Uric acid is an independent biomarker in the management of a chronic renal disease

Ácido úrico como biomarcador independiente en el control del enfermo crónico renal

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Received/Recibido: 06/21/2021 Accepted/Aceptado: 08/15/2021 Published/Publicado: 09/12/2021 DOI: http://doi.org/10.5281/zenodo.5812362

Abstract

Background. Several studies have documented uric acid as a predictor of decreased glomerular filtration rate. However, this relationship remains unclear in terms of renal disease progression.

Objectives. Evaluate the association of uric acid with the decrease in glomerular filtration rate in the progression of chronic kidney disease in adult patients. Methods. For this, we worked with 361 patients (132 women and 229 men) diagnosed with chronic kidney disease, corresponding to the period January 2019 - January 2020.

Results. The main risk factors reported were diabetes mellitus (35%), hypertension (24%) and diabetic nephropathy (10%). Correlational analysis in the general population and women in baseline UA indices correlated negatively with eGFR (r= -0.138, p= 0.009; r= -0.300, p<0.001, respectively), while in men we observed no significant correlation (r = -0.041, p= 0.539).

Conclusion. Recent evidence from this study showed UA as an independent biomarker with a significant correlation between uric acid levels and renal function concerning gender. Increased UA is associated with decreased eGFR and its progression in CKD with a higher risk in women than men.

Keywords: biomarker, chronic kidney disease, glomerular filtration rate, uric acid.

Resumen

Antecedentes. Varios estudios han documentado el ácido úrico como un predictor de la tasa de filtración glomerular disminuida. Sin embargo, esta relación sigue sin estar clara en términos de progresión de la enfermedad renal.

Obejtivos. Evaluar la asociación del ácido úrico con la disminución de la tasa de filtración glomerular en la progresión de la enfermedad renal crónica en pacientes adultos. Métodos. Para ello, se trabajó con 361 pacientes (132 mujeres y 229 hombres) diagnosticados de enfermedad renal crónica, correspondientes al período enero 2019 - enero 2020.

Resultados. Los principales factores de riesgo reportados fueron diabetes mellitus (35%), hipertensión (24%) y nefropatía diabética (10%). El análisis correlacional en la población general y las mujeres en los índices de AU basales se correlacionaron negativamente con la TFGe (r = -0,138, p = 0,009; r = -0,300, p <0,001, respectivamente), mientras que en los hombres no observamos correlación significativa (r = - 0,041, p = 0,539).

Conclusión. La evidencia reciente de este estudio mostró que la AU como un biomarcador independiente con una correlación significativa entre los niveles de ácido úrico y la función renal con respecto al género. El aumento de la AU se asocia con una disminución de la TFGe y su progresión en la ERC con mayor riesgo en mujeres que en hombres.

Palabras clave: biomarcador, enfermedad renal crónica, tasa de filtración glomerular, ácido úrico.

Introduction

Chronic kidney disease (CKD) is a problem of outstanding dimensions in public health in Mexico[1]. In 2017, a prevalence of 12.2% and 51.4 deaths per 100 thousand inhabitants in Mexico[2] was reported as a disorder of multifactorial origin and strongly associated with chronic diseases of higher prevalence in our population, such as obesity dyslipidemias, diabetes, and hypertension[3].

During the last decade, new insights into pathophysiology, epidemiology, and biomarkers have modified our understanding of dysfunction, acute kidney injury, and its association with chronic kidney disease. Thus, the estimated glomerular filtration rate (eGFR) is an index for assessing renal function, as it is considered an optimal measure of the kidney's filtering capacity; according to age, sex, and body mass, and is around 140 mL/min/1.73 m^2 in healthy adults, so that values lower than 60 mL/min/1.73 m^2 are associated with complications in CKD and cardiovascular risk[4,5].

On the other hand, serum creatinine (CrS), a metabolite of creatine phosphate, is a commonly used indicator to detect small changes in the estimated glomerular filtration rate (eGFR), especially in the early stages[6]. While uric acid (UA), a waste product of purine metabolism, is freely excreted in the urine, its serum concentration is significant among humans as a result of a number of factors that increase or decrease its excretion that also it is modified by eGF[7].

In recent years there is growing evidence of the relationship between elevated levels of UA in the blood (hyperuricemia), renal and cardiovascular pathology since 2/3 of UA is eliminated by the kidney. The adverse effects of hyperuricemia are endothelial dysfunction, activation of the local renin-angiotensin system (RAS), increased oxidative stress, and a proinflammatory and proliferative action[8–10]. Therefore, epidemiological studies suggest an independent association between asymptomatic hyperuricemia and an increased risk of arterial hypertension, chronic kidney disease, cardiovascular events, and mortality[11,12].

Recently, systematic review and meta-analysis of observational cohort studies are essential. For example, Ling et al. found hyperuricemia an independent predictor of persistent CKD[13]. Therefore, we planned retrospective observational studies to evaluate the association of uric acid with decreased glomerular filtration rate in the progression of CKD in adult patients.

Objective

Evaluate the association of uric acid with the decrease in glomerular filtration rate in the progression of chronic kidney disease in adult patients.

Methods

Type of study and population.

The present investigation was an observational, retrospective, analytical correlation study. The sample was calculated with the simple correlation formula. The formula used is the following $n = 3 + \frac{K}{C}$ $n = 3 + \frac{K}{C}$ where $K = (Z\alpha + Z\beta)^2$ $K = (Z\alpha + Z\beta)^2$, $C = 0.5\ In\ \frac{(1+r)}{(1-r)}$ $C = 0.5\ In\ \frac{(1+r)}{(1-r)}$ with a value of -= 0.05, 95 % confidence level and an expected correlation of ± 0.5.

Data collection: Information was extracted for analysis from the Clinical Laboratory Database of the participating hospital of patients from the Nephrology Unit of the ISSEMYM Medical Center "Lic. Arturo Montiel", State of Mexico, within the database concerning (age, gender, history of diseases and biochemical data at the time of admission to the hospital) corresponding to the period January 2019-January 2020. A database corresponding to 443 patients was analyzed, of which only 361 met the inclusion criteria.

Inclusion criteria: Patients assigned to the Nephrology Unit with complete and updated data confirmed with CKD diagnosis. According to clinical practice guidelines (NKF-KDOQI™)[14].

Exclusion criteria: Patients with renal replacement therapy (RRT), chronic lung disease, and autoimmune diseases.

Biochemical data.

A standardized operating manual for collecting peripheral blood samples in BD Vacutainer® SSTTM tubes for a serum with separator gel using the venous puncture technique was followed to obtain the biochemical parameter data. 1) Plasma glucose levels were measured primarily using the hexokinase enzymatic reference method, 2) Triglyceride and low-density lipoprotein (LDL) cholesterol concentrations were measured by enzymatic methods, and high-density lipoprotein (HDL) cholesterol concentrations were measured directly 3) For renal function assessment, serum uric acid levels were measured mainly by an enzymatic method, and 4) Serum creatinine was measured by an enzymatic method, and the estimated glomerular filtration rate (eGFR) was obtained by the CKD- EPI equation[15]. All the samples were processed in the Clinical Laboratory of the Centro Médico ISSEMYM "Lic. Arturo Montiel" (Toluca, State of Mexico) by colorimetry using reagents specified for each determination according to Roche Diagnostics. The determinations were made with the COBAS e 311 equipment (Roche Diagnostic GmbH, Sandhofer Strasse 116, D-68305 Manheim, Germany).

Subsequently, to classify the patients, three age groups were divided according to gender (young adult (YA) 18-40 years), (mature adult (MAd) 41-60 years), and (older adult (MAy) 61-90). Patients with a diagnosis of CKD were first identified for their respective classification, calculating the estimated GFR (eGFR) (mL/min/1.73 m^2) using the CKD-Epidemiology Collaboration (CKD-EPI) equation[15]

validated for the Mexican population.

According to the classification of CKD by the clinical practice guidelines of the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (NKF-KDOQI™)[14], patients were divided into five stages using the following ranges: Normal or high (Stage 1, >90 mL/min/1.73 m^2), Mild decline (Stage 2, 60-89 mL/min/1.73 m^2), Mild/moderate decline (Stage 3A, 45-59 mL/min/1.73 m^2), Moderate/severe decline (Stage 3B, 30-44 mL/min/1.73 m^2), Severe decline (Stage 4, 15-29 mL/min/1.73 m^2) and representing end-stage renal disease (Stage 5, < 15 mL/min/1.73 m^2). The research protocol complied with the ethical standards of the WMA Declaration of Helsinki 2013 (World Medical Association, 2013) and was approved by the Ethics and Research Committee of the Center for Research and Medical Sciences of the ISSEMyM Medical Center.

Statistical analysis

Statistics were performed with the statistical program IBM SPSS version 23 (2014). Continuous data were expressed with measures of central tendency and dispersion; qualitative data were expressed as percentages. Means were contrasted with Student's t-test and medians with the Mann-Whitney U test. Pearson's correlation coefficient was used for bivariate correlation studies, and for multivariate analysis, the ANOVA test with post hoc Bonferroni correction was used. The nonparametric Kruskal Wallis H test was applied to compare the groups, followed by the Mann Whitney U statistic. A value of $p \leq 0.05$ was considered significant.

Results

Biochemical data.

A database corresponding to 443 patients was analyzed, of which only 361 met the inclusion criteria. Of all the patients diagnosed with CKD, 63% were men and 37% women. The median age was 54 years with its quartiles (Q_{25} – Q_{75} 36-65) (Table 1). According to the data obtained from blood chemistry, apparent changes in the renal profile (BUN, urea, serum creatinine, and uric acid) were observed because they were elevated concerning their reference values. Furthermore, the central tendency values in GFRe, 21.57 mL/min/1.73 m^2 (Q_{25} – Q_{75} 6.89 - 51.61), showed a severe renal decline.

In this sense, the leading risk factor for kidney disease for both genders was hypertension (67.4% in women vs. 62.4% in men), followed by diabetes mellitus (32.6% in women vs. 37.6 % in men), diabetic nephropathy (11.4% in women vs. 9.2% in men), glomerulonephritis (9.1% in women vs. 8.3% in men) and other unknown causes (15.2% in women vs. 21.4% in men). None of these risk factors present in CKD patients showed statistical significance between genders (Table 2).

Table 1. General clinical characteristics of patients with CKD.

Biomarkers	Total (N = 361)
Age (Years)	54 (36 - 65)
Glucose (mg/dL)	95.40 (88.15 - 110.75)
BUN (mg/dL)	38.40 (23.05 - 56.5)
Urea (mg/dL)	81.90 (48.80 - 120.65)
Serum Creatinine (mg/dL)	2.82 (1.37 - 7.24)
Uric Acid (mg/dL)	6.43 (5.30 - 7.84)
Cholesterol (mg/dL)	170.20 (143.34 - 200.85)
Triglycerides (mg/dL)	145.60 (111.45 - 208.80)
LDL (mg/dL) n= 82	107.70 (84.75 - 130.95)
HDL (mg/dL) n= 82	43.35 (36.97 - 54.92)
eGFR (mL/min/1,73 m^2)	21.57 (6.89 - 51.61)

* Values expressed in medians and quartiles Q_{25} - Q_{75}. Abbreviations: BUN: blood urea nitrogen; LDL: low-density lipoproteins; HDL: high-density lipoproteins; eGFR: estimated glomerular filtration rate.

Table 2. Risk factors in the population with chronic kidney disease grouped by gender.

	Yes/ No	Women		Men		Total		p
		n	%	n	%	n	%	
Diabetes mellitus	Yes	43	32.6%	86	37.6%	129	35.7%	0.342
	No	89	67.4%	143	62.4%	232	64.3%	
Hypertension	Yes	42	31.8%	55	24.0%	97	26.9%	0.108
	No	90	68.2%	174	76.0%	264	73.1%	
Diabetic nephropathy	Yes	15	11.4%	21	9.2%	36	10.0%	0.504
	No	117	88.6%	208	90.8%	325	90.0%	
Glomerulonephritis	Yes	12	9.1%	19	8.3%	31	8.6%	0.796
	No	120	90.9%	210	91.7%	330	91.4%	
Unknown cause	Yes	20	15.2%	49	21.4%	69	19.1%	0.147
	No	112	84.8%	180	78.6%	292	80.9%	

Values expressed in totals (n) and percentages (%) p-values refer to the nonparametric Mann-Whitney U test.

The renal prognostic biomarkers grouped by gender are summarized in Table 3. The results obtained from UA determination showed hyperuricemia in both genders (women >6.20 mg/dL vs. men >6.5 mg/dL), with no statistical differences. Moreover, in the biomarkers of renal function, median eGFR showed a severe decrease in renal function in both genders with (21.54 mL/min/1.73 m^2 in women vs. 21.57 mL/min/1.73 m^2 in men). Also, the analytes that showed to be statistically significant were CrS and cholesterol (p=0.015, p=<0.01).

Abbreviations: BUN: blood urea nitrogen; eGFR: estimated glomerular filtration rate.

Apart from this, in the multivariate analysis, the three age groups, (young adult (YA) 18-40 years), (mature adult (MAd) 41-60 years), and (older adult (MAy) 61-90), in order to check had significant differences between biomarkers. Especially of women, they showed hyperuricemia with a decrease in eGFR by age group, but did not show statistical significance (p=0.217, p=0.484 respectively); in contrast, in men, UA levels and eGFR decreased substantially in (AJ) and (AMD) while in (Amy) showed an increase with statistical significance (p=0.003, p=0.036 respectively). The three groups differed for gender in the clinical characteristics associated with glucose, serum creatinine, and cholesterol and did not differ with BUN, urea, triglycerides, LDL, and HDL (Table 4).

Table 3. Clinical characteristics of CKD patients grouped by gender.

Biomarkers	Women	Men	p
	(N = 132)	(N = 229)	
Uric Acid (mg/dL)	6.20 (5.05 - 7.80)	6.61 (5.45 - 7.84)	0.136
eGFR (mL/min/1.73 m^2)	21.34 (7.04 - 52.66)	21.57 (6.80 - 51.17)	0.865
BUN (mg/dL)	36.30 (19.15 - 54.15)	39.80 (23.85 - 57.75)	0.096
Urea (mg/dL)	77.70 (40.95 - 115.90)	83.10 (50.35 - 122.70)	0.117
Serum Creatinine (mg/dL)	2.50 (1.27 - 5.80)	3.07 (1.51 - 8.27)	0.000
Cholesterol (mg/dL)	184.76 ± 48.95 **	163.50 (139.35 - 192.90)	0.000

* Values expressed in medians and interquartile ranges (Q_{25} - Q_{75}), and the p-values refer to the nonparametric Mann-Whitney U test.
** Values expressed as means and standard deviation (SD).

Table 4. Clinical characteristics by age group.

Biomarkers	Gender	Young Adult (AJ)	Mature Adult (AMd)	Older Adult (AMy)	p
		M (n= 42), H (n = 78)	M (n= 47), H (n = 78)	M (n = 43), H (n = 73)	
Glucose (mg/dL)	Women	89.71 ± 11.65	98.6 (92 - 119.60)	98 (88.70 - 120)	0.003
	Men	91.55 (87.20 - 98.25)	97.80 (88.38 - 118.78)	101.10 (90.80 - 129.45)	0.003
BUN (mg/dL)	Women	40.8 (16.60 - 56.63)	32.2 (21.10 - 50.60)	40.30 (20.40 - 55.50)	0.338
	Men	36.10 (22.17 - 56.72)	36.30 (23.20 - 57.63)	42.70 (28.30 - 60.90)	0.143
Urea (mg/dL)	Women	87.65 (35.48 - 121.15)	69 (45.20 - 108.20)	86.30 (43.60 - 118.80)	0.337
	Men	77.50 (47.45 - 121.47)	76.90 (48.60 - 122.13)	91.30 (60.60 - 130.30)	0.096
Serum Creatinine (mg/dL)	Women	3.06 (1.17 - 10.93)	2.08 (1.12 - 4.19)	2.52 (1.34 - 4.06)	0.013
	Men	2.59 (1.38 - 12.69)	3.42 (1.31 - 8.48)	2.90 (2.01 - 5.71)	0.041
Uric Acid (mg/dL)	Women	6.22 (5.52 - 7.89)	6.09 ± 1.94	6.73 ± 2.3	0.217
	Men	7.38 ± 1.96	6.62 ± 1.78	5.95 (5.19 - 7.24)	0.033
Cholesterol (mg/dL)	Women	172.72 ± 31.08	201.19 (53.20)	178.57 ± 54.28	0.013
	Men	178.94 ± 46.31	165.79 ± 39.49	159.30 ± 41.17	0.016
Triglycerides (mg/dL)	Women	145.15 (103.33 -174.53)	158.1 (127.50 - 22)	158.10 (112.40 - 196.80)	0.076
	Men	150.55 (107.58- 221)	145.55 (108.68 - 198.95)	138.30 (110.10 - 195.35)	0.313
LDL (mg/dL)	Women	111.61 ± 58.90	110.63 ± 23.92	100.97 ± 33.72	0.807
	Men	112.10 (97.57 - 132.80)	110.7 ± 36.71	118.27 ± 48.91	0.771
HDL (mg/dL)	Women	46.45 ± 15.33	47.70 ± 14.01	48.48 ± 20.09	0.968
	Men	46.56 ± 15.44	46.10 ± 12.22	48.90 ± 15.47	0.880
eGFR (mL/min/1.73 m^2)	Women	46.45 ± 15.33	26.89 (11.48 - 54.87)	18.53 (10.12 - 40.32)	0.484
	Men	32.06 (4.44 - 68.94)	18.98 (6.35 - 61.91)	20.95 (9.14 - 32.43)	0.036

* Values expressed in medians and Q_{25} - Q_{75}.
** Values expressed in means and standard deviation (SD), p-values refer to ANOVA test with Bonferroni post hoc correction.

Abbreviations: BUN: blood urea nitrogen; AU: uric acid; CrS: serum creatinine; LDL: low-density lipoproteins; HDL: high-density lipoproteins; eGFR: estimated glomerular filtration rate; AJ: young adult; AMd: mature adult; AMy: older adult.

Correlation between estimated glomerular filtration rate (eGFR) and uric acid (UA) grouped by general population and gender.

After this, to establish a possible correlation between eGFR and UA concentrations, we compared them in the general population and both genders independently (Figure 1). Then, we found that in women basal UA indices were negatively correlated with eGFR (r= -0.138, p= 0.009; r= -0.300, p <0.001, respectively), although we obtained satisfactory results in the general population and women correlation (Figure 1a,b) we did not observe significant correlation between basal UA and eGFR in men (r = -0.041, p= 0.539) (Figure 1c).

Finally, the study population was classified by stage according to eGFR (mL/min/1.73 m^2) and related to baseline UA mg/dL for each gender, respectively. As a result, Figure 2 represents the box plots showing the distribution of uric acid between the stages of severity or progression of chronic kidney disease. In this sense is observed for the group of women (Figure 2a) it showed a statistical significance between the advanced stages in relation to stage 1 (p = 0.022) in the case of men (Figure 2b) there was no statistical significance between advanced stages in relation to stage 1 (p = 0.022), subsequently analyzing between the severity stages in women in stages 4 and 5 who had significantly higher UA (p = 0.005, p = 0.004 respectively) compared to stages 1, 2, 3a and 3b that did not show significance. In men, we could not observe significant changes with UA between severity stages in men. In addition, the box plot in Figure 2 represents the constant increase in UA between subjects with decreased eGFR.

Figure 2. Mean distribution between estimated glomerular filtration rate (eGFR) in uric acid (UA) stages grouped by gender. Box plot showing mean distribution between estimated glomerular filtration rate (eGFR) in stages and uric acid (UA) by gender. p value= for stage 1, *p value= between groups by Kruskal Wallis nonparametric test.

Figure 1

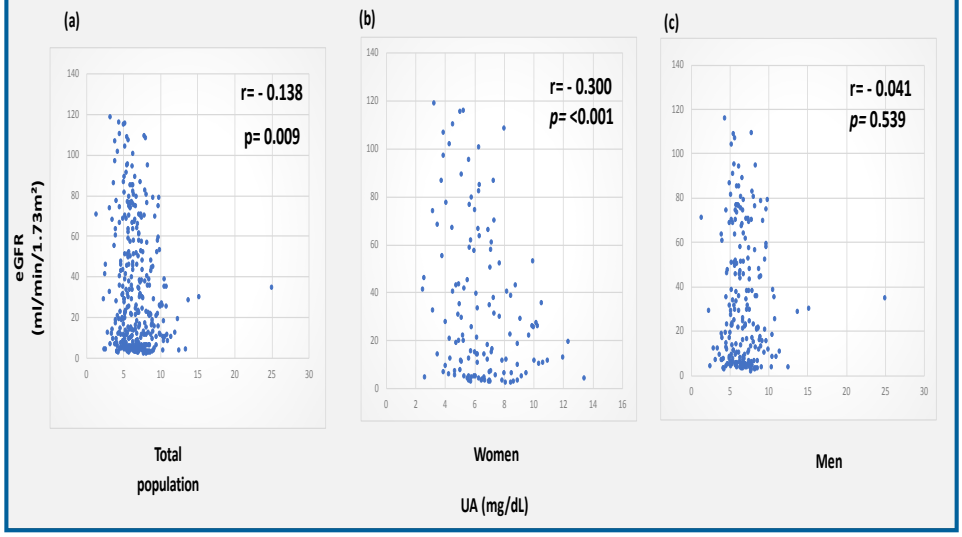
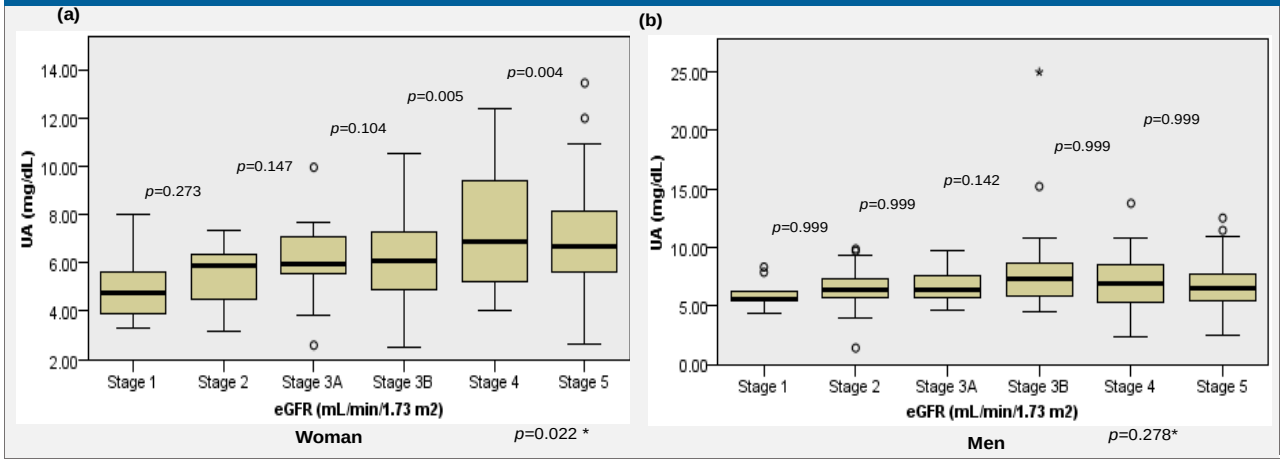


Figure 2



This study found evidence of a higher prevalence of men than women diagnosed with CKD (63% and 37%, respectively) aged over 54 years. In addition, these patients had a high prevalence of diabetes mellitus (36%), hypertension (27%), and diabetic nephropathy (10%). Consequently, renal disease in patients with diabetes may result from microvascular complications of diabetes, concomitant renal disease of another origin, or a combination of both. In patients with type 1 diabetes, it generally affects young and middle-aged patients. In the same way, chronic kidney disease is often caused by microvascular disease, a condition that has been termed diabetic nephropathy[16], while a spectrum of etiologies can cause kidney disease in patients with type 2 diabetes[16]. Additionally, Cordoba et al. (2008) mentioned that, although the risk factors for CKD include age over 60 years, cardiovascular disease, the main initiating factors contributing equally to its progression are diabetes mellitus and arterial hypertension[17].

Thus, during the determination of renal prognostic biomarkers, CrS (>1.0mg/dL) and urea (>50mg/dL) values outside the reference ranges were obtained. These have been widely used to indicate renal function, as they are mainly filtered by the glomerular pathway, even in decreased renal function, and are essentially reflected in eGFR[18]. Furthermore, uric acid levels showed hyperuricemia in both genders and decreased eGFR, with the female gender predominating in both nominal decreases in eGFR and disease severity. In addition, increasing evidence shows that UA is associated with reduced estimated glomerular filtration rate (eGFR) and increases the risk of early progressive loss of renal function. In both the general population and patients with diabetes and is a predictor of kidney injury, elevated UA is associated with increased risk of incident CKD and end-stage renal disease (ESRD)[19,20], compared with concentrations of other biomarkers of renal function.

Subsequently, we analyzed men and women separately in three age groups (AJ, AMd, and AMy). For this case, multivariate analysis showed hyperglycemia with increasing age. As a result, the management of hyperglycemia in patients with (CKD) presents complex challenges that trigger the generation of free radicals and oxidative stress and reduces the replication capacity in selected renal cell populations, either directly or indirectly, leading to loss of cell replication and repair capacity[21].

On the other hand, gender differences in the impact of elevated UA levels on an age-dependent decline in eGFR were present. The reason for gender differences in renal function is unclear. However, differences in the mechanisms of UA manipulation and modification of the renal response to sex hormone injury have been reported[22,23]. They are consistent with the finding that women are more susceptible than men to the uric acid-induced annual decline in eGFR[24]. Similarly, population-based studies indicate the epidemiology of CKD differing by sex, affecting 58% of women versus 42% of men, especially in CKD progression, adding to this advanced age. Reasons to be risk factors for a lower eGFR and a higher risk of CKD[8,25], considering that the relative balance of renal prognostic factors is related to this sex difference.

Likewise, when performing the bivariate correlation we obtained that, although UA and eGFR were negatively correlated with statistical significance in the total population and women ($r= -0.300$, $p <0.001$; $r= -0.138$, $p= 0.009$) (Figure 1a,b), there was no such relationship in men ($r = -0.041$, $p= 0.539$) (Figure 1b) and that it was independent of risk factors. The reason for the inconsistency is not clear, but there are some possible explanations. Firstly, the sample number was much smaller in women and, therefore, the statistical power was lower in men (132 women and 229 men, respectively). Secondly, age since in our study the population was mature and its influences on eGFR could have decreased the contribution of UA to eGFR variation. Similarly, Joo et al. in 2020 mentioned that a population of 16,232 Koreans showed that the higher the UA levels, the higher the probability of reduced renal function concerning gender ($p <0.001$ for men and women), which is supported by studies reported in the literature[26–28]. Although UA has not been confirmed to affect CKD progression, mounting evidence indicates that UA maintains a risk factor that causes or aggravates renal fibrosis in progressive CKD[29].

Finally, the increase in the mean distribution of UA between stages of severity or progression of CKD was demonstrated. In this case, recent studies mention that high uric acid level plays a direct detrimental role in CKD as elevated serum uric acid level induces oxidative stress and endothelial dysfunction, resulting in systemic and glomerular hypertension combined with elevated renal vascular resistance and reduced renal blood flow[30,31].

Without a doubt, our study has different limitations. Firstly, the sample size was relatively small, N=361. Secondly, we did not evaluate background information such as diet, smoking or alcohol consumption, etc. These limitations, as mentioned above, are a diagnostic tool for CKD, as studies with larger cohort populations would be needed to avoid biases and thus document the relationship between UA and eGFR more accurately. However, our research has several strengths since we identified high-risk groups that could benefit from timely, low-cost, and minimally invasive screening in the early stages of kidney disease and the use of representative data that will allow us to generalize our results to the Mexican population. Apart from this, it is essential to ensure the replication of the data and extrapolate them in different Mexican populations to assert the diagnosis. Last but not least, it is crucial to operating a set of actions within institutions and between health sectors to address the growing problem of chronic kidney

disease in Mexico since the measures of association between uric acid and CKD may be even more significant in other populations.

Conclusions

Our study showed significant evidence of the correlation between uric acid levels and kidney function according to gender. It also showed the decrease in GFR over the years as it was higher in patients with UA levels (>6.0 mg/dL) in adults older than 54 years. In addition, the impact of elevated UA on the decrease in eGFR is more significant in women than in men, indicating that women are more susceptible to renal dysfunction requiring better management in the follow-up and treatment of the disease to reduce the progression of renal damage and their complications.

Source of funding. This study received funding from SEIA UAEM 6247 / 2020.

Conflict of interests. There is no conflict of interest.

Acknowledgments

To Euridice L. Mejía-Argueta for helping to improve the manuscript.

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