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Factors affecting the progression of chronic kidney disease

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ABSTRACT

Aims: Chronic kidney disease (CKD) is characterized by irreversible and progressive loss of renal function. One of the most important goals in CKD management is to delay CKD progression. The aim of this study was to investigate the outcomes of non-dialysing CKD patients, rate of progression of disease and factors associated with CKD progression and mortality.

Methods: In this retrospective study, 245 non-dialysis CKD (stage 3-5) patients who presented to nephrology outpatient clinic between December 2013 and June 2015 were included. Patients' baseline demographic, clinical/laboratory data were obtained. Outcomes of the patients in terms of CKD progression (defined as the initiation of renal replacement therapy or death) between November 2022 and December 2022 were recorded.

Results: Patients' mean age (baseline) was 56±12 years; 116 patients (47.3%) were female. During median 46 months of follow-up period, 42.9% of the patients underwent renal replacement therapy and all-cause mortality rate was 9.8%. Baseline eGFR, proteinuria and having diabetes mellitus as a comorbidity were found to be associated with CKD progression, independently (the risk increases by 75% with each 1 ml/min decrease in eGFR, p<0.001; the risk increases approximately 1.8 times with each 1 gr/day increase in proteinuria, p=0.003; the risk increases approximately 3 times with diabetes mellitus, p=0.043).

Conclusion: Our findings showed that baseline eGFR level, having diabetes mellitus and baseline proteinuria values were independent risk factors associated with disease progression and mortality in non-dialysing CKD patients. Early diagnosis and close monitoring of CKD, applying interventions targeting risk factors associated with CKD progression should be considered to delay CKD progression.

Keywords: Chronic kidney disease, progression, renal replacement therapy, risk factors

INTRODUCTION

Chronic kidney disease (CKD) has a prevalence of 11-13% and in its course, there is irreversible and progressive loss of kidney function with increased morbidity, hospitalization, cardiovascular events and mortality.[1] CKD progresses gradually from stage 1, where the estimated glomerular filtration rate (eGFR) is within the normal range, to stage 5, where renal replacement therapy is required. Prevalence and progression of CKD vary between countries and also within countries by social determinants and ethnicity, possibly via epigenetic mechanisms.[2] CKD progression expresses cumulative loss of renal function over time (eventually leading to renal replacement therapy requirement).

The factors such as fibrosis, chronic inflammation, parenchymal cell loss, decreased regenerative capacity of kidney can contribute to progression of CKD.[3] Not all of the CKD patients progress to kidney failure; and prognosis of CKD and timing of adverse outcomes may vary between patients.[4] One of the most important goals in CKD management is to delay CKD progression and to reduce number of patients undergoing renal replacement therapy, by early diagnosis and close monitoring of CKD, by applying nephroprotective therapies and interventions targeting CKD progression and by modifying related risk factors. To delay CKD progression, effectiveness of current therapies are limited.[3] Interventions for specific symptoms, lifestyle recommendations or education considerations have beneficial effects.[2] Medical and non-medical interventions targeting glycol-metabolic control, hypertension, proteinuria and dyslipidemia can be useful. Previous studies showed that lowering sistolic blood pressure (≤130 mmHg) reduces cardiovascular risks and progression of CKD, but ideal sistolic blood pressure level in CKD patients has not yet been determined.[5] In a study, body mass index (BMI) in overweight range was found to be related with reduced risk for all-cause mortality and CKD progression.[6]

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There are limited number of study about long-term outcomes non-diaysing CKD patients and risk factors associated with CKD progression. In this study, we aimed to investigate the outcomes of CKD patients not requiring dialysis and independent risk factors affecting the CKD progression and mortality.

METHODS

All procedures performed in this study were in accordance with the ethical rules and with the principles of Helsinki Declaration and ethics committee permission was obtained from KTO Karatay University Faculty of Medicine Non-medicine and Non-medical Device Researches Ethics Committee (Date: 29.12.2022, Decision No: 2022/010). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

In this study with retrospective design, CKD patients (stage 3-5, aged ≥18 years) presented to the nephrology outpatient clinic between December 2013-June 2015 were included. The patients with cardiovascular disease, malignancy or with rapidly progressive glomerulonephritis or undergoing renal replacement therapy were excluded. The patients with missing baseline data were also excluded. Patients' demographic, clinical/laboratory parameters such as age, gender, comorbidities, smoking status, baseline BMI, sistolic and diastolic blood pressure values and initial laboratory parameters (hemoglobin, serum urea, creatinine, glucose, electrolites, calcium, magnesium, phosphorus, albumin, uric acid, C-reactive protein, lipids, parathormone, ferritin, eGFR, amount of proteinuria, venous blood gas) were all obtained from the patients' files. For eGFR calculation, Modification of Diet in Renal Disease Formula was used[7] and the CKD stage was classified as stage 3 (eGFR, 30–59 ml/min/1.73 m^2), stage 4 (eGFR, 15–29 ml/min/1.73 m^2) and stage 5 (eGFR, <15 ml/min/1.73 m^2).[8] For outcomes of the patients participated in this study, the patients' status between November 2022 and December 2022 were detected from the medical records of the hospital and the combined endpoint was defined as initiation of renal replacement therapy (dialysis or transplant) or death (whichever occurred first).

Statistical Analysis

For statistical analysis, SPSS 22.0 (IBM) software was used. To determine normally or non- normally distributed data Kolmogorov-Smirnov test was used. The results were shown as mean±SD (for variables distributed normally) and median (minimum-maximum) (for variables distributed non-normally). To compare variables, the T-test (for normal distributions) and the Mann Whitney-U test (for non-normal distributions) were used. The independent factors for primary outcomes were determined by performing Cox-regression analysis. A p value < 0.05 was considered statistically significant.

RESULTS

Data of 245 CKD patients were evaluated in this study: 116 (47.3%) were female and 129 (52.7%) were male; mean age (at baseline) was 56±12 years. CKD etiologies were diabetes mellitus (68 patients, 27.8%), hypertension (43 patients, 17.6%), glomerulonephritis (35 patients, 14.3%), polycystic kidney disease (31 patients,12.7%), urological causes (16 patients, 6.5%), amyloidosis (4 patients, 1.6%), unknown underlying etiologies (48 patients, 19.6%). Only 28 patient (11.4%) had smoking history. The median follow-up time was 46 months. During this period, regarding clinical outcome of the 245 patients, 64 (26.1%) had still non-dialysing CKD and were continiuing follow-up visits in nephrology outpatient clinic; 105 (42.9%) had required renal replacement therapy (85 patients (34.7%) were on dialysis and 20 patients (8.2%) underwent kidney transplantation); 24 patients (9.8%) died; and 52 (21.2%) patients were lost to follow-up (**Table 1**). In univariate correlation analysis, follow-up time (p<0.001), having diabetes mellitus as a comorbidity (p<0.001), baseline eGFR (p<0.001), calcium (p<0.001), phosphorus (p<0.001), albümin (p<0.001), potassium (p=0.025), hemoglobin (p<0.001), parathormone levels (p<0.001) and amount of proteinuria (p<0.001), baseline sistolic and diastolic blood pressure measurements (p<0.001 and p=0.002, respectively) were found to be related with CKD progression to end stage renal failure and all-cause mortality (**Table 1**). To determine the independant variables, Cox-regression analysis with the parameters found to be significant in univariate analysis were performed; and baseline eGFR (the risk increases by 75% with each 1 ml/min decrease in eGFR, p<0.001), baseline proteinuria (the risk increases approximately 1.8 times with each 1 gr/day increase in proteinuria, p=0.003) having diabetes mellitus as a comorbidity (the risk increases approximately 3 times with diabetes mellitus, p=0.043) were found to be associated with CKD progression, independently (**Table 2**).

DISCUSSION

CKD is the common and progressive result of various disease processes with different etiologies/pathogenesis rather than being one disease. The goal of nephrologists is to prevent or delay the progression of CKD as much as possible; and for this, knowing the risk factors affecting the progression of CKD is important. In our

study, the outcomes of non-diaysing CKD patients and the risk factors associated with CKD progression were investigated. During median 46 months of follow-up period, 42.9% of our patients underwent renal replacement therapy and all-cause mortality rate was 9.8%. In a previous study, of the 382 patients with non-dialysing CKD (stage 3-5), 190 patients progressed to renal replacement therapy requirement (dialysis or kidney transplant), (12.1%/year; mean follow-up, 4.1 years) and 150 died (6.5%/year; mean follow-up, 6.0 years).[9] In the study of Zhang et al.[10] rate of CKD progression (defined as initiation of dialysis) was 26.2% among 309 patients with CKD stage 3-4 (median follow-up time, 25.6 months). In another study from Sweden, included 26279 patients with CKD stage 3b-5, rate of CKD progression event (defined as initiation of renal replacement therapy or at least one CKD stage transition) was 19.6 patients /100 person-years; and 10.1 patients/100 person-years died.[11] These different CKD progression rates and mortality rates between studies may be attributed to the differences in sample size, CKD stage of study group, definition of CKD progression or follow-up time. In addition CKD progression time may vary between countries and even patient by patient.[4]

In our study, having diabetes mellitus as a comorbidity, baseline proteinuria and baseline eGFR values were found to be associated with CKD progression; the risk of CKD progression and mortality increased by 75% with each 1 ml/min decline in eGFR. In a previous study, each 30% decline in baseline eGFR was associated with 3-fold higher end stage renal failure rate and 1.3-fold higher death rate.[9] Similarly, previous other studies concluded that more baseline kidney impairment (CKD stage) is related with CKD progression and clinical events.[10,12,13] So, for the patients with more advanced stages of non-dialysing CKD, to develop strategies targeting improving dialysis provision and capacity of transplant services could be beneficial.[13] Regarding baseline proteinuria and having diabetes as a comorbidity, in our study, the risk of CKD progression increased approximately 1.8 times with each 1 gr/day increase in proteinuria; and it is increased 3 times in patients with diabetes mellitus. In concordance with our study, in the study of Zhang et al.[10] increased proteinuria associated with increased the risk for progression to initiation of dialysis by 2.592 fold and the patients with diabetes mellitus had 2.759 fold increase in CKD progression to renal replacement therapy compared to the patients without diabetes. In

Table 1. Baseline characteristics of the patients and univariate correlation analysis of chronic kidney disease progression with variables

Baseline characteristics	Overall* (n=245)	Non-dialysis during follow-up (n=64)	Underwent RRT or died during follow-up (n=129)	p
Age, year, mean±SD	56±12	54.4±11.4	56.7±12.4	0.220
Gender, female, n (%)	116 (47.3)	32 (50)	60 (46.5)	0.760
Presence of diabetes, n (%)	68 (27.8)	8 (12.5)	47 (36.4)	<0.001
Smoking history, n (%)	28 (11.4)	8 (12.5)	16 (12.4)	0.576
BMI, kg/m²	30.3±6.3	30.6±5.5	30.0±6.8	0.573
eGFR, ml/min/1.73 m²	30.1±13.1	56.0±13.5	33.4±14.8	<0.001
Serum creatinine, mg/dL	2.53 (1.14-6.35)	1.820.53	3.03±1.12	<0.001
Serum uric acid, mg/dl	7.1±1.7	6.95±1.79	7.17±1.67	0.402
Potassium (mmol/l)	4.7±0.5	4.67±0.55	4.86±0.55	0.025
Calcium, mg/dl	9.0±0.7	9.33±0.51	8.78±0.77	<0.001
Phosophorus, mg/dl	3.6±0.9	3.23±0.61	3.87±1.16	<0.001
Serum albumin , g/dl	3.9±0.4	4.11±0.29	3.81±0.49	<0.001
Systolic BP, mmHg	138±20	130.8±14.4	142.3±21.5	<0.001
Diastolic BP, mmHg	88±11	87.0 (47-115)	92 (52-141)	0.002
Hemoglobin, g/dl	12.8±1.9	13.7±2.1	12.3±1.8	<0.001
LDL- cholesterol, mg/dl	133 ±40	134.1±39.0	133.8±43.3	0.964
Triglyserides, mg/dl	186 (40-1191)	184±105	181±108	0.817
Bicarbonate (HCO_3^-), mmol/l	21.3±3.1	21.23±2.85	21.06±3.47	0.808
Parathormon, ng/l	82.85 (23-799)	82.85 (23-799)	172.8 (21-785)	<0.001
C-reactive protein, mg/l	3.44 (3-78)	3.44 (3-78)	3.7 (3-201)	0.077
Proteinuria (g/day)	2.16 (0.05-13.90)	0.87 (0.05-4.46)	3.17 (0.06-13.90)	<0.001
Follow-up time, month, median (range)	46 (2-108)	84 (62-91)	24 (2-84)	<0.001

*, 52 patients were lost to follow-up; RRT, renal replacement therapy; SD, standart deviation; BMI, bady mass index; eGFR, estimated glomerular filtration rate; BP, blood pressure; LDL-cholesterol, low-density lipoprotein cholesterol.

Table 2. Cox-regression analysis to determine independent variables

Variables	Step 1 Cox-Snell R2=0.321			Step 2 Cox-Snell R2=0.384			Step 3 Cox-Snell R2=0.399		
	p	Exp(β)	%95 CI	p	EExp(β)	%95 CI	p	Exp(β)	%95 CI
Baseline eGFR	<0.001	0.910	0.885-0.936	<0.001	0.926	0.899-0.954	<0.001	0.925	0.897-0.953
Baseline proteinuria				0.001	1.853	1.269-2.706	0.003	1.798	1.223-2643
Presence of diabetes							0.043	3.103	1.034-9314

eGFR, estimated glomerular filtration rate

another study, fast progression occurred in 23.0% of CKD patients with diabetes mellitus vs. 15.3% of CKD patients without diabetes during 24-month follow-up; and proteinuria was among the multivariable predictors of CKD progression.[14]

In our study, the factors including, baseline phosphorus, albümin, hemoglobin levels, baseline sistolic and diastolic blood pressure measurements were associated with CKD progression in univariate correlation analysis, but in multivariate analysis these factors could not retain their significance. Unlike our study, in some previous studies, the risk factors such as age,[13] male gender,[11] current smoker,[13] hypoalbuminemia,[10,13] increased low-density lipoprotein levels,[10] elevated blood pressure,[10,14] anemia,[13,14] higher serum phosphorus levels[13] were found to be associated with CKD progression. These different finding between studies can be atributed to the differences in study design, sample size or CKD stages of study group.

There are some limitations of this study: First, it is a retrospective study including patients from a single center; second we did not include data on the drugs used by the patients.

CONCLUSION

Our findings in this study showed that baseline eGFR level, having diabetes mellitus and baseline proteinuria values were independent risk factors affecting CKD progression and mortality in non-dialysing CKD patients. Early diagnosis and close monitoring of CKD, applying nephroprotective therapies and interventions targeting risk factors associated with CKD progression should be considered to delay CKD progression and to reduce number of patients requiring renal replacement therapy.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethics Committee permission was obtained from KTO Karatay University Faculty of Medicine Non-medicine and Non-medical Device Researches Ethics Committee (Date: 29.12.2022, Decision No: 2022/010).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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