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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. We defined a 50% increase in serum creatinine level as baseline, and determined the progression and non-progression groups based on this definition. Systolic blood pressure (SBP), estimated glomerular filtration rate (eGFR), triglyceride, and urinary protein were significantly different between the progression and non-progression groups. The percentage of individuals in the non-progression group decreased with increasing proteinuria (<0.2 g/gCr: 83.3%, <0.3 g/gCr: 82.1%, <0.5 g/gCr: 78.3%, <1.0 g/gCr: 72.8%). In the multiple regression model, the number of clinical criteria achieved was significantly associated with renal progression. Moreover, the model including SBP, HbA1c, urinary protein, and triglyceride; e.g. 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 in CKD patients. Intensive treatment of SBP, HbA1c, urinary protein, and triglyceride is essential. Even in patients with low eGFR, exacerbation of renal injuries was prevented with intensive treatment.

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 ($eGFR = 194 \times age\ [year]^{-0.287} \times S\text{-}Cr\ [mg/dL]^{-1.094}$ ($\times 0.739$ 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 adsorptive 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/1.73m^2 vs. 29.4 ± 15.0 mL/min/1.73m^2; $p < 0.01$). 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, and Hb, 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

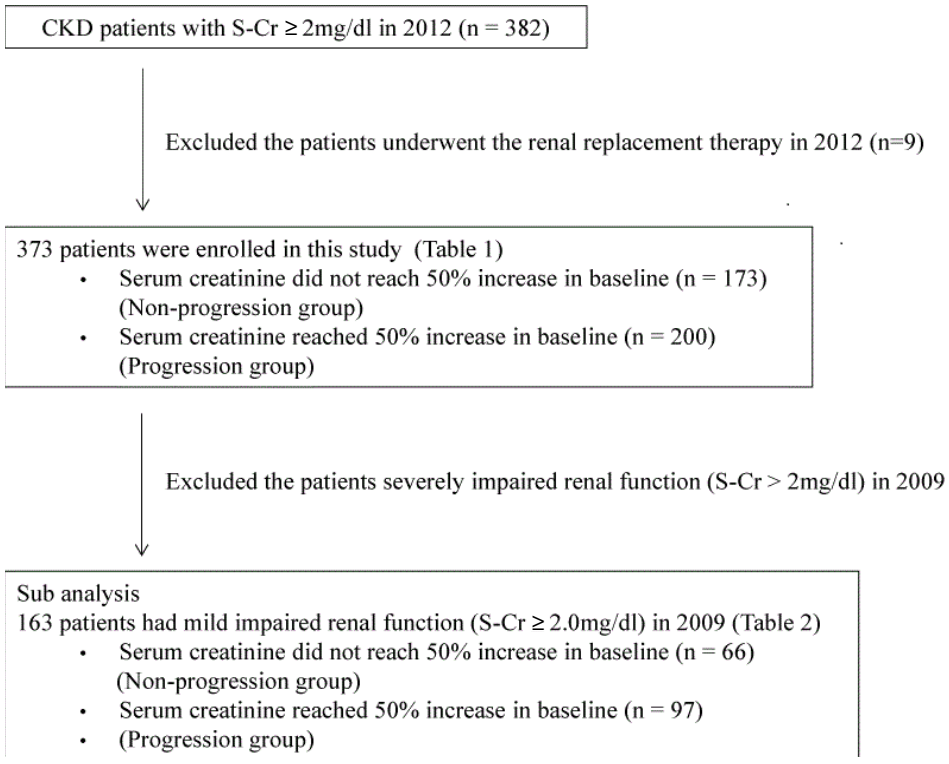

Figure 1: Flow diagram with inclusion/exclusion criteria.

	All patients	Non-progression group	Progression group	*p*-value
	(n=373)	(n=173)	(n=200)	
Age (years)	66.1 (± 13.9)	66.8 (± 14.1)	65.5 (± 13.8)	0.39
Sex (male/female)	278/95	132/41	146/54	0.47
Height (cm)	162.0 (± 9.4)	162.1 (± 9.0)	161.8 (± 9.7)	0.78
Body weight (kg)	61.3 (± 13.0)	60.4 (± 12.0)	62.1 (± 13.07)	0.23
SBP (mmHg)	135.2 (± 54.8)	129.5 (± 17.2)	140.4 (± 73.4)	<0.01
DBP (mmHg)	72.8 (± 11.9)	72.4 (± 10.7)	73.1 (± 12.9)	0.55
Alb (g/dL)	4.0 (± 0.44)	4.1 (± 0.40)	3.9 (± 0.47)	<0.01
S-cre (mg/dL)	2.25 (± 0.92)	2.36 (± 0.86)	2.15 (± 0.96)	0.03
eGFR (mL/min)	26.8 (± 12.5)	23.8 (± 7.8)	29.4 (± 15.0)	<0.01
BS (mg/dL)	113.7 (± 37.9)	112.2 (± 41.9)	115.0 (± 34.0)	0.48
HbA1c (%)	6.0 (± 0.9)	6.0 (± 0.8)	6.0 (± 0.9)	0.43
LDL-cho (mg/dL)	101.3 (± 29.2)	99.3 (± 26.8)	103.0 (± 31.0)	0.22
HDL-cho (mg/dL)	50.6 (± 16.0)	49.7 (± 15.3)	51.3 (± 16.5)	0.31
TG (mg/dL)	159.5 (± 99.1)	145.6 (± 68.1)	171.5 (± 118.3)	0.01
UA (mg/dL)	6.9 (± 1.3)	6.9 (± 1.2)	7.0 (± 1.3)	0.22
Hb (g/dL)	11.8 (± 1.8)	11.9 (± 1.7)	11.7 (± 1.8)	0.24
Ca (mg/dL)	9.2 (± 0.7)	9.3 (± 0.6)	9.1 (± 0.7)	0.05
Pi (mg/dL)	3.5 (± 0.8)	3.5 (± 0.9)	3.5 (± 0.7)	0.67
K (mg/dL)	4.7 (± 0.5)	4.7 (± 0.5)	4.7 (± 0.5)	0.82
UP (g/day)	1.05 (0.42-2.1)	0.69 (0.19-1.49)	1.45 (0.57-2.91)	<0.01
Hematuria (%)	128 (34.5)	52 (30.4)	76 (38.0)	0.12
Use of RAS-I (%)	282 (75.6)	126 (72.8)	156 (78.0)	0.24
Use of statin (%)	121 (32.4)	61 (35.3)	60 (30.0)	0.27

Table 1: Baseline characteristics and clinical parameters of the patients.

	All patients	Non-progression group	Progression group	*p*-value
	(n = 163)	(n = 66)	(n = 97)	
Age (years)	66.7 (± 14.0)	66.0(± 14.3)	67.2 (± 13.8)	0.59
Sex (male/female)	123/40	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 (0-1.4)	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 of the patients with mild impaired renal function.

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

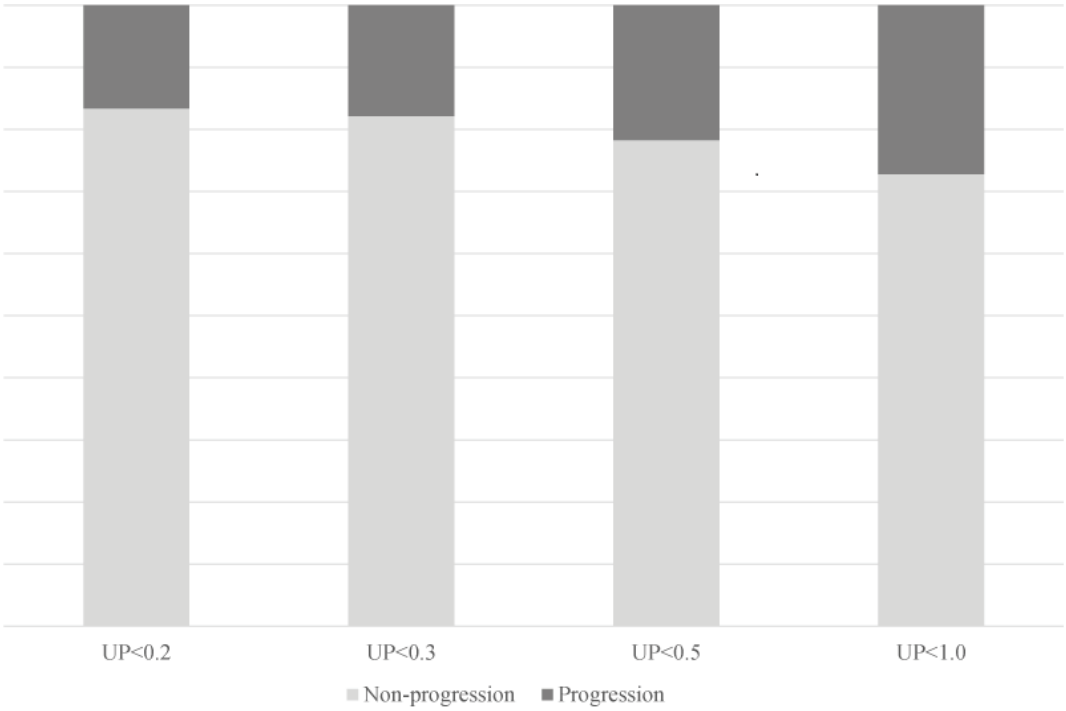

Figure 2: The amount of urinary protein associated with renal progression. The percentage of patients who did not show progression at each level of urinary protein. The percentage of patients with no progression of renal dysfunction decreased with increasing levels of urinary protein.

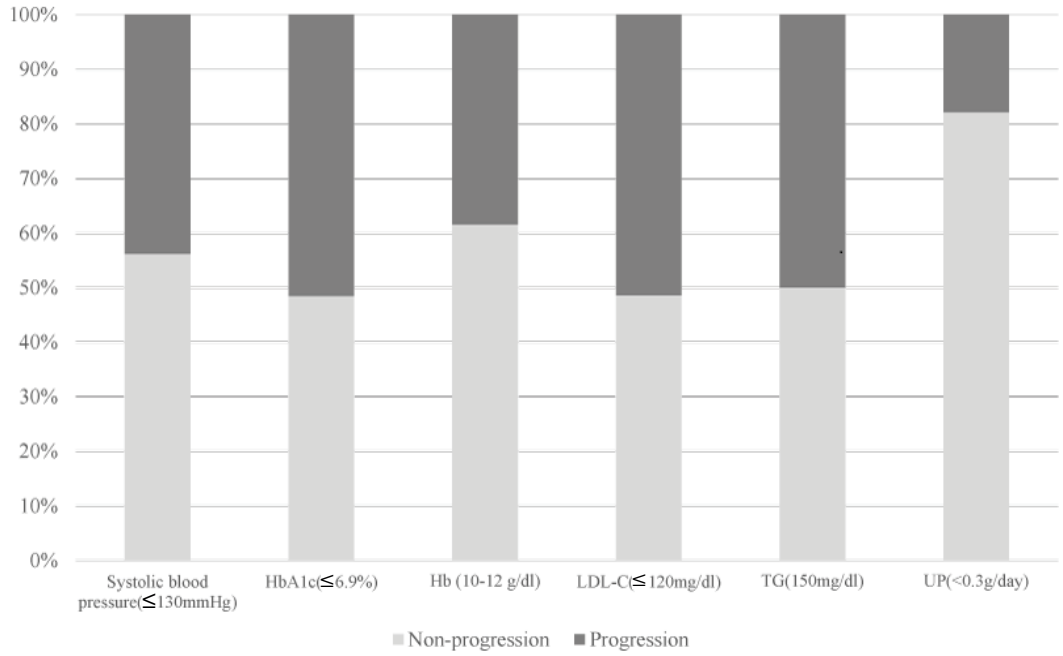

Figure 3: The contribution of each clinical criterion in the progression of renal function. The percentage of patients with no decline in renal function in each category of the CKD guide. The percentages of patients who achieved the clinical targets for systolic blood pressure and hemoglobin level were over 50%.

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

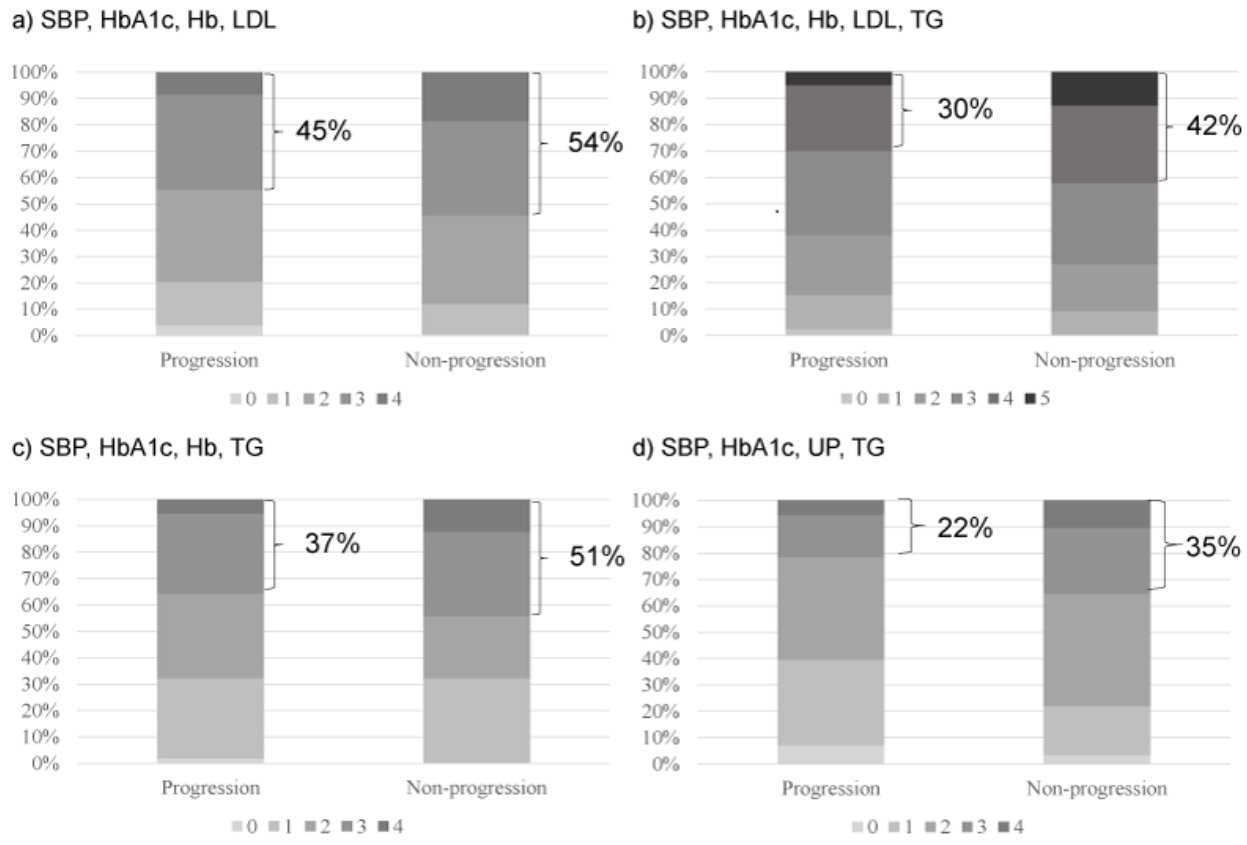

Figure 4: The numbers of achieved clinical criteria in 2009. The number of achieved clinical criteria in the non-progression group was significantly greater than that in the progression group for all models.

disease (CVD). Moreover, dyslipidemia is a significant risk factor for CKD progression and CVD. According to the Japanese CKD guide [7], the therapeutic target of LDL cholesterol is < 120 mg/dL. In this study, the levels of LDL cholesterol were not significantly different between the progression and non-progression groups. In fact, 57.1% of patients in non-progression group did not achieve the therapeutic target for LDL cholesterol in both 2009 and 2012. These results do not confirm the importance of the therapeutic target for LDL cholesterol in CKD patients. Next, we investigated the clinical importance of serum TG levels. Although there was no significant difference in the level of LDL cholesterol between the progression and non-progression groups, serum TG levels were significantly lower in the non-progression group. We determined the therapeutic target for TG level as < 150 mg/dL and performed the same evaluation (Figures 4b and 4c). Several epidemiologic studies have shown that the incidence of CKD is associated with increased serum TG and LDL cholesterol levels, as well as decreased HDL cholesterol level. Since dyslipidemia induces arteriosclerosis in CKD patients, treating dyslipidemia is very important. However, the appropriate target lipid profile is unclear. Our results suggested that the management of TG levels is more important than those of LDL cholesterol. In the future, a large-scale clinical study is required to investigate the role of TG in the progression of CKD. Soluble tumorigenicity 2 (ST2) is suggested to be an early biomarker for CVD [18]. It is important to assess the serum levels of ST2 in progressive CKD patients in the future.

The Japanese CKD guide suggested the therapeutic targets for clinical criteria in CKD patients. However, to date, there is no evidence to suggest that the achieved numbers of clinical criteria is significant to protect progression of CKD. In order to investigate this hypothesis, we analyzed the achieved numbers of criteria in both groups in 2009 and 2012. The achieved numbers of clinical criteria was positively correlated with the maintenance of renal function (Figure 3, $p = 0.04$). The logistic regression model clearly indicated that intensive treatment for BP, diabetes, high TG level, and proteinuria is essential to prevent progression of renal dysfunction (OR 0.65 95% CI 0.53-0.82 $p < 0.001$: Table 3).

Importantly, eGFR in the non-progression group was significantly lower than that in the progression group at baseline (Table 1). However, mean eGFR at 2012 in the non-progression group was significantly higher than that in the progression group (19.7 ± 0.44 vs. 12.6 ± 0.47, $p < 0.001$). In the mild impaired group (S-Cr ≤ 2.0 mg/dL in 2009), eGFR at baseline did not predict the progression of CKD during the 3-year period of the study (Table 2). These results suggested that the intensive treatment of various clinical targets affected renal outcomes even in patients with low eGFR at baseline.

Study Limitation

This study has several limitations. First, we only included patients 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.

Model	OR	95%CI	*p*-value
Model 1 (SBP, HbA1c, Hb, LDL-C)	0.71	0.57-0.88	0.002
Model 2 (SBP, HbA1c, Hb, LDL-C, TG)	0.75	0.62-0.89	0.001
Model 3 (SBP, HbA1c, Hb, TG)	0.73	0.59-0.89	0.002
Model 4 (SBP, HbA1c, TG, UP)	0.65	0.53-0.82	<0.001

Table 3: Association between the achieved numbers of clinical criteria and renal progression.

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.

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