Analysis of Predictive Factors for Deterioration of Renal Function in Chronic Kidney Disease Patients

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Abstract

Chronic kidney disease (CKD) management requires a multidisciplinary approach. Although several treatment targets exist, the relationships between a number of clinical criteria and CKD progression have not been studied. Here, we investigated the association between renal dysfunction progression and a number of clinical parameters. We retrospectively enrolled 373 patients with mild impaired renal function indicated by a serum creatinine level > 2.0 mg/dL measured in 2012. We assessed clinical parameters both in 2009 and 2012, and analyzed whether each clinical parameter (e.g., hypertension, diabetes, dyslipidemia, and anemia) met therapeutic targets. To prevent renal dysfunction progression, treatment with renin-angiotensin system inhibitor and statin are not sufficient intensive treatment, showed the strongest relationship (odds ratio 0.65, 95% confidence interval 0.53-0.82, p < 0.001). To prevent renal dysfunction progression, treatment with renin-angiotensin system inhibitor and statin are not sufficient intensive treatment, showed the strongest relationship (odds ratio 0.65, 95% confidence interval 0.53-0.82, p < 0.001).

Keywords: Chronic kidney disease; Urinary protein; Blood pressure; Triglyceride; Predictive factor

Introduction

Recently, the increased number of patients with end-stage renal disease has become a major global health problem [1,2]. In 2002, the Kidney Disease Outcomes Quality Initiative proposed a new concept of renal disease known as chronic kidney disease (CKD) [2]. The association between CKD and adverse cardiovascular events has been established in several clinical studies [3-4]. Moreover, recent studies revealed that CKD is associated with dementia [5] and depression [6]. Intensive treatment for CKD is important to protect renal dysfunction and damage to other organs. Thus, the management of CKD improves patients' activities of daily living and quality of life. In 2007 and 2012, the Japanese Society of Nephrology (JSN) proposed a guide for the management of CKD for nephrologists and primary care physicians in Japan [7]. In this guide, the JSN proposed several therapeutic targets for each clinical criterion, such as hypertension, diabetes, dyslipidemia, and anemia. Furthermore, several studies revealed that urinary protein (UP) is one of the major factors affecting CKD progression [8]. The objective of the present study was to investigate the association between renal progression and the clinical criteria of CKD management. In addition, we showed that the CKD guide was useful in the prevention of CKD progression in our cohort.

Methods

Study design and subjects

This study is a retrospective cohort study conducted in the outpatient clinic of Department of Nephrology and Hypertension at Juntendo University Hospital. CKD patients with serum creatinine (S-Cr) level ≥ 2.0 mg/dl in 2012 (n=382) were eligible for present study (Figure 1). We assessed serum creatinine both in 2009 and in 2012. Of the 382 patients, 9 patients were excluded because patients underwent the dialysis from 2009 to 2012. Moreover, we defined the patients who has serum creatinine level ≤ 2.0 mg/dl in 2009 as the “mild impaired renal function group”. This study was approved by the Ethical Committee of Juntendo University Hospital (13-021), and all participants gave written informed consent.

Clinical data and definitions of outcomes

We collected data on baseline clinical characteristics from a review of medical records in both 2009 and 2012. Clinical characteristics comprised age, gender, height, body weight, systolic blood pressure (SBP), diastolic blood pressure, albumin level, S-Cr level, estimated glomerular filtration rate (eGFR) estimated by the modified modification of diet in renal disease equation (eGFR = 194 × age [year] - 0.286 × S-Cr [mg/dl]1.154 × 0.739 if female) [9]. Levels of plasma glucose, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglyceride (TG), uric, hemoglobin (Hb), serum calcium, serum phosphorus, serum potassium, UP, and urinary occult blood on dipstick analysis were also comprised. We collected data on therapeutic interventions as follows: use of erythropoiesis stimulating agents, antihypertensive drugs including RAS-I, statins, anti-diabetic drugs, insulin, spherical adsorbent carbon, and sodium bicarbonate. We defined that a primary outcome that was the 50% increase in S-Cr as

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baseline, and determined the progression and non-progression groups based on this value. We defined patients who had mild impaired renal function (S-Cr ≤ 2.0 mg/dL) at 2009 as a separate subgroup.

Management indicators for each parameter

Based on the clinical practice guidebook for the diagnosis and treatment of CKD from 2012 [7], we determined the criteria for the management of CKD (i.e., SBP ≤ 130 mmHg, HbA1c ≤ 6.9%, LDL cholesterol ≤ 120 mg/dL). We also determined the criteria of UP (< 0.3 g/gCr) and TG level (≤ 150 mg/dL). We categorized the patients according to these criteria in both 2009 and 2012.

Statistical Analysis

We performed statistical analyses using Stata Version 13 (StataCorp, Collage Station, TX, USA). Normally distributed continuous variables were expressed as means with standard deviations and compared using Student’s t-test. Non-normally distributed continuous variables were expressed as medians (interquartile ranges) and compared using the Mann-Whitney U test. Categorical variables were expressed as numbers (proportions) and analyzed using the chi-square test or Fisher’s exact test. Logistic regression was used to calculate the odds ratio (OR) for the association between the number of clinical criteria satisfied and the percentage of patients with progression of renal dysfunction. All probability values were two-tailed, and all confidence intervals were compared at the 95% level.

Results

Clinical characteristics and demographic data of the enrolled CKD patients

We compared baseline characteristics between the progression and non-progression groups (Table 1). SBP was significantly lower (129.5 ± 17.2 mmHg vs. 140.4 ± 73.4 mmHg; p < 0.01) in the non-progression group. TG levels were also significantly lower in the non-progression group (145.6 ± 68.1 mg/dL vs. 171.5 ± 118.3 mg/dL; p = 0.01). Renal function in the non-progression group was significantly lower than that in the progression group (S-Cr: 2.36 ± 0.86 mg/dL vs. 2.15 ± 0.96 mg/dL; p < 0.03, eGFR: 23.8 ± 7.8 mL/min/1.73 m² vs. 29.4 ± 15.0 mL/min/1.73 m²; p < 0.01). Median UP level was significantly lower in the non-progression group (0.69 vs. 1.45; p < 0.01). No significant differences were observed with respect to HbA1c, LDL cholesterol, HDL cholesterol, Hb, and ratio of medication with renin-angiotensin system inhibitor (RAS-I) and statin between the two groups.

Analysis of parameters associated with renal deterioration in patients with mild impaired renal function

The baseline characteristics of the patients with mild impaired renal function are shown in Table 2 (n = 163). SBP, S-Cr, eGFR, and UP were significantly different between the non-progression and progression groups. In patients in the non-progression group, serum TG levels were lower than in patients in the progression group (150.2 ± 68.6 vs. 179.4 ± 117.8; p = 0.07). Levels of HbA1c, LDL cholesterol, HDL cholesterol, and ratio of medication with RAS-I and statin were not significantly different between the two groups.

The amount of urinary protein was a major factor for renal progression

We evaluated the association between UP level and CKD progression in both 2009 and 2012 (Figure 2). About 83% of patients who achieved the criterion of < 0.2 g/gCr in 2009 and 2012 did not experience a decline in renal function. The percentage of patients with
no progression of renal dysfunction decreased with increasing UP level (< 0.2 g/gCr: 83.3%, < 0.3 g/gCr: 82.1%, < 0.5 g/gCr: 78.3%, < 1.0 g/ gCr: 72.8%). Next, we evaluated whether the patients achieved the treatment criteria in 2009 and 2012. The percentage of patients who did not show a decline in renal function in each category of the CKD guide is shown in (Figure 3). Of the 105 patients who achieved the clinical criterion for SBP in both 2009 and 2012, 59 patients did not experience a decline in renal function (56.2%). Of the 124 patients who achieved the criterion of HbA1c at both 2009 and 2012, 57 patients did not experience a decline in renal function (45.9%). Of the 245 patients

| Table 1: Baseline characteristics of the patients with mild impaired renal function. |
|-------------------------------|-------------------|-------------------|-------------------|-------------------|
| Age (years)                   | 66.7 (± 14.0)     | 66.0 (± 14.3)     | 67.2 (± 13.8)     | 0.59              |
| Sex (male/female)             | 23 (40)           | 53 (13)           | 70 (27)           | 0.24              |
| Height (cm)                   | 162.6 (± 9.7)     | 164.3 (± 8.6)     | 161.6 (± 10.3)    | 0.05              |
| Body weight (kg)              | 62.8 (± 13.0)     | 63.5 (± 11.4)     | 62.3 (± 13.9)     | 0.56              |
| SBP (mmHg)                    | 132.0 (± 16.5)    | 126.3 (± 13.9)    | 136.0 (± 17.1)    | <0.001            |
| DBP (mmHg)                    | 73.0 (± 13.6)     | 72.5 (± 10.8)     | 73.4 (± 15.3)     | 0.69              |
| Alb (g/dL)                    | 3.9 (± 0.5)       | 4.1 (± 0.3)       | 3.8 (± 0.5)       | <0.001            |
| S-Cre (mg/dL)                 | 1.52 (± 0.3)      | 1.73 (± 0.17)     | 1.33 (± 0.39)     | <0.001            |
| eGFR (mL/min)                 | 36.9 (± 12.0)     | 31.1 (± 5.5)      | 40.8 (± 13.6)     | <0.001            |
| BS (mg/dL)                    | 115.8 (± 40.7)    | 113.5 (± 46.3)    | 117.4 (± 36.6)    | 0.56              |
| HbA1c (%)                     | 6.1 (± 1.0)       | 6.0 (± 0.9)       | 6.2 (± 1.1)       | 0.15              |
| LDL-cho (mg/dL)               | 105.3 (± 27.7)    | 105.2 (± 25.3)    | 105.4 (± 29.3)    | 0.96              |
| HDL-cho (mg/dL)               | 50.4 (± 17.1)     | 48.3 (± 14.3)     | 51.9 (± 18.7)     | 0.2               |
| TG (mg/dL)                    | 167.5 (± 99.5)    | 150.2 (± 68.6)    | 179.4 (± 117.8)   | 0.07              |
| UA (mg/dL)                    | 6.9 (± 1.3)       | 6.9 (± 1.1)       | 6.8 (± 1.3)       | 0.77              |
| Hb (g/dL)                     | 12.4 (± 1.9)      | 11.7 (± 1.8)      | 12.2 (± 2.0)      | 0.1               |
| Ca (mg/dL)                    | 9.3 (± 0.6)       | 9.3 (± 0.4)       | 9.2 (± 0.7)       | 0.16              |
| Pi (mg/dL)                    | 3.4 (± 0.6)       | 3.2 (± 0.5)       | 3.5 (± 0.6)       | <0.001            |
| K (mg/dL)                     | 4.6 (± 0.5)       | 4.6 (± 0.5)       | 4.6 (± 0.6)       | 0.95              |
| UP (g/day)                    | 1.17 (0.42-2.5)   | 0.70 (0.1-1.4)    | 2.0 (0.57-4.39)   | <0.001            |
| Hematuria (%)                 | 55 (33.7)         | 23 (34.9)         | 32 (33.0)         | 0.81              |
| Use of RAS-I (%)              | 123 (75.5)        | 48 (72.7)         | 75 (77.3)         | 0.5               |
| Use of statin (%)             | 47 (28.8)         | 17 (25.8)         | 30 (30.9)         | 0.47              |

Table 2: Baseline characteristics and clinical parameters of the patients.
who achieved the criterion for LDL cholesterol at both 2009 and 2012, 119 patients did not experience a decline in renal function (48.5%). Of the 166 patients who achieved the criterion for TG at both 2009 and 2012, 83 patients did not experience a decline in renal function (50.0%). Of the 28 patients who achieved the criterion for UP at both 2009 and 2012, 23 patients did not experience a decline in renal function (82.1%).

The number of achieved clinical criteria was a significant
factor for the prevention of renal function loss

The numbers of achieved clinical criteria in 2009 is shown in (Figure 4). The ratio of patients in the non-progression group who achieved above three clinical criteria (SBP, HbA1c, LDL, and Hb: model 1) was 54%, while the ratio of those patients in the progression group was 45% (Figure 4a). The ratio of patients in the non-progression group who achieved above four criteria (model 1 + TG: model 2) was 42%, while the ratio of those patients in the progression group was 30% (Figure 4b). In model 3 including SBP, HbA1c, TG and Hb, the ratio of patients in the non-progression and progression groups who achieved above three criteria were 51% and 37%, respectively (Figure 4c). The ratio of patients in the non-progression and progression groups who met above three criteria (SBP, HbA1c, TG, UP: model 4) were 35% and 22%, respectively (Figure 4d).

In logistic regression analysis, the specific criteria achieve by patients was a significant factor for renal function dysfunction in each model (model 1: OR 0.71, 95% confidence interval [CI] 0.57-0.88, p = 0.002; model 2: OR 0.75, 95% CI 0.62-0.89, p = 0.001; model 3: OR 0.73, 95% CI 0.59-0.89, p = 0.002; model 4: OR 0.65, 95% CI 0.53-0.82, p < 0.001).

Discussion

In this retrospective cohort study, we enrolled 373 patients with CKD and evaluated major factors associated with the progression of CKD during a 3-year period. This study showed that high levels of SBP, TG and UP, and low eGFR were key factors for progression of CKD, even though the ratio of treatment with RAS-I and stain were not significantly different between the progression and non-progression groups. Moreover, we found that the achieved numbers of clinical criteria was related to protection of renal dysfunction. This is the first study to investigate this association. Control of BP is fundamental to the treatment of patients with CKD, and is relevant at all stages of the disease [10]. The aim of BP control is to reduce the risk of renal dysfunction and mortality. Several studies have suggested that BP control using mainly RAS-I slows the progression of renal dysfunction at all stages of CKD [11-13]. In this study, 56.2% of the non-progression group achieved the therapeutic target for BP in both 2009 and 2012. In contrast, only 23.0% of CKD patients in the progression group achieved the therapeutic target for BP in both 2009 and 2012.

Several randomized controlled trials and meta-analyses [14-17] have suggested that the intensive control of plasma glucose levels inhibits the progression of diabetic nephropathy in the early stage. According to the Japanese CKD guide [7], the therapeutic target of HbA1c is below 6.9%. In this study, only 22.7% of patients in the non-progression group did not achieve the therapeutic target for HbA1c in both 2009 and 2012. In contrast, in the progression group, 77.3% of patients did not achieve the therapeutic target for HbA1c in both 2009 and 2012.

CKD is a significant risk factor for the incidence of cardiovascular
who could be followed up in our outpatient clinic in both 2009 and 2012. Therefore, some selection bias may have occurred. Second, the patients were administered various medicine in each clinical criteria. However, we could not estimate different efficacy in each treatment. Third, we defined the primary outcome as a 50% increase in S-Cr. However, we could not evaluate the cause of CKD in each patient.

Conclusion

In conclusion, we confirmed that hypertension, diabetes and amounts of UP are risk factors for the progression of CKD. However, high serum TG levels also affected the deterioration of renal function. Importantly, reducing proteinuria had a strong effect on preventing CKD progression. Moreover, we detected that achieving more therapeutic criteria had a strong effect on protecting renal function, even in the case with treatment with RAS-I and statin. Together, these results suggest that intensive treatment is essential in patients with CKD, regardless of baseline eGFR.

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Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References


