.5%)	
	Pharmacological	1 (0%)	5 (27.8%)	1 (5.6%)	3 (17.65%)	5 (29.4%)	1 (5.9%)	
Acidosis metabolic		3 (16.7%)	3 (16.7%)	3 (16.7%)	7 (41.2%)	5 (29.4%)	5 (29.5%)	1.11
Treatment	Oral HCO3-	2 (11.1%)	3 (16.7%)	3 (16.7%)	7 (41.2%)	4 (23.6%)	4 (23.6%)	
Hyperphosphatem ia		2 (11.1%)	3 (16.7%)	5 (27.8%)	2 (11.8%)	2 (11.8%)	1 (5.9%)	1.1
Treatment	Dietary	1 (0%)	1 (0%)	1 (0%)	1 (5.9%)	1 (0%)	1 (5.9%)	
	Chelating	1 (0%)	2 (11.1%)	3 (16.7%)	1 (5.9%)	2 (11.8%)	1 (0%)	

HTA: arterial hypertension. 2DA: Second medical consultation (2 or 3 months apart). 3RA: Third medical consultation (from the 6th month on-ward).

Discussion

One of the most frequent etiologies of CKD in children is urinary tract malformations; in this study, urinary tract malformations were the most frequent cause. In girls, the most frequent malformation was vesicoureteral reflux, and in boys, posterior urethral valves. This behavior could be explained by the less aggressive damage mechanism in vesicoureteral reflux, unlike posterior urethral valves, where much of the damage is intrauterine. Therefore, although there are more girls with stage 3 malformations, stage 4 men predominate.

Both the ItalKid project [3] and the REPIR II project [1], studying pediatric patients from stages 2 to 5, reported urinary tract malformations as the most common etiology in 53.6 and 59% of patients, respectively. In the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) [4], which gathers information on the pediatric population of the United States, Mexico, and Canada, stage 3 to 5 CKD, uropathies were also reported as the leading cause of kidney disease. Chronic (48%), this prevalence has also been reported in Latin America [10].

The median of GFR found at the beginning of this study was 31.7 ml/min/1.73 m2, which was lower for the ItalKid project (41.7 ml/min/1.73 m2) and the REPIR II project (39.5 ml/min/1.73 m2). These studies included patients from stages 2 to 5 without renal replacement therapy.

In this study, a median GFR loss of 6.6 ml/min/1.73 m2 per year was calculated in stage 3. Considering that these patients started with a median GFR of 42 ml/min/1.73, they could require renal therapy replacement in approximately three years. In stage 4 patients who had an initial median GFR of 18 ml/min/1.73 m2, a rate of progression of renal damage of 2.8 ml/min/1.73 m2 per year was calculated, and considering that most patients are admitted on dialysis with a GFR of less than 10 ml/min/1.73, this group is expected to be on renal replacement therapy for 3 years.

Proteinuria is one of the main factors associated with the progression of kidney damage, causing interstitial inflammation and fibrosis. Ardissino et al. [3] demonstrated an association between CKD progression and proteinuria, where initial proteinuria was correlated as a predictor of kidney damage. In this study, it was not statistically proven to be a factor of progression, probably due to the low number of cases included.

Arterial hypertension is a factor associated with the progression of kidney damage since it results in an increase in intraglomerular pressure that leads to glomerular hypertrophy and glomerulosclerosis. In the present study, it was not possible to demonstrate a significant difference in hypertension as a risk factor for progression. This result is different from what was found in the NAPRTCS23, which included 3834 patients, from 2 to 17 years of age, with a GFR of less than 75 ml/min/1.73 m2. It was identified that 48% of the patients were hypertensive at the beginning of the study. In addition, there were statistically significant differences between hypertensive and normotensive patients (58% vs. 49%, respectively, $P<0.0001$) with a GFR between 50-75 ml/min/1.73 m2 ($P<0.0001$).

Dyslipidemia conditions capillary endothelial damage in mesangial cells and podocytes. In patients with chronic kidney disease, the typical lipid pattern consists of elevated triglycerides (TGs) and decreased HDL cholesterol, especially after stage 3. Experimental studies have shown that dyslipidemia conditions the development of progressive proteinuria and glomerular damage without the presence of hemodynamic changes. In this study, there was a higher frequency of hypertriglyceridemia in stage 4 patients than in stage 3 patients (40% vs. 30%), which is consistent with the hypothesis that the greater the renal damage is, the more hyperlipidemia there is. However, at follow-up, the proportion in both groups differed according to progression; there was no difference.

Saland et al. [11], in the CKiD study, studied dyslipidemia in children with chronic kidney disease, including 391 children under 16 years of age. It showed a high prevalence of hypertriglyceridemia in 126 patients, with a median of 106 mg/dl, an increase in non-HDL cholesterol in 62, and a reduction in HDL in 83. The decrease in the glomerular filtration rate was related to the increase in triglyceride levels of 8% on average (95% CI: 5%, 11%) for each 10 ml/min/1.73 m2 decrease in glomerular filtration rate. They confirmed that hypertriglyceridemia is associated with decreased glomerular filtration. For this study, it was not possible to demonstrate it due to the sample size. However, the median triglycerides in the group that presented progression were higher than reported.

Regarding cholesterol, in this study, it was observed that there was an association of progression with high levels of cholesterol at the beginning of the study ($P = 0.03$), in addition to an increase in frequency both in the group that progressed and in the group that did not; however, the proportion was higher hypercholesterolemia in the group that progressed at the beginning. In this regard, Holl R et al. [12], in 2011, conducted a study in German, Swiss, and Austrian adolescent patients, showing that for every 10 ml/min/1.73 m2 decrease in GFR, there is a positive correlation with the increase in GFR in cholesterol, triglycerides and non-HDL cholesterol as well as a negative correlation with HDL cholesterol. Children with GFR < 30 ml/min/1.73m2 had a higher risk of presenting dyslipidemia. Isolated diet-induced hypercholesterolemia is associated with glomerular damage of focal segmental glomerulosclerosis and progressive renal failure in different experimental models.

Anemia has been related to cellular hypoxia, which increases oxidative stress, influencing the deterioration of renal function. In addition to the symptoms typical of any chronic

anemia, it affects cognitive functions and especially the cardiovascular system, significantly contributing to the development of left ventricular hypertrophy. In this study, 25% of the patients had anemia at the beginning, with a similar proportion in both groups. This differs from what was reported in the NAPRTCS23 study, where the prevalence of anemia in children was 73% in stage 3, 87% in stage 4, and more than 93% in stage 5. In REPAIR II [1], 30% of patients had anemia; thus, as the disease progressed, the percentage of anemics increased, being 14, 33, 58, and 54% in stages 2, 3, 4, and 5, respectively. This is expected since, as kidney disease progresses, renal mass decreases and, with it, the production of erythropoietin.

Obesity is related to the early appearance of glomerulomegaly, hemodynamic alterations of the hyperfiltration kidney, and increased albuminuria, manifestations related to the time of evolution and degree of severity but reversible with weight loss. The higher rate of children with chronic kidney diseases responds to a higher rate of childhood obesity, in addition to the association between obesity and proteinuria, due to focal segmental glomerulosclerosis in adolescents, which could lead to critical renal sequelae [13]. Cao et al. [14] studied 6852 patients between 20 and 79 years of age to identify whether the coexistence of metabolic syndrome is necessary for developing CKD in overweight and obese patients. At the 5-year follow-up, 776 patients developed CKD (GFR less than 60 ml/min/1.73m2). The risk of CKD, adjusted to multivariate hazard ratios for average weight in people without metabolic syndrome vs. overweight, was 1.31 (95% CI, 0.89 to 1.92), and for obese individuals, it was 2.39 (95% CI, 1.27-4.52).), being higher in patients with metabolic syndrome with an average weight of 1.54 (95% CI, 1.18-3.95), 2.06 (95% CI, 1.27 to 3.36) in overweight, and 2.77 (95% CI, 1.42 to 4.31) in obese individuals with metabolic syndrome. This suggests that being overweight and obese are risk factors for chronic kidney disease, regardless of the presence or absence of metabolic syndrome. In this study, 10% of the patients were obese at the beginning; when comparing the proportions at the beginning of the study, a higher proportion was identified in the group that progressed.

Conclusions

During the first year of follow-up, it was observed that approximately 50% of the patients had kidney disease progression. Stage 3 patients had a higher rate of deterioration of renal disease progression than stage 4 patients (6.6 ml/min/1.73 m2 vs. 2.8 ml/min/1.73 m2). The only factor related to progression was hypercholesterolemia at the beginning of the follow-up. The treatment directed at the different factors related to progression is likely related to the lack of association with other factors.

Abbreviations

CKD: Chronic kidney disease.
HTA: arterial hypertension.
GFR: glomerular filtration rate.

Supplementary information

Supplementary materials have not been declared.

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Does not apply.

Author contributions

Alma Rebeca Mota Nova: Conceptualization, Data Curation, Formal Analysis, Fundraising, Research, Methodology, Project Management, Resources, Software, Writing – original draft.
María Alejandra Aguilar Kitsu: Conceptualization, supervision, validation, visualization, and writing: review and editing.
Miguel Angel Villasis Keever: Methodology, validation, supervision, writing: Review and editing.
All authors read and approved the final version of the manuscript.

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Availability of data or materials

The data sets generated and analyzed during the current study are not publicly available due to participant confidentiality but are available from the corresponding author upon reasonable scholarly request.

Statements

Ethics committee approval and consent to participate

The research ethics committee approved this study of the High Specialty Medical Unit Hospital de Pediatría CMN.

Consent for publication

It does not apply when images or photographs of the physical examination or X-rays/CT/MRI of patients are not published.

Conflicts of interest

The authors report having no conflicts of interest.

References

1. Areses R, Sanahuja M, Navarro M. Epidemiology of end-stage chronic kidney disease in the Spanish pediatric population. REPIR II project. Nephrology 2010; 30:508-17. SCIELO: S0211
2. García de Vinuesa S. Progression factors of chronic kidney disease. Secondary prevention. Nephrology 2008; 3:17-21. SCIELO: 32352

3. Ardissino G, Daccò V, Testa S, Bonaudo R, Claris-Appiani A, Taioli E, Marra G, Edefonti A, Sereni F; ItalKid Project. Epidemiology of chronic renal failure in children: data from the ItalKid project. Pediatrics. 2003 Apr;111(4 Pt 1):e382-7. **DOI**: 10.1542/peds.111.4.e382. **PMID**: 12671156.

4. Mitsnefes M, Ho PL, McEnery PT. Hypertension and progression of chronic renal failure in children: a report of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS). J Am Soc Nephrol. 2003 Oct;14(10):2618-22. **DOI**: 10.1097/01.asn.0000089565.04535.4b. **PMID**: 14514740.

5. Sandhu S, Wiebe N, Fried LF, Tonelli M. Statins for improving renal outcomes: a meta-analysis. J Am Soc Nephrol. 2006 Jul;17(7):2006-16. **DOI**: 10.1681/ASN.2006010012. Epub 2006 June 8. **PMID**: 16762986.

6. Holl RW, Hoffmeister U, Thamm M, Stachow R, Keller KM, L'Allemand D, Widhalm K, Flechtner-Mors M, Wiegand S. Does obesity lead to a specific lipid disorder? Analysis from the German/Austrian/Swiss APV registry. Int J Pediatric Obes. 2011 Sep;6 Suppl 1:53-8. **DOI**: 10.3109/17477166.2011.604325. **PMID**: 21905817.

7. Furth SL, Cole SR, Fadrowski JJ, Gerson A, Pierce CB, Chandra M, Weiss R, Kaskel F; Council of Pediatric Nephrology and Urology, New York/New Jersey; Kidney and Urology Foundation of America. The association of anemia and hypoalbuminemia with accelerated decline in GFR among adolescents with chronic kidney disease. Pediatric Nephrol. 2007 Feb;22(2):265-71. **DOI**: 10.1007/s00467-006-0313-1. Epub 2006 November 21. **PMID**: 17120062

8. Brown DD, Roem J, Ng DK, Reidy KJ, Kumar J, Abramowitz MK, Mak RH, Furth SL, Schwartz GJ, Warady BA, Kaskel FJ, Melamed ML. Low Serum Bicarbonate and CKD Progression in Children. Clin J Am Soc Nephrol. 2020 Jun 8;15(6):755-765. **DOI**: 10.2215/CJN.07060619. Epub 2020 May 28. **PMID**: 32467307; **PMCID**: PMC7274283.

9. Lalan S, Jiang S, Ng DK, Kupferman F, Warady BA, Furth S, Mitsnefes MM. Cardiometabolic Risk Factors, Metabolic Syndrome, and Chronic Kidney Disease Progression in Children. J Pediatric 2018 Nov;202:163-170. **DOI**: 10.1016/j.jpeds.2018.06.007. Epub 2018 July 2. **PMID**: 30041938; **PMCID**: PMC6203642.

10. Piedrahita V, Flórez J, Martínez J, Prada M, Vanegas J, Vélez C, Serna L, Serrano A, Cornejo J. Causes of chronic kidney disease in children treated at the Pediatric Nephrology Service of the San Vicente de Paúl University Hospital, in Medellín, Colombia, between 1960 and 2010 Iatreia [online] 2011, 24 (October-December). **REDALYC**: 180522525001

11. Saland JM, Pierce CB, Mitsnefes MM, Flynn JT, Goebel J, Kupferman JC, Warady BA, Furth SL; CKiD Investigators. Dyslipidemia in children with chronic kidney disease. Kidney Int. 2010 Dec;78(11):1154-63. **DOI**: 10.1038/ki.2010.311. Epub 2010 August 25. **PMID**: 20736985; **PMCID**: PMC3222564.

12. Holl RW, Hoffmeister U, Thamm M, Stachow R, Keller KM, L'Allemand D, Widhalm K, Flechtner-Mors M, Wiegand S. Does obesity lead to a specific lipid disorder? Analysis from the German/Austrian/Swiss APV registry. Int J Pediatric Obes. 2011 Sep;6 Suppl 1:53-8. **DOI**: 10.3109/17477166.2011.604325. **PMID**: 21905817.

13. Gunta SS, Mak RH. Is obesity a risk factor for chronic kidney disease in children? Pediatric Nephrol. 2013 Oct;28(10):1949-56. **DOI**: 10.1007/s00467-012-2353-z. Epub 2012 November 14. **PMID**: 23150030.

14. Cao X, Zhou J, Yuan H, Wu L, Chen Z. Chronic kidney disease among overweight and obesity with and without metabolic syndrome in an urban Chinese cohort. BMC Nephrol. 2015 Jun 18;16:85. **DOI**: 10.1186/s12882-015-0083-8. **PMID**: 26084279; **PMCID**: PMC4471928.

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