Revista Colombiana de Nefrología
Vol. 10, Núm. 2 (2023) - Publicación continua
http://doi.org/10.22265/acnef.10.2.659

Original article

Progression of Chronic Kidney Disease in over 65-year-old Nephroprotection Program Patients in Colombia

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How to cite: Miranda-Machado P. Progression of Chronic Kidney Disease in over 65-year-old Nephroprotection Program Patients in Colombia. Rev. Colomb. Nefrol. 2023; **10**(2), **e659**. https://doi.org/10.22265/acnef.10.2.659

Abstract

Background: Studies evaluating chronic kidney disease in older adults are scarce despite the high prevalence of the disease in this age group. In this study we have tried to determine the factors associated with the progression of chronic kidney disease in a group of patients over 65 years old.

Methods: An analytical observational study of a prospective non-concurrent cohort was performed. We included patients older than 65 years belonging to a nephroprotection program and then, we followed them for 12 months. The variables of interest were age, sex, history of diabetes mellitus, serum creatinine at baseline and at 12-month follow-up, blood pressure and use of antihypertensive drugs, high density lipoprotein and low density lipoprotein, cholesterol levels, proteinuria, and use of antiplatelet agents. The estimated glomerular filtration rate (eGFR) was calculated at baseline and at 12-month follow-up, lastly the progression of chronic kidney disease was established.

Results: 200 patients were included with an average age of 78.9 + 7.6 years, 51 % (102) females, 33 % (66) with a history of diabetes mellitus, with a mean initial eGFR 38.8 + 12.1 mL/min/1.73 m^2. The mean of the final eGFR was 36.4 + 11.0 mL/min/ 1.73 m^2; 17.5 % (35) presented a decrease $>$ 25 % of the initial eGFR (progression) and 37.5 % (75) showed a decrease $>$ 5mL/min/1.73m^2/ year (rapid progression). Progression and rapid progression were significantly associated with age ($p = 0.03$ and $p = 0.001$, respectively), male sex ($p < 0.001$ and $p < 0.001$, respectively) and proteinuria ($p < 0.001$ and $p < 0.001$, respectively). There were no significant associations with other variables of interest.

Submission:
14/Sep/2022
Acceptance:
13/Mar/2022
Published:
25/May/2023

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E-ISSN: 2500-5006/L-ISSN: 2389-7708

Conclusion: In our study, the progression of chronic kidney disease in patients older than 65 years in a nephroprotection program was significantly associated with the increased age, male sex, and presence of proteinuria.

Keywords: Chronic kidney disease, progression, older adults.

Progresión de la enfermedad renal crónica en mayores de 65 años en el Programa de Nefroprotección Pacientes en Colombia

Resumen

Antecedentes: los estudios que evalúan la enfermedad renal crónica en adultos mayores son escasos, a pesar de la alta prevalencia de esta enfermedad en este grupo de edad. En este estudio hemos intentado determinar los factores asociados a la progresión de la enfermedad renal crónica en un grupo de pacientes mayores de 65 años.

Métodos: se realizó un estudio observacional analítico de una cohorte prospectiva no concurrente. Se incluyeron pacientes mayores de 65 años pertenecientes a un programa de nefroprotección y se les siguió durante 12 meses. Las variables de interés fueron edad, sexo, antecedentes de diabetes mellitus, creatinina sérica al inicio y a los 12 meses de seguimiento, presión arterial y uso de fármacos antihipertensivos, niveles de colesterol, lipoproteínas de alta densidad y lipoproteínas de baja densidad, proteinuria y uso de antiagregantes plaquetarios. La tasa de filtración glomerular estimada (TFGe) se calculó tanto al inicio como a los 12 meses de seguimiento y se estableció la progresión de la enfermedad renal crónica.

Resultados: se incluyeron 200 pacientes con una edad promedio de 78,9 + 7,6 años, 51 % (102) mujeres, 33 % (66) con antecedentes de diabetes mellitus, con TFGe inicial promedio 38,8 + 12,1 mL/min/1,73 m^2. La media del TFGe final fue de 36,4 + 11,0 mL/min/ 1,73 m^2; El 17,5 % (35) presentó una disminución $>$ 25 % del TFGe inicial (progresión) y el 37,5 % (75) presentó una disminución $>$ 5mL/min/1,73m^2/año (progresión rápida). La progresión y la progresión rápida se asociaron significativamente con la edad ($p = 0,03$ y $p = 0,001$, respectivamente), el sexo masculino ($p < 0,001$ y $p < 0,001$, respectivamente) y la proteinuria ($p < 0,001$ y $p < 0,001$, respectivamente). No hubo asociaciones significativas con otras variables de interés.

Conclusión: en nuestro estudio, la progresión de la enfermedad renal crónica en pacientes mayores de 65 años en programa de nefroprotección se asoció significativamente con el aumento de la edad, el sexo masculino y la presencia de proteinuria.

Palabras clave: enfermedad renal crónica, progresión, adultos mayores.

Introduction

The natural history or clinical course of chronic kidney disease (CKD) is characterized by a progressive decrease in glomerular filtration rate (GFR) decreases over time towards more advanced stages of kidney failure [1]. The speed of progression towards kidney

failure is variable. Possible factors associated with progression have been identified as the etiology of kidney failure, proteinuria, metabolic control of diabetes, hypertension, smoking, dyslipidemia, calcium, phosphorus, uric acid, and use of nephrotoxics, among others [2]

Some of these factors are associated with rapid progression such as diabetic nephropathy, chronic glomerulonephritis and polycystic kidney disease of the adult. Hypertensive vascular disease and tubulointerstitial nephropathies are associated with slow progression [1, 2]. Proteinuria, in addition to being a marker of kidney damage, is a factor associated with rapid progression and is a cardiovascular risk factor [3, 4]. The evidence for the effect of the correction of these factors to reduce the speed of progression or the correction of CKD is contradictory, although its benefit on cardiovascular risk has been demonstrated at other levels [1, 2]. The objective of the present prospective study was to determine the factors associated with the progression of CKD in a population of adults over 65 years of age.

Methods

Study population

We included 200 patients older than 65 years belonging to a nephroprotection program in a primary health care institution in Colombia and were followed for 12 months. The criteria for admission to the nephroprotection program include patients with a confirmed diagnosis of chronic kidney disease according to international definitions, mainly captured from the follow-up of patients with diagnoses of high blood pressure and confirmed diabetes mellitus, where clinical parameters and progression are monitored. of pathologies of specific underlying risk.

History of Chronic Kidney Disease

Data on history of chronic kidney disease (CKD) was collected by study investigators at including patients with ICD-10 diagnosis of CKD, or with a personal history of CKD; or with eGFR measured using the Cockcroft - Gault formula of $<$60 mL/min/1.73 m^2 ([(140 - age (years)) $\times$ actual body weight (kg) $\times$ (0.85 if female)] / [72 $\times$ Creatinine (mg/dl)]; or patients in follow-up at nephrology clinics. Patients with CKD in renal replacement therapy, including kidney transplant history were excluded.

Definitions of CKD and stages of the disease

We defined as CKD case the presence of structural abnormalities (markers of renal damage: albuminuria, urinary sediment abnormalities, hydroelectrolytic disorders and other

anomalies secondary to tubulointerstitial disorders, abnormalities detected by histology or radiological studies, and functional decrease in eGRF <60 ml/min/1.73 m^2) present for more than three months, with health implications [5]. CKD was classified based on the cause, category according to eGFR, and level of proteinuria/albuminuria.

The variables of interest were recorded (age, sex, history of diabetes mellitus, serum creatinine at baseline and at 12-month follow-up, high blood pressure (>140/90 mmHg), altered high density lipoprotein (HDL) and low density lipoprotein (LDL), cholesterol levels, proteinuria/albuminuria, use of antihypertensive drugs, use of antidiabetics, allopurinol, proton pump inhibitors, antiplatelet agents, and folic acid). The eGFR was measured at baseline and at 12-month follow-up and the progression of CKD were established. A decrease of > 25 % of the initial GFR was defined as a global progression of CKD. Rapid progression of the CKD was defined as the decrease > 5mL/min/1.73m^2/year of the initial GFR [5].

Statistical analysis

Descriptive analysis was performed using proportions (%) or means with standard deviations. We used Pearson Chi-square and Student's t-test for the comparisons between variables. To establish the association between the variables of interest and global or rapid progression of CKD, a Multivariate Logistic Regression model was used. All statistical analyses were conducted using the Stata version 14.2 software (StataCorp, College Station, TX) and R version 3.4.3 (R Core Team, R Foundation for Statistical Computing), p value <0.05 was considered statistically significant for all tests.

Results

Baseline characteristics

200 patients were included with an average age of 78.9 + 0.5 years, 51 % (102) of females, 33.5 % (66) with a history of diabetes mellitus, with a mean initial eGFR 38.8 + 12.1 mL/min/1.73 m^2. The mean of the final GFR was 36.4 + 11.0 mL/min/1.73 m^2. Baseline characteristics are shown in Table 1. The changes in the CKD stage are shown in Table 2.

Progression of CKD

17.5 % (35) presented a decrease > 25 % of the initial GFR (global progression) and 37.5 % (75) showed a decrease > 5ml/min/1.73m^2/year (rapid progression).

Table 1. Baseline characteristics in people older than 65 years

Baseline Characteristics	n	%
Age (years) mean + SD	78,5	0,5
Sex (female)	102	51
Comorbidities		
Hypertension	198	99
Diabetes	67	33,5
Overweight	64	32
Obesity	23	11,5
Creatinine (mg/dl) mean + SD	1,64	0,05
Glycated Hemoglobin (%) mean + SD	6,5	0,05
ACE-I	12	6
ARA-II	167	83,5
Calcium channel blockers	125	63,7
Platelet anti-aggregants	67	33,5
Allopurinol	30	15
Proton pump inhibitors	98	49
Folic acid	144	72
Metformin	45	22,5
Analogues Insulin	17	8,5
DPP-4 inhibitors	14	7
SGLT-2 inhibitors	9	4,5
GLP-1 agonist	2	1

SD = standard deviation; ACE-I = angiotensin-converting enzyme inhibitors; ARA-II = angiotensin receptor antagonists-II; DPP-4 inhibitors = Dipeptidyl Peptidase Iv inhibitor; SGLT-2 inhibitor = sodium-glucose cotransporter-2 inhibitor; GLP-1 agonist = glucagon-like peptide-1 receptor agonist.

Table 2. Change of CKD stage in subjects older than 65 years

Initial GFR*	Final GFR*			
	>60 (%)	**30-59 (%)**	**<30 (%)**	**Total (%)**
>60 (n)	2 (33.3)	4 (66.6)	0 (0)	6 (3)
30-59 (n)	5 (3.18)	128 (81.5)	24 (15.2)	157 (78.5)
<30 (n)	0 (0)	10 (27.0)	27 (72.9)	37 (18.5)
Total (n)	7 (3.5)	142 (71.0)	51 (25.5)	200 (100)

*Cockcroft - Gault (ml/min/1.73m^2) n = number % = percentage

Factors associated with the progression of CKD

Global progression (Table 3) was significantly associated with age (p = 0.004) and male sex (p <0.001). There were no significant associations with other variables of interest.

Table 3. Factors associated with global progression of CKD in subjects older than 65 years

CKD Progression	Crude Analysis OR (95 % CI)*	Adjusted Analysis OR (95 % CI)*
Age (years)	**1.09 (0.99-1.09)**	**1.10 (1.03-1.18)**
Male (%)	**5.42 (2.24-13.13)**	**7.47 (2.48-22.51)**
Diabetes Mellitus (%)	0.63 (0.28-1.45)	0.59 (0.20-1.73)
Systolic Blood Pressure (mmHg)	1.36 (0.46-3.95)	2.55 (0.62-10.45)
Diastolic blood pressure (mmHg)	0.98 (0.95-1.02)	0.95 (0.90-1.01)
Initial Creatinine (mg/dl)	1.01 (0.95-1.08)	1.03 (0.93-1.14)
Proteinuria (mg/g)	1.48 (0.96-2.26)	1.46 (0.80-2.68)
HDL cholesterol (mg/dl)	1.12 (0.39-3.16)	1.48 (0.29-7.51)
LDL cholesterol (mg/dl)	1.00 (0.97-1.04)	1.00 (0.96-1.05)
ACE-I (%)	0.99 (0.98-1.00)	0.99 (0.97-1.00)
ARA-II (%)	0.41 (0.05-3.29)	0.24 (0.01-4.37)
Platelet anti-aggregants (%)	0.94 (0.35-2.49)	0.91 (0.20-4.09)
Calcium channel blockers (%)	2.17 (1.03-4.55)	1.90 (0.68-5.26)
Allopurinol (%)	0.87 (0.41-1.85)	1.14 (0.40-3.22)
Proton pump inhibitors (%)	1.77 (0.81-3.85)	1.00 (0.28-3.52)
Folic acid (%)	0.85 (0.41-1.77)	1.20 (0.45-3.17)

*Multivariate Logistic Regression OR = odds ratio; 95 % CI = confidence interval 95 %; % = percentage; mmHg = millimeters of mercury; mg/dL = milligrams / deciliters; ACE-I = angiotensin-converting enzyme inhibitors; ARA-II = angiotensin receptor antagonists-II

Rapid progression (Table 4) was significantly associated with age (p = 0.003), male sex (p <0.00), proteinuria (p = 0.03) and angiotensin receptor antagonist-II (ARA-II) (p = 0.03). There were no significant associations with other variables of interest.

Discussion

The factors associated with progression of CKD may be classified as modifiable and not modifiable [1,2]. Among the non-modifiable factors, we have the initial kidney function, race, sex, age, birth weight and specific genetic factors. Advanced kidney failure at the time of diagnosis of CKD is a factor of poor prognosis [6]. A faster CKD progression has been observed in the black race associated with socioeconomic, dietary and environmental factors [7].

In men, prognosis seems to be worse compared to women, and in the elderly there is a greater frequency of structural abnormalities that increases with the years [8].

In our study, the progression of CKD was significantly associated with the increase in age and male gender.

Table 4. Factors associated with rapid progression of CKD in subjects older than 65 years

CKD Rapid progression	Crude Analysis OR (95 % CI) *	Adjusted Analysis OR (95 % CI) *
Age (years)	1.03 (0.99-1.07)	1.09 (1.03-1.15)
Male (%)	4.28 (2.31-7.93)	6.40 (2.71-15.11)
Diabetes Mellitus (%)	1.12 (0.61-2.06)	1.35 (0.60-3.02)
Obesity (%)	0.99 (1.97-1.02)	1.27 (0.37-4.36)
Systolic Blood Pressure (mmHg)	1.00 (0.95-1.05)	0.99 (0.95-1.03)
Diastolic blood pressure (mmHg)	1.59 (1.03-2.44)	0.97 (0.89-1.04)
Initial Creatinine (mg/dl)	2.10 (2.05-3.20)	1.06 (0.63-1.78)
Proteinuria (mg/g)	1.01(0.98-1.04)	4.61 (1.16-18.28)
HDL cholesterol (mg/dl)	0.99 (0.98-0.99)	1.00 (0.96-1.04)
LDL cholesterol (mg/dl)	1.72 (0.53-5.55)	0.99 (0.98-1.00)
ACE-I (%)	0.43 (0.20-0.91)	0.60 (0.08-4.19)
ARA-II (%)	1.58 (0.86-2.89)	0.26 (0.07-0.90)
Platelet anti-aggregants (%)	0.89 (0.49-1.62)	1.76 (0.77-4.02)
Calcium channel blockers (%)	1.00 (0.98-1.05)	1.47 (0.64-3.37)
Allopurinol (%)	0.95 (0.42-2.14)	1.15 (0.41-3.20)
Proton pump inhibitors (%)	1.15 (0.90-1.20)	1.34 (0.63-2.86)
Folic acid (%)	1.03 (0.99-1.07)	2.22 (0.89-5.53)

*Multivariate Logistic Regression OR = odds ratio; 95 % CI = confidence interval 95 %; % = percentage; mmHg = millimeters of mercury; mg/dL= milligrams / deciliters; ACE-I = angiotensin-converting enzyme inhibitors; ARA-II = angiotensin receptor antagonists-II.

Among the modifiable factors are proteinuria, high blood pressure, poor glycemic control in diabetes, dyslipidemia, uric acid, use of nephrotoxic-medication, among others [1, 2]. Proteinuria is an independent risk factor most important in the progression of CKD [7, 9, 10]. ACE-I and ARA-II are recommended in the guidelines for the management of arterial hypertension, due to their effectiveness in the control of proteinuria [11, 12]. In our study, the rapid progression of CKD was significantly associated with the presence of proteinuria and the blocking drugs of the renin angiotensin aldosterone system.

Although the evidence is contradictory, long-term treatment with allopurinol may slow the rate of progression of kidney disease [13, 14]. The association between the use of proton pump inhibitors and the deterioration of CKD has been reported in clinical trials and observational studies [15, 16]. The reports of the association between the use of folic acid and decrease in the progression of CKD are also contradictory [17, 18]. In our study, no significant association was found between the progression of CKD and the use of allopurinol, proton pump inhibitors and folic acid.

The absence of data on the specific race, the use of other specific nephrotoxic drugs and the short duration of follow-up are the main limitations of our study.

In conclusion, the progression of CKD in those older than 65 years in a nephroprotection program in Colombia was significantly associated with the increase in age, male sex, and presence of proteinuria.

Availability of data and material

The data that supports the findings of this study are from a private health insurance company in Colombia; this information could be obtained by making a formal request and it may have sharing restrictions.

Ethical implications

The data collection of this research was approved by the ethics committee of a Private Health Insurance Company in Colombia and was carried out in accordance with Resolution No. 8430 of 1993 by the Ministry of Health and Social Protection of Colombia. This study was classified as a No Risk investigation, according to the categories established in the resolution, and the ethics committees dispensed to the authors of the written consent of the informed consent of the participants.

Funding

The author received no funding for the writing or publication of this article.

Conflict interests

The author declares no conflict of interests for this study.

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