Evaluation of KIM-1, Cystatin-C and glomerular filtration rate in schoolchildren exposed to inorganic fluoride

Jiménez-Córdova MI[1], González-Horta MC[1], Aguilar-Madrid G[3], Barrera-Hernández A[1], Sánchez-Peña LC[3], Barbier OC[1], Del Razo LM[1]

[1]Toxicología, Cinvestav-IPN. Ciudad de México, México. [3]Universidad Autónoma de Chihuahua, Chihuahua México. [3]Salud en el Trabajo, Instituto Mexicano del Seguro Social, México City., México.

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Introduction

The inorganic fluoride (F^-) is widely distributed in the environment. It has been estimated more than 200 millions of people worldwide are exposed to elevated levels of F^- (>1.5 mg/L) through drinking water. The children are a risk group susceptible to damage by F^- exposure. Experimental data and some epidemiological studies had shown renal toxic effects induced by F^- exposure. However, the information in susceptible populations such as children is limited.

Objective

The aim of this study was to evaluate in a children population the association between F^- exposure and early biomarkers of kidney injury as the urinary levels of Kidney injury molecule 1 (KIM-1), Cystatin-C (Cys-C) and estimated glomerular filtration rate (eGFR).

Methodology

A cross-sectional study was conducted in Chihuahua, Mexico

417 children → No urine sample (n=2)

415 children

- **Clinic examination and interview** (Height, weight, blood pressure and dental fluorosis)
- **Samples**
  - **Water** → **F- quantification** F- ion selective electrode
  - **Urine** → **Quantification KIM-1 and Cystatin C** Microsphere immunoassay
  - **Blood** → **Calculation of estimated glomerular filtration rate (eGFR)** (Bedside-Schwartz equation) Using serum creatinine concentration; **Blood chemical analysis** Creatinine, BUN, lipid profile

Biomarker	NS	Comments
Cystatin C	PT ,Glom	Cysteine protease inhibitor. Filtered in Glom and reabsorbed in PT.
KIM-1	PT	Glycoprotein expressed in epithelial dedifferentiated cells in PT

NS, Nephron segment; TP, Proximal tubule; Glom, Glomerulus.

Results

I. General characteristics

Table 1. General characteristics of the study population.

Variable	n(%)	Mean ± SD (min-max)
Sex		
Male	191 (46)	
Female	224(54)	
Age (years)	401	8.7 ± 1.8 (5-13)
BUN (mg/dL)	406	9.8 ± 2.7 (4.2-23.8)
BMI (Kg/m^3)		
Underweight	9(2)	
Normal	278 (72)	
Overweight	49 (13)	
Obesity	48 (13)	
F$^-$ water		
≤1.5 mg F$^-$/L	263 (64)	0.19 ± 0.2 (0.01-1.3)
>1.5 mg F$^-$/L	149 (36)	2.2 ± 0.5 (1.7-5.8)
F$^-$ urine[a]		
≤2 µg F$^-$/mL	146 (41.5)	1.4 ± 0.3 (0.6-1.9)
>2 µg F$^-$/mL	206 (58.5)	3.2 ± 1.2 (2.01-14.2)

SD, standard deviation. BUN, blood urea nitrogen. BMI, Body mass index. F$^-$, fluoride.
[a]Normalized by urine specific gravity

58% of the population present high F$^-$ urine levels

II. F$^-$ exposure

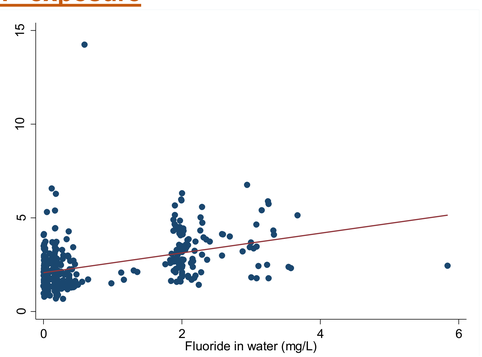

Fig 1. Relationship of fluoride levels between urine and water (n=350, r_s=0.379, p<0.0001)

Drinking water contribute to fluoride exposure in the study population

III. Kidney biomarkers and F$^-$ exposure

Table 2. Kidney function biomarkers and F- urine levels

Variable	n	Mean ± SD or GM (RIQ)
eGFR (mL/min/1.73m^2)		
≤2 µg F$^-$/mL	123	79 ± 0.8
>2 µg F$^-$/mL	182	81 ± 0.7
Cys-C (ng/mL)[a]		
≤2 µg F$^-$/mL	123	42 (22-71)
>2 µg F$^-$/mL	189	53 (34-87)
KIM-1 (pg/mL)[a]		
≤2 µg F$^-$/mL	93	145 (65-322)
>2 µg F$^-$/mL	142	225 (78-498)

SD, standard deviation. IQR, interquartile range (25%-75%). eGFR, estimated glomerular filtration rate. [a]Normalized by urine specific gravity

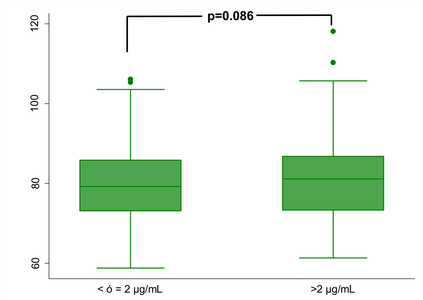

Fig 2. Estimated glomerular filtration rate by level of urinary F$^-$ in children, *t*-test was performed.

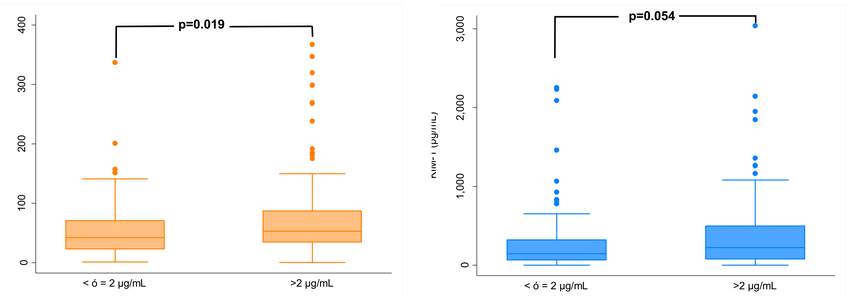

Fig 3. Cys-C and KIM-1 by level of urinary F$^-$ in children, Mann Whitney test was performed.

Levels of Cys-C were significant higher in the F$^-$ exposed group, and marginally significant to KIM-1 and eGFR.

Table 1. Simple and robust regression analysis between F- exposure and kidney function biomarkers

Kidney injury biomarkers	F$^-$ urine (>2 µg/mL)	
	Simple	Adjusted
	β (p-*value*)	β (p-*value*)
eGFR (mL/min/1.73m^2)	1.87 (0.086)	2.09 **(0.045)**[a]
Cys-C (ng/mL)	15.2 **(0.022)**	19.3 **(0.005)**[b]
KIM-1 (pg/mL)	71.3 (0.224)	52 (0.186)[c]

[a]Adjusted by age, BMI, atherogenic index and sex (R^2=0.104, n=320). [b]Adjusted by sex and urate amorphous crystals (R^2=0.036, n=311). [c]Adjusted by age, sex and BMI (R^2=0.052, n=219).

The multiple regression analysis shows a positive and significant relationship between Cys-C, eGFR and the F$^-$ urine levels

Conclusions

This results show an association between the F$^-$ exposure and the increase in the urinary excretion of Cystatin-C and the estimated glomerular filtration rate, suggesting a relationship between early kidney injury and the F$^-$ exposure. This early injury may contribute to the development of diseases in the adultness.

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