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Glomerular filtration rate variations in a pediatric population: A prospective cohort study

Variaciones en la tasa de filtrado glomerular en una población pediátrica: un estudio de cohorte prospectivo

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Abstract

OBJECTIVE: To determine GFR variations in children < 17 years with albuminuria.

MATERIALS AND METHODS: A prospective cohort study was carried out in a rural community of Agua Caliente, Jalisco in México where the prevalence of albuminuria and kidney diseases are recognized as a public health problem. The GFR was measured in 2017 and one year later.

RESULTS: A total of 62 children participated. The GFR was measured and adjusted to the body surface using Creatinine-cystatin c-based CKiD and the Creatinine-based "Bedside Schwartz" Equation Differences were significant for both methods ($p < 0.001$).

CONCLUSIONS: Chronic kidney diseases and its causes have been studied during the last 4 years in this rural community. At the time, there is not a clear cause. More studies are necessary to discover a risk factor that is present in this rural community were 15 of 1000 inhabitants have CKD, and the prevalence of albuminuria in children is 47.5%.

KEYWORDS: Glomerular filtration rate; Children population; Albuminuria; Creatinine-cystatin c-based CKiD equation; Creatinine-based "Bedside Schwartz" Equation; Rural community.

Resumen

OBJETIVO: Determinar las variaciones de la tasa de filtrado glomerular en niños menores de 17 años con albuminuria.

MATERIALES Y MÉTODOS: Estudio de cohorte, prospectivo, llevado a cabo en una comunidad rural de Agua Caliente, Jalisco, donde la prevalencia de albuminuria y enfermedades renales representan un problema de salud pública. La tasa de filtrado glomerular se midió en el año 2017 y un año después.

RESULTADOS: Se seleccionaron 62 pacientes. La tasa de filtrado glomerular se midió y ajustó a la superficie corporal, utilizando las formulas *Creatinine-cystatin c-based CKiD y Creatinine-based "Bedside Schwartz" equation*, las diferencias fueron significativas para ambos métodos ($p < 0.001$).

CONCLUSIONES: Aunque en los últimos 4 años se han estudiado las enfemredades renales crónicas en los niños de esta región, no se ha identificado una causa clara que las genere. Se necesitan más estudios para detectar el o los factores de riesgo implicados, en donde 15 de cada 1000 habitantes tienen enfermedad renal crónica, y la prevalencia de albuminuria es de 47.5%.

PALABRAS CLAVE: Tasa de filtrado glomerular; población infantil; albuminuria; Formula Creatinine-cystatin c-based CKiD equation; Formula Creatinine-based "Bedside Schwartz"; comunidad rural.

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BACKGROUND

The kidney is involved in several functions for homeostasis of the body. Among these are found specific excretory, endocrine, and metabolic characteristics. The glomerular filtration rate (GFR) is one of the components of excretory function and is accepted as the best indicator of renal function, in that it presents a decrease in the cause of structural damage and in parallel decreases other renal functions.[1]

For over four decades Schwartz has developed a formula to estimate GFR based on serum creatinine, size, and an empirical constant.[2] Due to the variation and methods for determining serum creatinine, the formula was considered to overestimate GFR. In 2009, Schwartz and colleagues generated an equation in the cohort study Chronic Kidney Disease in Children (CKiD) with a group of 349 children between the ages of 1 and 16 years of age. The purpose was to develop a formula to estimate GFR using demographic variables and biological markers of renal function that included creatinine, Cystatin C, and urea nitrogen (BUN).[3]

Since 2012, GFR was estimated using Cystatin C as a very useful biological marker. However, the National Kidney Foundation considered that the values of Cystatin C still did not resolve the problems of the International Federation for Clinical Chemistry and Laboratory Medicine (IFCC), as it can overestimate the value of GFR.[4,5]

Based on the above, the "Bedside Schwartz" formula updated in 2009 had been determined to date as the best method to measure GFR in children.[6] GFR as a clinical indicator of renal function is used in patients with chronic kidney disease as an example of the research referenced previously.[3] Other researchers had measured GFR in pediatric agricultural populations starting with albuminuria parameters.[7] These studies focused on the determination of risk factors for albuminuria and determined GFR at a single point in time. However, the study subjects were not monitored to determine changes in the GFR over a given period of time.

For approximately 10 years, there have been newspaper reports on kidney diseases that affect residents from the community of Agua Caliente, Jalisco, Mexico. At present, this community has approximately 1,000 inhabitants, 15 of whom have a diagnosis of chronic renal failure, who are undergoing substitutive treatment and waiting for a kidney transplant. In addition, there were 9 deaths resulting from this pathology in the last 5 years.

The objective of this study was to determine the changes in the GFR during a one-year period in children younger than 17 years of age living in the rural community of Agua Caliente, where in 2017 there was a 47.5% prevalence of albuminuria.

MATERIALS AND METHODS

A prospective cohort study was conducted in the community of Agua Caliente, Jalisco, under the authorization of the Ethics Committee of the Doctorate in Public Health Sciences of the University of Guadalajara (DCSP/CEI/2016/10/176). The first research report was published as a cross-sectional study in December 2017.[8]

The study included children with persistent albuminuria who were not diagnosed with chronic kidney disease, diabetes, hypertension, or another disease that could affect kidney function. There were children who were not included in the study because their parents did not allow them to participate.

After one year of the first GFR measurement, the authors invited the same children to participate again. Informed consent was obtained from the parents of the minors to obtain data

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corresponding to age, weight, height, urine samples (first morning spot) and blood sampling to determine, again, albuminuria (Micral-Test®, Roche Diagnostics GmbH, Mannheim, Germany), creatinine, urea, and Cystatin C with the Diazyme Cystatin C Calibrator Set® for immunoturbidometry assay (Diazyme Laboratories, Inc., San Diego, CA, USA).

The samples were processed to obtain the levels of the previously specific biological markers. GFR was calculated in two ways: with the CKiD equation based on creatinine-cystatin C,[4] and with the "Bedside Schwartz" equation based on creatinine.[6] GRF results were adjusted to the body surface.[9]

The information obtained was organized in a database. Descriptive statistics were employed for general information utilizing measures of central tendency, frequencies, and proportions.

As an independent variable, the period of time (1 year) was taken and analyzed with the dependent variable (GFR) to calculate the frequency of change in the GFR from one KDIGO stage to another.

To determine magnitude and the null hypothesis test, the mean of the paired differences and their SD were calculated. With these numbers, 95% CI was calculated, along with a *p* value for the Student t test for paired samples. Data was processed with Excel® (Microsoft, Redmond, WA, USA), Epi Info ver. 7.2 (Centers for Disease Control and Prevention (CDC), Atlanta, GA, USA) and with Open Epi (Open Source Epidemiologic Statistics for Public Health, Bill and Melinda Gates Foundation, Emory University, Atlanta, GA, USA).

ETHICS APPROVAL

This research was done with the authorization of the Ethics Committee of the Doctorate in Public Health Sciences of the University of Guadalajara (DCSP/CEI/2016/10/17.6). Informed consent was obtained from parents and children with permission from municipal authorities.

RESULTS

At the beginning of the investigation, 565 children under the age of 17 years were registered. A total of 394 children (69.7%) agreed to participate with the consent of their parents. Persistent albuminuria was detected in 180 children (two urine samples, at first-morning spot, the second measurement after 12 weeks). Of these 180 children, only 160 agreed to continue with the study by providing blood samples to determine GFR. In September 2017, a new urine sampling (first morning spot) was performed. A total of 173 children tested positive for albuminuria. Only 62 children with previous GFR measurement (33 girls and 29 boys) and their parents agreed to participate again.

Seven samples for cystatin C were excluded due to insufficient quantity. The glomerular filtration rate was determined with the creatinine-cystatin c-based CKiD equation in 55 minors, and in 62, with the creatinine-based "Bedside Schwartz" equation.

GFR Calculation: Creatinine-cystatin c-based CKiD Equation Results

Of the 55 children who continued with the study, the average weight was 29.5 kg (range, 16.6-59 kg, SD 10.59), and the average height was 1.32 m (range, 1-1.56 m, SD 0.15). Cystatin C-based results (n=55) for GFR showed a significant increase in values after 1 year of follow-up from 53.38 mL/min/1.73m^2 in 2017 (SD 16.04, 95%CI 49.04 to 57.72) to 69.0 mL/min/1.73m^2 in 2018 (SD 25.64: 95% CI 64.12-73.88) The mean of differences was 15.59 (SD 30.69: 95% CI 7.29 to 23.89, p <0.001). **Table 1** shows the percentages and KDIGO stages of patients based on GFR calculated with the CKiD equation by age groups with the biological markers affected in 2018.[1]

The highest percentage of children was concentrated in stage 2 (47%), in contrast with the measurement of the previous year, in reference to that of the group in general (*n* = 160), which was concentrated in 68.1% in stage 3. When determining the stages of the measurement in 2017 of the 55 patients, the majority of the participants were in stage 3a. The increase in the percentage of children in stage 1 is also noticeable, while for stage 4 the percentage did not change. **Table 2** reveals the average of the GFR by age group based on the GFR calculation in 2017.

GFR Calculation: Creatinine-based "Bedside Schwartz" Equation Results

The results of this research can be observed from another perspective if we use the serum creatinine-based formula (Creatinine-based "Bedside Schwartz" equation), which is determined by the National Kidney Foundation as a better option for the calculation of GFR in children, due to the calibration problems encountered in standardizing Cystatin C determinations.[1,4,5]

With this method, it was possible to evaluate the total number of minors who continued in the second stage (n = 62) and to calculate the GFR without using the data obtained from the cystatin C measurement. In order to perform a mean difference analysis, the GFR was measured without cystatin C in the two time periods (2017 and 2018).

Of the 62 minors, an average weight of 29.7 kg (range, 14.6-59, SD 10.17) was calculated, and the average height was 1.30 m (range, 1-1.56, SD 0.14). The Bedside Schwartz Equation results (n = 62) for GFR shows a difference in GFR between 2017 (53.04 mL/min/1.73m^2, SD 15.82: 95%CI 40.49-57.52) and 2018 (73.39 mL/min/1.73m^2 SD 27.17: 95%CI 60.49-80.29). The mean of differences was 19.89 (SD 31.09: 95% CI 18.19 to 60.17, p<0.001). Based on this analysis, a total of 25 children showed an improvement in the GFR; 17 showed a decrease and 20 remained in the same KDIGO stage. The prevalence of KDIGO 3 remained unchanged (as expected, due to no change in GFR and the prevalence of KDIGO 4 which decreased from 8% (2017) to nil (2018) as patients improved their KDIGO grading. Data from the KDIGO stage and by age group are summarized in **Tables 3 and 4**.

Table 1. Staging of patients according to KDIGO sampling guidelines for 2018 (Creatinine-cystatin c-based CKiD Equation)

Age (yr)	KDIGO1	KDIGO2	KDIGO 3A	KDIGO 3B	KDIGO 4	Total
1 to 4	0	0	0	0	0	0
5 to 9	4	13	3	2	1	23
10 to 14	6	13	8	3	2	32
n (%)	10 (18.2)	26 (47.3)	11 (20)	5 (9.1)	3 (5.4)	55 (100)

Table 2. Staging of patients according to KDIGO sampling guidelines for 2018 (Creatinine-cystatin c-based CKiD Equation)

Age (yr)	KDIGO1	KDIGO2	KDIGO 3A	KDIGO 3B	KDIGO 4	Total
1 to 4	0	0	0	0	1	1
5 to 9	0	3	14	13	1	31
10 to14	1	12	7	2	1	23
n (%)	1 (1.8)	15 (27.3)	21 (38.2)	15 (27.3)	3 (5.4)	55 (100)

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Table 3. Staging of patients according to KDIGO sampling guidelines 2018 (Creatinine-based "Bedside Schwartz" equation)

Age (yr)	KDIGO1	KDIGO2	KDIGO 3A	KDIGO 3B	KDIGO 4	Total
1 to 4	0	0	0	1	0	1
5 to 9	0	3	18	3	0	24
10 to 14	1	26	6	4	0	37
n (%)	1 (1.6)	29 (46.8)	24 (38.7)	8 (12.9)	0	62 (100)

Table 4. Staging of patients according to KDIGO sampling guidelines 2017 (Creatinine-based "Bedside Schwartz" equation)

Age (yr)	KDIGO1	KDIGO2	KDIGO 3A	KDIGO 3B	KDIGO 4	Total
1 to 4	0	0	0	0	1	1
5 to 9	1	2	10	17	4	34
10 to 14	14	10	2	1	0	27
n (%)	15 (24.2)	12 (19.4)	12 (19.4)	18 (29)	5 (8)	62 (100)

Magnitude

Regarding magnitude (in the GFR change), Table V depicts the modification of the difference between the two measurements with a 1-year difference. For this purpose, a pairing process is shown between samples that are not independent of each other. The SD of the sample differences and their CI can also be observed.

When analyzing the results in the previous table, it is important to emphasize that the GFR showed a significant increase in the 5-9 age group (31.09 mL/min/1.73 m^2, SD 25.23: 95%CI: 22.28-39.89), while in the 10-14 year age group no change was observed during a one-year period. It can also be identified that in analyzing the total sample (n = 62), we are also able to observe a significant change of 19.88 mL/min/1.73 m^2.

DISCUSSION

Among our results, a high prevalence of albuminuria stands out regarding the levels of GFR. From year one of the first determination, an increase was observed in the total group (19.88 mL/min/1.73 m^2 SD 31.08, CI: 11.98-27.77), which could be directly related to age. This is clearly reflected in the group 5-9 year age group in which the change was significant. The 10-14 year age group, despite having presented a minimally increased level in the difference of the averages of the sample, does not highlight a statistically significant difference, and it can be deduced that the average of the GFR is neutral.

When we analyzed the GFR changes from 2017 to 2018 using the CKiD formula (n = 55), an increase from 53.38 mL/min/1.73 m^2 to 69.0 mL/min/1.73 m^2 can be observed ($p < 0.001$). Studies and sampling from 2016 to date in the community clearly show this relationship and, as expected, the prevalence of KDIGO stage in 2018 decreased from 65% to 29% for KDIGO 3 status as patients moved to the lower stages (2 and 1). It is noteworthy that, in general, during the second round, the trend showed an increase in the GFR, thereby achieving positive changes for stages 1, 2, and 3a. Another noteworthy fact is that the number of children in stage 3b decreased from 27% to 9% from 2017 to 2018.

The other perspective was that of the determination of the GFR without cystatin C with the

Creatinine-based "Bedside Schwartz" equation.[6] The results found a significant increase ($p < 0.001$) in the GFR in 2017 from 53.04 to 73.39 mL/min/1.73 m^2 in 2018. With this method, trends differed in terms of the percentage of minors in stage 1, which fell from 24.2% to 1.6% in 1 year, with an 85% concentration of minors in stages 2 and 3a. **Table 5**

Regardless of the differences in reported GFR by the two methods, (paired analysis), there was an improvement in KDIGO status after one year. Obviously, and by definition, an improvement in KDIGO class must be the result of an increase in GFR. This is evident when using Cystatin GFR. For the bedside GFR, this is noted by an increase in KDIGO 1-2 from 42% (2017) to 48% (2018) while Stage 3 remained unchanged. Most of the change occurred in the older age group (10 to 14). It is clear that, for the analysis without Cystatin C, fourteen children changed from stage 1 to stages 2 and 3a; however, a decrease in the number of children in stages 3b and 4 is also evident, which can be assumed based on the results of this study, in that the GFR tends to decrease in children between 5 and 9 years of age, and that subsequently, the values increased proportionally with age.

Since 2016, The University of Guadalajara had created a multidisciplinary group with the purpose of investigating the possible causes of the high prevalence of kidney diseases in the population of Agua Caliente. As a starting point, a review was conducted in to the causes of albuminuria in the pediatric population in which systemic arterial hypertension and diabetes mellitus were excluded, because there were no minors with either of these diseases in the community.[10] During the first stage of the study, 16 children with GFR ranging from 15-29 ml/min/1.73 m^2 were detected and were given priority based on this data. Fourteen of them agreed to undergo renal ultrasound; 13 of the studies reported normal results, and only one-showed nephropathy- compatible images. As part of the research, there are also studies to determine pesticides in urine, and the results were published in February 2019.[11] Prior to publication of the results, tests were performed to determine whether the presence of pesticides in the urine were related to the presence of albuminuria or a decreased GFR. However, no relationship was found between the study variables.

In Mexico, other authors have conducted studies on kidney diseases and associated risk factors (12,13). The investigations involved cross-sectional models with measurements at a single time, which renders it difficult to compare them with our research. Globally, there are also longitudinal investigations that determine changes in GFR after a period of time;[14] however, the methodology included children with a diagnosis of chronic kidney disease, and our study group only has a determination of albuminuria and a calculation of the GFR, but without the definitive diagnosis of chronic kidney disease, the latter is definitely a weakness of the present research.

Table 5. Calculation of the magnitude by sample differences. (Creatinine-based "Bedside Schwartz" equation)

Age (2017)	n	Mean			Differences (SD)	*CI95% of differences (p)	
		2017	2018	Differences			
1 to 4 yr	1						
5 to 9 yr	34	45.69	76.78	31.09	25.23	22.28-39.89	<0.01
10 to 14 yr	27	64.24	70.12	5.88	33.03	-7.18-18.94	<0.05
All group	62	53.50	73.39	19.88	31.08	11.98-27.77	<0.01

*Confidence interval 95% calculated for paired samples

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The results obtained are useful in order to understand the behavior of KDIGO stages in this group of vulnerable children. The community of Agua Caliente shares conditions with other communities, so results can be used not only for regional comparisons, since the study model can be employed in various countries that have similar conditions to those in Mexico. Although there is not as of yet a definitive answer to the problem, we were able to accomplish the general and specific objectives of our investigations, which brought us closer to a cause or response. It is also important to specify that since this research and the published results, the authorities have recognized that there is a problem and have been improving some community conditions by establishing community kitchens in schools, improving medical services, and certain other details that make the effort worthwhile, in that the real beneficiaries are the inhabitants.

The effort of the team of researchers integrated into the project should be highlighted. To date, there are lines of research that include the analysis of DNA, nutrition, heavy metals, and environmental pollution. We think that, as a whole, we will obtain a concrete response to the solution of this phenomenon that affects the public health of this agricultural community that shares similarities with many other communities in Mexico and other countries.

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