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Original article

Evaluation of the correlation between renal tubular uric acid handling and chronic kidney disease progression

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Abstract

Introduction: Current chronic kidney disease (CKD) classification is based solely on the patient's glomerular filtration rate and albuminuria. However, it has been recently proposed that at least a tubular function marker should be incorporated into this classification. One of these proposed markers is one that evaluates urinary uric acid excretion. Additionally, it has been proposed that hyperuricemia predicts the worsening of renal function.

Objective: We decided to evaluate if there was any correlation between renal tubular uric acid handling and chronic kidney disease progression.

Keywords: Chronic kidney disease, Uric acid, Tubular function.

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Materials y method: A retrospective study was performed among adult patients with stage 4-CKD who periodically attended the nephrology ambulatory consult for at least the previous 3 years. From each patient, the current fractional excretion of uric acid (FEUA) and the urine uric acid/urine creatinine ratio (UACR) were obtained, as well as a marker of GFR preservation, which was obtained as the difference (delta value) between the patient's GFR value at the time of the study (current GFR) and their GFR three years earlier (past GFR). Finally, the correlation (Spearman test) between GFR preservation, proteinuria, FEUA, and UACR was evaluated.
Results: A total of 45 patients were included. The main findings were as follows: GFR: 21.8 ml/min/1.73 m^2 ± 20.1; CKD progression: -7.9 ± 9.1; FEUA: 10.9 % ± 4.5; and UACR: 4.4 mg/g ± 2.8. A positive moderate correlation (R: 0.4, p = 0.05) was documented between CKD progression and FEUA, UACR (R: 0.4, p = 0.05), and proteinuria (R: -0.4, p = 0.006).
Conclusion: FEUA and UACR showed a significant positive correlation with chronic kidney disease progression.

Evaluación de la correlación entre el manejo tubular renal del ácido úrico y la progresión de la enfermedad renal crónica

Resumen

Introducción: la clasificación actual de la enfermedad renal crónica (ERC) se basa únicamente en la tasa de filtración glomerular y la albuminuria del paciente. Sin embargo, recientemente se ha propuesto incorporar al menos un marcador de función tubular a esta clasificación. Uno de estos marcadores propuestos es la excreción urinaria de ácido úrico. Además, se ha sugerido que la hiperuricemia predice el empeoramiento de la función renal.
Objetivo: evaluar si existía alguna correlación entre el manejo tubular renal del ácido úrico y la progresión de la enfermedad renal crónica.
Material y método: se realizó un estudio retrospectivo en pacientes adultos con ERC en estadio 4 que acudieron periódicamente a la consulta ambulatoria de nefrología durante al menos los últimos 3 años. De cada paciente se obtuvo la excreción fraccional actual de ácido úrico (FEUA) y la relación ácido úrico en orina/creatinina en orina (UACR), así como un marcador de "preservación de la TFG", calculado como la diferencia (valor delta) entre el valor de la TFG del paciente en el momento del estudio (TFG actual) y la TFG registrada tres años antes (TFG pasada). Finalmente, se evaluó la correlación (prueba de Spearman) entre la preservación de la TFG, la proteinuria, la FEUA y la UACR.
Resultados: se estudiaron 45 pacientes. Los principales resultados fueron TFG: 21,8 ml/min/1,73 m^2 ± 20,1, progresión de la ERC: -7,9 ± 9,1, FEUA 10,9 % ± 4,5; y UACR: 4,4 mg/g ± 2,8. Se documentó una correlación positiva moderada (R = 0,4, p = 0,05) entre la progresión de la ERC y la FEUA, la UACR (R = 0,4, p = 0,05) y la proteinuria (R = -0,4, p = 0,006).
Conclusión: la FEUA y la UACR mostraron una correlación positiva significativa con la progresión de la ERC.

Palabras clave: enfermedad renal crónica, ácido úrico, función tubular.

Introduction

Chronic kidney disease (CKD) is a major public health problem in modern societies, and among all renal functions, the main one is the maintenance of a constant internal milieu by excreting waste products, an activity that depends on both glomerular and tubular function [1, 2]. However, current CKD classification is based solely on the patient's glomerular filtration rate (GFR) and urine albumin excretion level. In this sense, it has been recently proposed that CKD stratification should also take into account the patient's tubular function, for instance, by evaluating the patient's fractional excretion capability of particular substances [3]. Uric acid (UA) is the final oxidation product of purine metabolism. The kidneys excrete around 70 % of UA, while the remaining 30 % is excreted by the digestive tract [1]. UA is filtered by the glomeruli, and its final excretion depends on a balance between reabsorption and secretion, mainly at the proximal tubules, with a normal fractional excretion of 5-10 % [4]. Therefore, elevated serum uric acid levels are usually seen in patients with reduced GFR [5,6].

Bellomo et al. found that a 1 mg/dL increase in UA among healthy individuals was correlated with an odds ratio of 1.28 for reduced GFR at 5 years. However, despite the fact that hyperuricemia (HU) is commonly observed in CKD patients, whether it is simply a biomarker of impaired kidney function or plays a true pathogenic role in kidney function remains inconclusive [7]. Different mechanisms have been described through which hyperuricemia (HU) can lead to renal damage (vascular, glomerular, or tubule-interstitial), allowing the induction of metabolic alterations, oxidative stress, parenchymal precipitation, chronic inflammation, fibrosis, and apoptosis.

Even though several authors state that HU predicts renal functional worsening independently of age, gender, race, diabetes, hypertension, alcohol use, smoking, or dyslipidemia; and it has been reported that HU leads to the progression of existing nephropathy, particularly in patients without proteinuria, as well as an increase in patients' mortality, other authors have not supported these findings [3–8]. Therefore, we decided to evaluate whether there was any correlation between renal tubular uric acid handling and chronic kidney disease progression.

Materials and method

An observational, retrospective, and transversal study was performed in a group of adult patients ($\geq$18 years of age) who met the following inclusion criteria:

- Ambulatory patients with CKD-stage 4 who periodically attended nephrology consultations for at least the last 3 years.

- Availability of annual measurements of GFR (calculated using the creatinine-based CKD-EPI equation) and albumin/creatinine index (ACI) values at least once throughout the follow-up period, including the study period.

In this study, the concept of GFR preservation was defined as a yearly GFR decline <2 ml/min [6]. For this purpose, a variable called "GFR preservation" was created. This variable was calculated by obtaining the difference (delta value) between the patient's GFR three years before the study (past GFR) minus the GFR at the time of the study (current GFR):

GFR preservation = past GFR - current GFR.

Thus, GFR preservation was defined as a delta GFR ≤ 2.

In addition, urinary uric acid excretion was evaluated using two variables: fractional excretion of uric acid (FEUA) and the urine uric acid-to-creatinine ratio (UACR). These variables were obtained by applying the following equations [6, 9]:

Fractional excretion of uric acid (FEUA):

(Urine uric acid / serum uric acid) $\times$ (serum creatinine / urine creatinine) x 100

Urine uric acid-to-creatinine ratio UACR:

Urine uric acid / urine creatinine

Finally, the correlation between GFR preservation, albuminuria, proteinuria, and urinary uric acid excretion (FEUA and UACR) was evaluated. A Student's t-test, Wilcoxon test, and Spearman correlation analysis (95 % significance) were applied for data analysis. A p value <0.05 was considered statistically significant. Informed consent was obtained from all patients included in the study, and the study was approved by the local ethics committee.

Results

A total of 45 patients were selected from the database. Their mean age was 74 ± 16.5 years; 58 % were women; the mean GFR was 21.8 ± 20.1 ml/min/1.73 m^2; serum uric acid was 7.4 ± 6.1 mg/dL; proteinuria was 35.5 ± 48.1 mg/dL; the progression in filtration rate decrease over the previous 3 years -7.9 ± 9.1; FEUA was 10.9 ± 4.5 %; and UACR was 4.4 ± 2.8 mg/g. Patients' demographics, baseline characteristics, and follow-up eGFR values are summarized in table 1.

Table 1. Patients' demographics, baseline and follow-up eGFR values

Numberof patients: 45 individuals **Age: 74± 2 years Female-to-male ratio: 1.7:1.**				
Renal function parameters per year	**Basal**	**First year**	**Second year**	**Third year**
Serum creatinine (mg/dL)	2 ± 0.5	2.2 ± 0.5	2.3 ± 0.6	2.6 ± 2.5
eGFR (ml/min/1.73 m2)	31.4 ± 11.4	28.1 ± 8.5	25.1 ± 7.6	22.6 ± 7.5

Source: The authors.

In the present study, a positive moderate significant correlation (R = 0.4, p = 0.04) was documented between CKD progression (positive delta GFR) and urinary uric acid excretion: FEUA (figure 1) and UACR (figure 2), as well as with proteinuria (R = -0.4, p = 0.006). Additionally, a negative moderate significant correlation (R = 0.4, p = 0.004) was documented between UACR and proteinuria (figure 3).

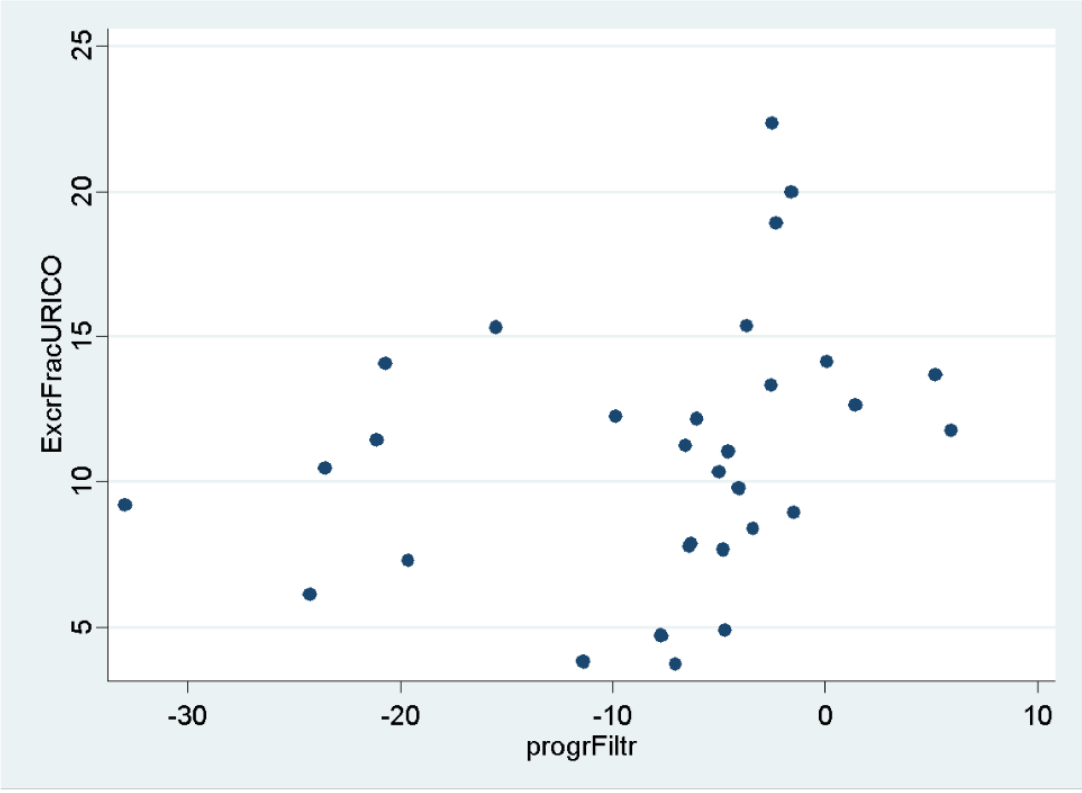

Figure 1. Correlation between fractional excretion of uric acid (FEUA) and nephropathy progression

Source: The authors.

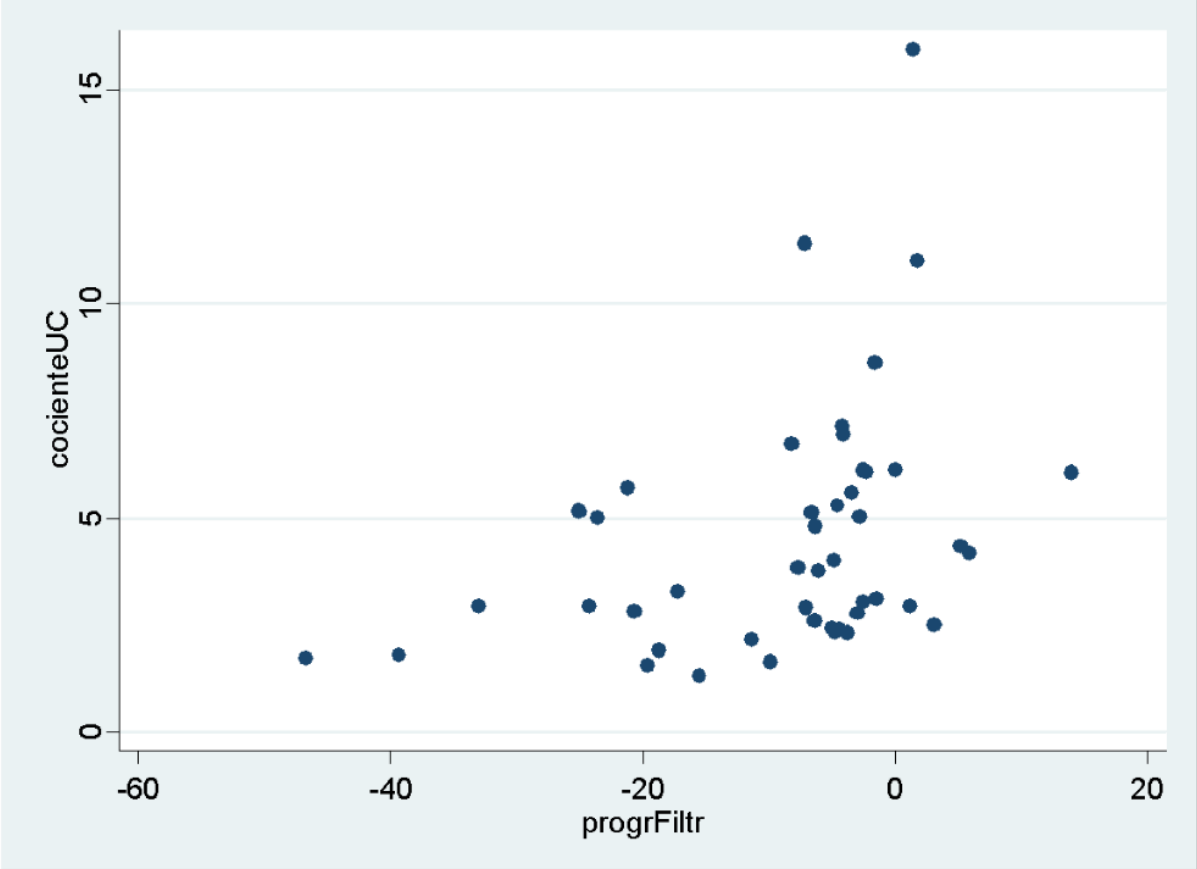

Figure 2. Correlation between the urine uric acid/creatinine ratio (UACR) and nephropathy progression

Source: The authors.

Discussion

The pathogenic role of uric acid in CKD progression is still not completely understood. In our study, which included 45 patients suffering from advanced CKD with 3 years of follow-up, it was found, as expected, elevated serum uric acid values (7.4 ± 6.1 mg/dL) with correspondingly elevated FEUA values (10.9 ± 4.5 %), according to their low GFR (21.8 ± 20.1 ml/min/1.73 m^2) [6]. Additionally, higher urinary excretion of uric acid was significantly correlated with CKD progression, although it remains to be clarified whether this correlation is due to the potential damaging effect of uric acid on the kidney or whether it reflects the importance of preserved tubular function for maintaining adequate uric acid excretion in patients with advanced GFR deterioration.

Regarding the potential role of HU (serum uric acid: ≥6.0 mg/dL) in inducing chronic renal damage, several research findings support this hypothesis [3–7]:

1. HU has been shown to induce endothelial dysfunction, arteriolopathy, hypertension, glomerulosclerosis, tubule-interstitial fibrosis, and tubular cell apoptosis in animal models of chronic nephropathy [4–6].

2. UA precipitation in the medullary interstitium induces the secretion of cytokines (IL-1β, IL-6), which recruit inflammatory cells, causing chronic inflammation and fibrosis in the kidneys [4, 6].

3. HU promotes insulin resistance and hyperinsulinemia through increasing oxidative stress by inhibiting pancreatic β-cell function [4].

Although a meta-analysis found that elevated serum UA levels were associated with incident CKD, the role of UA in CKD progression is still under debate, since many authors state that HU could be considered a CKD epiphenomenon and not its real cause [3]. In this sense, a large cohort of the Swedish Renal Registry showed that neither GFR decline nor rapid CKD progression was associated with serum UA levels in patients with CKD stages 3 through 5. This finding is consistent with those of observational studies conducted among patients with CKD in the USA, Taiwan, and Europe (Germany, Austria, South Tyrol, and the

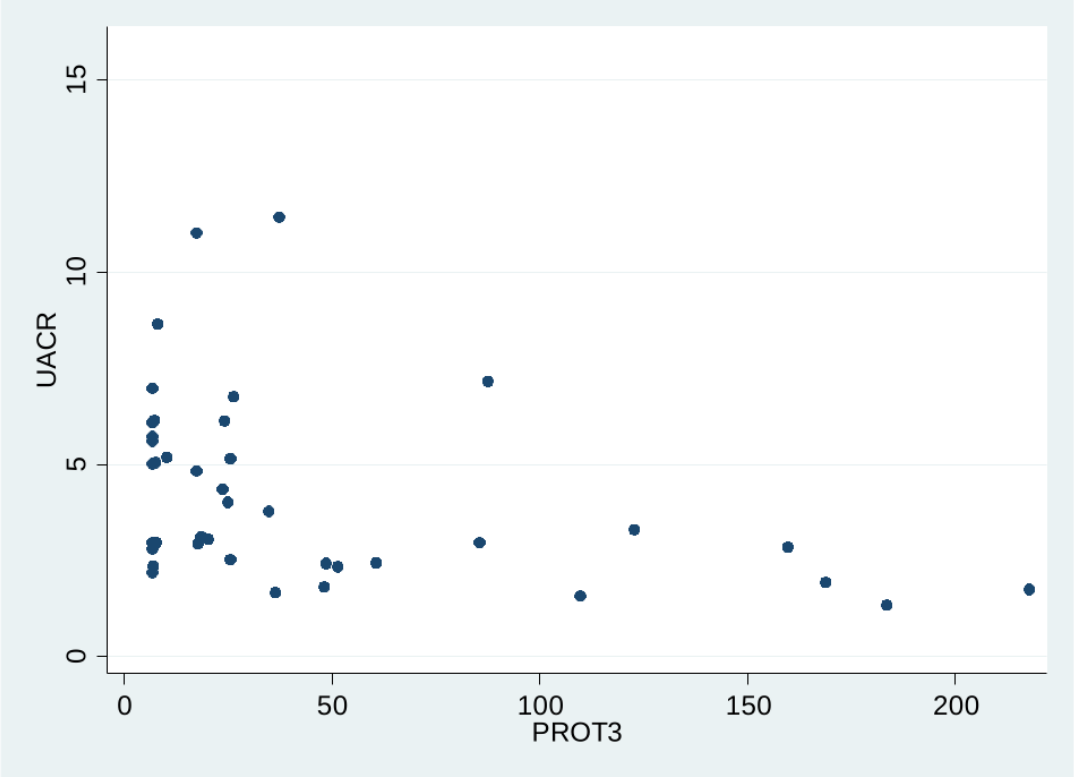

Figure 3. Correlation between the urine uric acid/creatinine ratio (UACR) and proteinuria (PROT3)

Source: The authors.

Netherlands), although large heterogeneity was found in the definitions of CKD progression and the analytical methods used among these studies [5].

Nevertheless, it has been proposed that renal damage induced by uric acid could be a consequence of increased uric acid concentration in the tubules, independently of HU. Under these circumstances, uric acid could cause [4, 5]:

- Intra-tubular obstruction with local inflammation induced by the stimulation of macrophages and lymphocytes, as well as an increase in intrarenal pressure, which leads to reduced renal perfusion and glomerular filtration.
- A pro-inflammatory and oxidative stress effect on tubular cells. The beneficial role of allopurinol in HU could be related not only to its serum UA-lowering effect but also to its antioxidant effect by acting as a free radical scavenger.

The above-mentioned mechanisms could lead to tubular damage, which contributes to a greater and faster progression of renal deterioration. It should be pointed out that, since it has been reported that AUCR >1 would be enough to induce renal injury secondary to UA, and the patients' AUCR value documented in our study was 4.3, UA may be a potential CKD progression factor in our evaluated population [4].

Additionally, proteinuria showed a significant positive correlation with GFR deterioration in our study. In this sense, other studies have documented a significant positive correlation between inflammatory markers (e.g., C-reactive protein) and serum UA levels. These studies also found that these inflammatory markers can influence the development of albuminuria and CKD progression in type 2 diabetic patients. In this regard, HU has been proposed as an inflammatory marker associated with CKD [4].

It is worth mentioning that the effect of HU on GFR decline has been reported to be greater among patients without proteinuria compared with those with proteinuria.

This phenomenon could be explained by the fact that chronic glomerulonephritis is the main cause of renal damage in these patients, in which proteinuria is the major predictor of CKD progression, thereby making the role of UA less important. In contrast, tubulointerstitial diseases, including urate nephropathy, are the predominant conditions in patients with CKD without proteinuria. In this setting, HU stands out as a strong prognostic factor for nephropathy progression [7]. In this sense, we found a significant negative correlation between UACR and proteinuria.

From our findings, it needs to be addressed whether the documented positive correlation between CKD progression and urinary uric acid excretion (documented by two markers: FEUA and UACR) is a cause (UA's damaging effect on the kidney), a consequence (tubular adaptation to filtered AU reduction), or both of renal functional deterioration. This is relevant because tubular UA excretion, which is an adaptation to reduced UA filtration secondary to CKD progression, can also lead to a potentially harmful increase in tubular work overload, thereby contributing further to disease progression [10].

Finally, another question that arises as a result of our findings is whether measuring FEUA or UACR could help us in routine clinical practice to decide on a therapeutic intervention or as a predictor of renal deterioration progression. Future studies should be performed to answer these queries.

Conclusion

In our study, fractional excretion of uric acid and urinary uric acid-creatinine ratio levels showed a significant positive correlation with chronic kidney disease progression.

Limitations

Unfortunately, this study had neither urine pH nor crystalluria data in order to be able to perform further exploration.

Authors' contributions

Carlos G. Musso: study design, article discussion, and writing; Giomar Urzola-Rodriguez: data collecting; Pablo Luis Sánchez-Garrote: data collecting; Sergio Terrasa: statistical analysis; Manuel Heras-Benito: data collecting; Sonia Velasco-Ballestero: data collecting; Leonardo Calle-García: data collecting; Gustavo Aroca-Martinez: study design and article discussion; Carmen Rita Martin-Varas: data collecting; María J. Fernández-Reyes Luis: study design, article discussion, and data collecting.

Ethical statement

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all the participants included in the study.

Conflicts of interest

The authors declare that they have no conflict of interest.

Funding statement

No funds were received for performing this study.

Use of artificial intelligence (AI)

The authors declare that they did not use artificial intelligence in the preparation or writing of this article.

Data statement

The authors declare that there are no open access data for this article. Any questions regarding this matter should be directed to the corresponding author.

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