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Original Article

Natural History of Chronic Kidney Disease Stages 2-4

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Abstract

Introduction: Chronic kidney disease (CKD) is a worldwide problem. The majority of patients in stage 3-5 CKD progress relentlessly to end stage renal disease (ESRD). This study aimed to measure the rate of decline in kidney function among a group of CKD patients and to examine risk factors associated with disease progression.

Methods: This is a retrospective study of 300 CKD patients in stages 2-4, that were randomly selected from patients who were on regular follow up in Sheffield Kidney Institute (SKI), Sheffield, UK, up to June 2007. Patients whose estimated glomerular filtration rate (GFR) declined by more than 1 ml/min/year according to the MDRD formula during a 5-year follow up period were classified as progressors. Baseline parameters that may be associated with a more rapid decline in GFR were evaluated.

Results: Males constituted 57.7% of the study population, one third of patients were older than 65 years of age, 93% were white and 39.7% were diabetic. The study showed that 52.7% of patients had a progressive course of CKD. Gender, old age, ethnicity and diabetic status were not significantly different between progressors and non-progressors. Progressors tended to have higher 24-hour urinary protein excretion (2.6 ± 3.6 versus 1.8 ± 3.5 g/day) and higher blood pressure measurements at baseline that did not reach statistical significance. The slope of reciprocal serum creatinine (1/S. Cr) was significantly and negatively correlated with systolic blood pressure (SBP). It was also significantly and negatively correlated to baseline serum creatinine.

Conclusion: Almost half the patients had a rate of decline in estimated GFR that exceeded 1 ml/min/year and were classified as progressors.

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Keywords: CKD progression; ESRD; progressors; non-progressors.

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Introduction

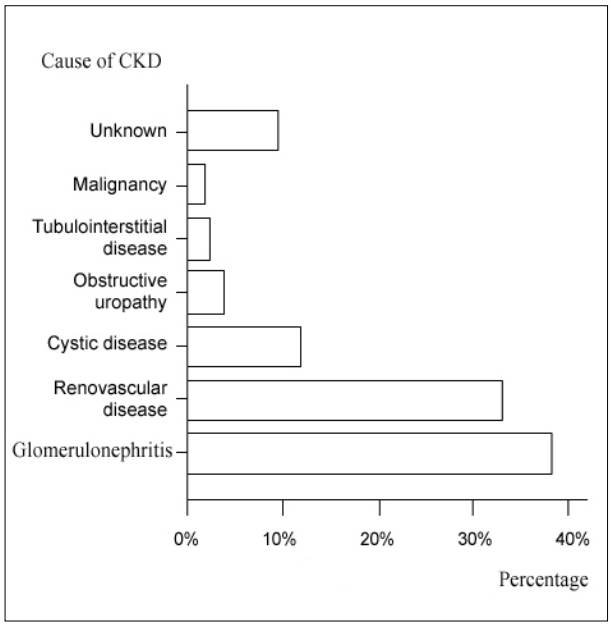
Chronic kidney disease (CKD) is a worldwide problem that is increasing in magnitude [1-5] and that requires concert work to control. The global distribution of renal replacement therapy (RRT) facilities is not homogenous. Most of RRT resources are available in developed countries [6]. According to the NHANES III survey, 11% of the American population had some degree of renal disease [7]. Population screening for CKD is an important preventive measure against progression to kidney failure [8]. Targeted screening of high risk populations in particular is comfirmed to be cost-effective [1, 8, 9]. Targeted populations include elderly people, diabetics, hypertensives, obese individuals, patients with autoimmune diseases, patients who have frequent urinary tract infections and patients with family history of CKD. The majority of patients in stage 3-5 CKD progress relentlessly to ESRD. A significant proportion of patients do not progress in a predictable linear fashion and have breakpoints in their progression slopes [10].

This study aimed to measure the rate of decline in kidney function among CKD patients on regular follow up in Sheffield Kidney Institute (SKI), Northern General Hospital NHS Trust, Sheffield, UK, and to examine the risk factors associated with this progression.

Methods

This is a retrospective study of CKD patients who were on regular follow up in SKI, Northern General Hospital NHS Trust, Sheffield, UK. Patients with initial diagnosis of CKD due to diabetic nephropathy were excluded. The estimated glomerular filtration rate (GFR) was used to stratify patients into CKD stages according to the KDOQI guidelines. GFR was estimated using the modification of

Figure 1: Causes of chronic kidney disease (CKD) in the study



diet in renal disease formula (MDRD). A sample of 300 patients was randomly selected from a list given by the computer in June 2007, including 100 patients each from CKD stage 2, CKD stage 3 and CKD stage 4. Patients' data were retrieved from the computer database and if further information were required we resorted to our hospital file system.

The rate of decline in the estimated GFR was the main outcome of the study. Progressors were defined as patients whose estimated GFR declined by more than 1 ml/min/year during a 5-year follow up period. Non-progressors were patients whose estimated GFR declined by ≤ 1 ml/min/year. Potential risk factors for CKD progression were evaluated. The data of the study were analyzed using SPSS software. P values were considered significant if < 0.05.

Results

The different causes of CKD in the study population are shown (Figure 1). Demographic data and clinical characteristics of the study sample at baseline are shown (Table1).

Overall, 52.7% of patients were classified as progressors with a rate of decline in estimated GFR exceeding 1 ml/min/year. The proportion of progressors was not different between the three CKD stages; 59% in stage II, 55% in stage III and 44% in stage IV CKD. Gender, older age, ethnic origin and diabetic status were not significantly associated with progressor status (Table 2).

Table 1: Demographic and clinical characteristics of the study sample at baseline

Parameters	Value
Gender	
Males, number (%)	173 (57.7%)
Females, number (%)	127 (42.3%)
Age	
≤ 65 years, number (%)	207 (69%)
> 65 years, number (%)	93 (31%)
Ethnicity	
White, number (%)	280 (93.3%)
Non-white, number (%)	20 (6.6%)
Diabetic status	
Diabetic, number (%)	119 (39.7%)
Non-diabetic, number (%)	181 (60.3%)
Blood pressure	
Systolic pressure (mmHg), mean ± SD	142 ± 23
Diastolic pressure (mmHg), mean ± SD	79 ± 13
Mean BP (mmHg), mean ± SD	94 ± 20
Laboratory data	
Proteinuria (g/day), mean ± SD	2.2 ± 3.5
Cholesterol (mg/dl), mean ± SD	223.9 ± 73.8
HbA1c (%), mean ± SD	7.8 ± 2.0
Hemoglobin (g/dl), mean ± SD	13.5 ± 2
Creatinine (mg/dl), mean ± SD	1.48 ± 0.86
Calcium (mg/dl), mean ± SD	10 ± 0.9
Phosphate (mg/dl), mean ± SD	3.7 ± 0.8
Ca x PO (mg^2/dl^2), mean ± SD	34.7 ± 8.1
Albumin (g/dl), mean ± SD	3.8 ± 0.6
Serum uric acid (mg/dl), mean ± SD	6.9 ± 2.2

Patients proven on follow up to be progressors tended to have higher 24-hour urinary protein excretion than in non-progressors (2.6 ± 3.6 versus 1.8 ± 3.5 g/day, respectively), but the difference did not reach statistical significance. They also tended to have higher blood pressure measurements at baseline that did not reach statistical significance (Table 3).

After 5-year follow-up, the mean 24-hour urinary protein excretion fell in both groups, from 1.8 ± 3.5 to 1.1 ± 1.8 g/day in non-progressors, and from 2.6 ± 3.6 to 2.2

Table 2: Proportion of progressors and non-progressors in different patient groups

Parameter		Progressors (n= 158)	Non-progressors (n= 142)	P value
Gender	Male	88 (50.9%)	85 (49.1%)	0.47
	Female	70 (55.1%)	57 (44.9%)	
Age in years	≤ 65 years	111 (53.6%)	96 (46.4%)	0.56
	> 65 years	47 (50.5%)	46 (49.5%)	
Ethnic origin	White	148 (52.7%)	132 (47.3%)	0.76
	Non-white	10 (50%)	10 (50%)	
DM	Non-diabetic	91 (50.3%)	90 (49.7%)	0.21
	Diabetic	67 (56.3%)	52 (43.7%)	

± 3.4 g/day in progressors. The difference in urinary protein excretion at 5-year between the two groups was statistically significant (P=0.003). Progressors also had a slightly but significantly lower hemoglobin at follow-up than non-progressors (13.2±1.7 versus 13.8±2.2 g/dl respectively, P = 0.01).

Among patients in stage 2 CKD, the only significant difference in base-line parameters was a lower body weight in progressors compared to non-progressors (82 ± 20 versus 92 ±18 kg, P = 0.02).

Among patients in stage 3 CKD, progressors had higher systolic blood pressure at base-line (147 ± 24 versus 134 ± 22 mmHg, P = 0.02), lower serum cholesterol (216.5 ± 43.5 versus 271.9 ± 107.3 mg/dl, P = 0.02) and lower calcium-phosphorus product (31.4 ± 7.7 versus 35.6 ± 11.1 mg^2/dl^2, P = 0.04) compared to non-progressors, respectively. Progressors continued to have a lower serum cholesterol at 5-year follow-up (206.9 ± 37.3 versus 227.7 ± 47.8 mg/dl, P = 0.03).

Among patients in stage 4 CKD, the only significant difference in base-line parameters was higher mean 24-hour urinary protein excretion among progressors compared to non-progressors (2.4 ± 3.3 versus 1.1 ± 1.7 g/day respectively, P = 0.01). At 5-year follow up, progressors had higher mean 24-hour urinary protein excretion (2.3 ± 3 versus 0.9 ± 1.4 g/day, P = 0.01), lower mean hemoglobin (12 ± 1.2 versus 13.1 ± 2.6 g/dl, P = 0.01), higher mean phosphorus (4.3 ± 1.1 versus 3.9 ± 0.9 mg/dl, P = 0.03), higher calcium-phosphorus product (40.9 ± 10.9 versus 36 ± 8 mg^2/dl^2, P = 0.01) and higher serum uric acid (8.7 ± 1.8 versus 7.9 ± 1.7 mg/dl, P = 0.03) compared to non-progressors, respectively.

We performed correlation analysis between different baseline parameters and the slope of decline in reciprocal serum creatinine (1/S. Cr). The slope of 1/S. Cr was significantly and negatively correlated to SBP. It was also significantly and negatively correlated to baseline serum creatinine (Table 4).

Discussion

Most of the study patients were white (93.3%) as the study was done in Sheffield city in UK where the general population are descendants of white ethnicity. The proportion of patients who had rapid deterioration in their kidney function, referred to as progressors, comprised 52.7% of the study sample. This is not very different from other studies that reported a rapid progression rate in 69.6% [11]. Male gender has been linked to rapid progression of kidney disease [12, 13], although some studies showed only borderline differences between genders [14]. Other authors described that stages 2 and 3 of CKD are more common in women than men [15, 16]. Autopsy series, arteriography studies, and review of populations of patients in ESRD programs all suggest that ischemic renal disease has a high and increasing prevalence in the aging population [17]. In this study, we detected no significant differences in progression between patients above 65 years of age and younger patients, nor between males and females.

DM is well known to be one of the most important causes of CKD, and is expected to become the commonest cause of CKD worldwide. In this study, the proportion of progressors was 56.3% among diabetic patients compared to 50.3% among non-diabetic patients, but the difference was not statistically significant. Controlling hyperglycemia was proven to reduce the rate of decline in renal function by many studies [16]. We failed to show the correlation between HbA1c and the progression of CKD in this study; this could be due to the small number of diabetics among our study population as patients

Table 3: Statistics for progressors and non-progressors at baseline

Baseline Parameters (mean ± SD)	Progressors	Non-progressors	P value
Proteinuria (g/day)	2.6 ± 3.6	1.8 ± 3.5	0.3
Systolic blood pressure (mmHg)	145 ± 21	139 ± 24	0.8
Diastolic blood pressure (mmHg)	80 ± 15	77 ± 11	0.06
Mean blood pressure (mmHg)	96 ± 22	92 ± 18	0.8
Cholesterol (mg/dl)	226.2 ± 74.5	220.7 ± 73.4	0.6
HbA1c (%)	8 ± 2.3	7.5 ± 1.6	0.1
Hemoglobin (g/dl)	13.5 ± 2.1	13.6 ± 1.8	0.2
Creatinine (mg/dl)	1.4 ± 0.5	1.6 ± 1.1	0.04
Calcium (mg/dl)	9.4 ± 0.5	10.5 ± 1.3	0.7
Phosphate (mg/dl)	3.6 ± 0.8	3.7 ± 0.8	0.5
Ca x PO4 (mg^2/dl^2)	33.7 ± 8.3	34.6 ± 7.8	0.4
Albumin (g/dl)	3.7 ± 0.7	3.8 ± 0.6	0.2
Serum uric acid (mg/dl)	7.0 ± 2.4	6.8 ± 2.1	0.3

Table 4: Correlation between different parameters at baseline and the slope of 1/serum creatinine

Baseline parameters	Pearson Correlation coefficient with the slope of 1/serum creatinine	P value
Age (years)	0.03	0.6
Urinary protein excretion (g/day)	- 0.11	0.09
Systolic blood pressure (mmHg)	- 0.14	0.03 *
Diastolic blood pressure (mmHg)	- 0.12	0.07
Mean blood pressure (mmHg)	- 0.08	0.2
Serum cholesterol (mg/dl)	- 0.04	0.6
HbA1c (%)	- 0.13	0.2
Hemoglobin (g/dl)	0.03	0.6
Serum creatinine (mg/dl)	0.13	0.03 *
Serum calcium (mg/dl)	0.06	0.3
Serum phosphorus (mg/dl)	0.05	0.4
Calcium phosphorus product (mg^2/dl^2)	0.06	0.3
Serum albumin (g/dl)	0.07	0.2
Serum uric acid (mg/dl)	- 0.04	0.5

* statistically significant

who had diabetes as the primary cause of their renal impairment were excluded.

The relation between higher levels of proteinuria and faster decline in kidney function was well documented by many studies that also confirmed the therapeutic role of ACEI/ARBs in this regard [18]. In a multivariate analysis, higher mean arterial pressure predicted a faster decline in GFR [19, 20]. Better control of systolic pressure may halt the progression of CKD [21, 22]. Blood pressure control is crucial for preventing kidney loss as has been shown by many investigators [14]. In this study, progressors tended to have higher blood pressure measurements at baseline.

There is increasing evidence to support the role of dyslipidemia as a contributing factor to the progression of chronic renal disease [14, 19, 23, 24]. Such an effect

was not detected by this study. In fact, progressors in stage III CKD had significantly lower serum cholesterol level at baseline.

Anemia is a common comorbidity of chronic kidney disease [25]. In both progressor and non-progressor groups the baseline hemoglobin level was above the KDOQI guidelines of 11-13 gm/dl. Although there is not much data to support this correlation some investigators showed that low hematocrit correlates with faster progression of kidney impairment. Anemia in some models was found to be a potent modulator of renal hemodynamics [26]. Effect of early Correction of Anemia on the Progression of chronic kidney disease (ECAP) study will try to address the effect of anemia and it's early treatment on the progression of CKD [27].

The calcium and phosphate levels, both at baseline and follow up, were within the KDOQI guidelines targets for CKD stages 3 and 4. The calcium phosphate product is a reflection of both measurements and its baseline and follow-up values in both progressors and non-progressors also reflected reasonable control in the study population.

Albumin is a surrogate marker of patients' nutritional wellbeing. In our study there was no difference in albumin levels between the two groups. The uric acid level was also within the normal range for the study population at baseline and at follow-up. There is now increasing evidence that uric acid is associated with CKD progression [28].

Glomerulonephritis (GN) was the commonest cause of CKD in our study (38.1%). Patients who were diagnosed as having GN tended to be non-progressors. This is concordant with the current literature in UK.

Proteinuria is a potent and powerful predictor for the progression of CKD and reducing it contributes to preventing CKD progression [29, 30] . Lower 24-hour urinary protein excretion is associated with better kidney survival.

Conclusion

Overall, 52.7% of the study population had a rate of decline in estimated GFR that exceeded 1 ml/min/year and were classified as progressors. Patients proven on follow-up to be progressors tended to have higher 24-hour urinary protein excretion and higher blood pressure measurements at baseline.

Aknowledgement

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