Table 8 Factors associated with anemia (univariate and multivariate logistic regression analysis)

	Univariate OR (95% CI)	*P* value	Multivariate OR (95% CI)	*P* value
Sex (female)	2.096 (1.789–2.456)	<0.0001		
Age (≥65 year)	1.766 (1.511–2.065)	<0.0001		
Causative diseases of CKD				
Diabetic nephropathy	2.357 (1.963–2.830)	<0.0001	1.899 (1.530–2.357)	<0.0001
Glomerulonephritis	0.685 (0.582–0.806)	<0.0001		
Others	0.773 (0.659–0.906)	0.0015		
Medical history				
Hypertension	1.294 (1.053–1.591)	0.0145	0.952 (0.750–1.208)	0.6857
Myocardial infarction	0.995 (0.697–1.421)	0.9799		
Angina	1.260 (0.963–1.649)	0.0919		
Congestive heart failure	1.553 (1.062–2.272)	0.0231	1.016 (0.649–1.590)	0.9463
ASO	1.744 (1.182–2.574)	0.0051		
Stroke	1.148 (0.905–1.456)	0.2554		
Diabetes	1.655 (1.413–1.938)	<0.0001		
Cancer	0.894 (0.660–1.211)	0.468		
Serum creatinine (mg/dL)	2.168 (1.993–2.357)	<0.0001		
eGFR (mL/min/1.73 m^2)	0.914 (0.906–0.922)	<0.0001	0.916 (0.908–0.924)	<0.0001
P (mg/dL)	3.138 (2.719–3.623)	<0.0001		
CRP (≥1 mg/dL)	1.806 (1.229–2.656)	0.0026		
Serum albumin (g/dL)	0.284 (0.233–0.346)	<0.0001	0.355 (0.285–0.441)	<0.0001

OR odd ratio, *CI* confidence interval

Table 9 Factors associated with ESA therapy (univariate and multivariate logistic regression analysis)

	Univariate OR (95% Cl)	*P* value	Multivariate OR (95% Cl)	*P* value
Sex (female)	1.637 (1.319–2.031)	<0.0001		
Age (≥65 year)	1.848 (1.487–2.298)	<0.0001		
Causative diseases of CKD				
Diabetic nephropathy	2.236 (1.771–2.823)	<0.0001	1.641 (1.248–2.157)	0.0004
Glomerulonephritis	0.603 (0.477–0.763)	<0.0001		
Others	0.847 (0.679–1.056)	0.1398		
Medical history				
Hypertension	1.925 (1.381–2.683)	0.0001	1.367 (0.949–1.969)	0.0932
Myocardial infarction	0.865 (0.516–1.452)	0.5834		
Angina	1.118 (0.772–1.619)	0.5555		
Congestive heart failure	1.521 (0.935–2.473)	0.0908	0.962 (0.553–1.671)	0.8897
ASO	1.451 (0.873–2.410)	0.1511		
Stroke	1.289 (0.943–1.762)	0.1120		
Diabetes	1.766 (1.424–2.191)	<0.0001		
Cancer	1.091 (0.730–1.630)	0.6718		
Serum creatinine (mg/dL)	2.192 (1.997–2.407)	<0.0001		
eGFR (mL/min/1.73 m^2)	0.884 (0.871–0.897)	<0.0001	0.885 (0.872–0.899)	<0.0001
P (mg/dL)	2.973 (2.512–3.518)	<0.0001		
CRP (≥1 mg/dL)	1.525 (0.941–2.470)	0.0868		
Serum albumin (g/dL)	0.379 (0.301–0.478)	<0.0001	0.514 (0.392–0.675)	<0.0001

OR odd ratio, *CI* confidence interval

The percentage of CKD patients receiving anemia treatment increased as the Hb level declined, but patients on ESA therapy accounted for only 32.4% of those with an Hb of <11 g/dL. Even among patients with an Hb of <10 g/dL, the ESA use was only 44.3%. These results suggest that not enough anemic patients are receiving ESA therapy. The rates of ESA use by CKD progression showed that the earlier the CKD stage, the less ESA therapy was prescribed to treat anemia. Even when the Hb level dropped to below 11 g/dL, the rate of patients not on ESA therapy remained high, suggesting a low awareness for anemia treatment in the early stages. Multivariate analyses of patient characteristics that influence ESA therapy also identified low eGFR levels, reflecting the difficulty of administering ESA at high eGFR levels, or, in other words, in the early stages of CKD.

Analyses of dosing frequency of ESA revealed that only 30.4% of patients were receiving ESA at the approved dosage and administration and that most patients (67.8%) were receiving ESA once every 3 weeks or monthly, indicating that the current practice of anemia treatment for CKD patients deviates from the approved dosage interval for the current ESA preparations.

The mean Hb level was 10.28 ± 1.19 g/dL (mean ± SD) among all patients undergoing ESA therapy. Patients who had an Hb level of ≥11 g/dL, the target level proposed by the treatment guideline for renal anemia in CKD patients [12], accounted for 30.1%. Among these patients, 39.5% were receiving ESA based on the currently approved dosage interval or more frequently, and 31.6% were on lower dosing frequencies, showing a low percentage of patients were achieving the target Hb level proposed by the treatment guideline through ESA therapy, with such a trend being more prominent among patients receiving less frequent treatment of ESA. This can be attributed to the difficulty for outpatients with early stage CKD to visit a hospital for the sole purpose of receiving ESA with few subjective symptoms.

At the start of the present study in 2007, with no treatment guidelines available in Japan for renal anemia in CKD patients not on dialysis, anemia treatment was based on an approximate level of 10 g/dL, which is the target Hb level provided in the current ESA package insert. The results from the present study showed that even when adhering to this level, the present ESA does not provide adequate anemia management in CKD patients. We expect the CKD-JAC study to show how such inadequate anemia management affects the outcome of CKD patients.

Acknowledgments This study was conducted by principal investigators at the following medical centers: Sendai Social Insurance Hospital (Miyagi), Toride Kyodo Hospital (Ibaraki), Jichi Medical University (Tochigi), Tokyo Women's Medical University Hospital (Tokyo), St. Luke's International Hospital (Tokyo), Showa University Hospital (Tokyo), Showa University Yokohama Northern Hospital (Kanagawa), Showa University Fujigaoka Hospital (Kanagawa), Gifu Prefectural General Medical Center (Gifu), Kasugai Municipal Hospital (Aichi), Tosei General Hospital (Aichi), Osaka University Hospital (Osaka), Osaka General Medical Center (Osaka), Osaka City General Hospital (Osaka), Kurashiki Central Hospital (Okayama), Fukuoka Red Cross Hospital (Fukuoka), Iizuka Hospital (Fukuoka).

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Hypertension Research (2011) 34, 1106–1110

www.nature.com/hr

ORIGINAL ARTICLE

Increased risk of cardiovascular events and mortality among non-diabetic chronic kidney disease patients with hypertensive nephropathy: the Gonryo study

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To examine the clinical significance of hypertensive nephropathy (HN) among non-diabetic chronic kidney disease (CKD) patients. The study comprised 2692 CKD patients recruited from 11 outpatient nephrology clinics; these included 1306 patients with primary renal disease (PRD), 458 patients with HN, 283 patients with diabetic nephropathy (DN) and 645 patients with other nephropathies (ONs). All patients fulfilled the criteria of CKD, with a persistent low estimated glomerular filtration rate (eGFR) $<60\,ml\,min^{-1}$ per $1.73\,m^2$ or proteinuria as determined by a urine dipstick test. The risk factors for cardiovascular disease (CVD), such as ischemic heart disease, congestive heart failure and stroke; all-cause mortality; and progression to end-stage renal failure (dialysis induction) were analyzed using a Cox proportional hazards model in each group. During a mean follow-up period of 22.6 months from recruitment, 100 patients were lost to follow-up and 192 patients began chronic dialysis therapy. A total of 115 CVD events occurred (stroke in 37 cases), and 44 patients died. Regarding CVD events and death, there were significant differences in the hazard ratios (HRs) for the groups of patients with different underlying renal diseases as determined by both univariate and multivariate analysis adjusted for confounding factors including estimated glomerular filtration rate: PRD, 1.0 (reference); HN, 3.33 (95% confidence interval, 1.82–6.09); DN, 5.93 (2.80–12.52); and ON, 2.22 (1.22–4.05). However, there were no differences in the hazard ratio for dialysis induction for the groups of patients with different underlying renal diseases. HN is associated with an increased risk of CVD events and death among non-diabetic CKD patients, which highlights the clinical significance of HN.
Hypertension Research (2011) **34**, 1106–1110; doi:10.1038/hr.2011.96; published online 28 July 2011

Keywords: cardiovascular disease; chronic kidney disease; hypertensive nephropathy

INTRODUCTION

Chronic kidney disease (CKD)[1] is a well-known independent risk factor for cardiovascular disease (CVD), including stroke, progression to end-stage renal failure and all-cause mortality in the general population.[2–8]

The relation between excess CVD morbidity and mortality, and decreased kidney function has been well demonstrated in diabetic patients[9,10] in specific sub-populations with preexisting heart disease,[11,12] hypertension[13] and dislipidemia,[14] and in the elderly.[15]

Patients with primary or secondary kidney diseases are exposed to several unique factors that increase the frequency of CVD events. These factors include hyperlipidemia and coagulopathy due to nephritic syndrome, systemic inflammation-associated vasculitides, underlying collagen or infectious disease, and the use of therapeutic agents such as steroids.[16–18] Even though patients with hypertensive nephropathy (HN, nephrosclerosis) are believed to be at high risk for progression to kidney failure,[19] the impact of HN on the frequency of CVD events compared with the impact of other nephropathies (ONs) has not been clearly demonstrated.

Accordingly, in terms of risk stratification of patients, it is crucially important to clarify the clinical outcomes of CKD with respect to the underlying renal diseases, especially for CKD cases that are not the result of diabetes. Only a few reports have examined this issue, including our preliminary report.[20–22]

The present study aimed to address this issue in a cohort of patients from nephrology clinics.

METHODS

Study population (Gonryo CKD cohort)

The Gonryo CKD project is a prospective survey of the patient characteristics and outcomes of individuals who visit outpatient nephrology clinics in the Miyagi Prefecture (Northeast area of Japan), the details of which have been

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Received 21 January 2011; revised 23 March 2011; accepted 11 April 2011; published online 28 July 2011

reported elsewhere.[22] Eleven affiliated hospitals with Tohoku University, including one university hospital (Tohoku University Hospital), are participating in the project. Patient registration was originally requested for all patients who provided informed consent for participation in the project. The study protocol was approved by the institutional review board of the Tohoku University School of Medicine and by the respective participating hospitals.

Registration was conducted from May 2006 to November 2008, and 4015 patients were registered. Among the original registered patients, certain subjects were excluded from the present analysis—150 cases lacking data on serum creatinine levels and 241 cases with unknown underlying renal diseases. Among patients with essential hypertension and estimated glomerular filtration rates (eGFRs) above 60 ml min^{-1} per 1.73 m^2, those who did not have positive proteinuria findings at registration (n=836) and those lacking urinary testing results (n=96) were excluded. As a result, 2692 patients with complete CKD criteria were selected[1] and were subjected to analysis.

Patient classification and primary outcomes

Patients were classified according to one of four underlying renal diseases diagnosed by the attending physicians at the participating hospitals (Table 1): primary renal disease (PRD), defined by primary glomerulonephritis and tubulointerstitial nephritis, including biopsy-proven cases (81%); HN, defined by a history of hypertension and the absence of other possible disorders, including cases of biopsy-proven nephrosclerosis (20.8%); diabetic nephropathy, defined by a history of diabetes accompanying nephropathy and the absence of other possible renal disorders or presenting with nephropathy with diabetic retinopathy and the absence of other possible renal disorders, including biopsy-proven diabetic nephropathy (24.9%); and ONs, defined by ONs not included in the other three groups, including biopsy-proven cases (24.9%). The HN cases included in the present classification were in those patients who had an eGFR below 60 ml min^{-1} per 1.73 m^2 or positive proteinuria as determined by a dipstick test.

The primary outcomes of this survey included CVD events, such as angina pectoris, acute myocardial infarction, congestive heart failure, stroke (cerebral bleeding and infarction), and all-cause death before commencement of chronic dialysis therapy. Outcomes within 12 months after registration were surveyed using the medical records of the hospitals, death certificates and interviews with attending physicians at the time of annual checkups. An episode of CVD was defined as disease of the circulatory system (International Classification of Disease, 10th revision: I00 to I99), and the number of patients with angina pectoris or acute myocardial infarction included those who had received coronary stenting, angioplasty or bypass surgery, or who had a definite clinical course of acute myocardial infarction. In patients with congestive heart failure, only those who were admitted for treatment were counted. Diagnosis of stroke and stroke subtypes was based on the Classification of Cerebrovascular Diseases III by the National Institute of Neurological Disorders and Stroke,[23] and only cases confirmed by computed tomography or magnetic resonance imaging of the brain were counted.

Table 1 Patient characteristics

	All	*PRD*	*ONs*	*HN*	*DN*
n	2.694	1.306	643	462	283
Age (years)	60.0 ± 16.2	55.7 ± 16.6	58.6 ± 15.7	70.3 ± 11.4	66.5 ± 12.6
Gender (male)	1441 (53.5%)	716 (54.8%)	275 (42.8%)	262 (56.7%)	188 (66.4%)
BMI	23.5 ± 3.8	23.4 ± 3.8	22.9 ± 3.7	24.2 ± 3.8	24.1 ± 3.8
Blood pressure (mmHg)					
Systolic	130.95 ± 16.2	129.21 ± 15.1	129.33 ± 15.8	134.68 ± 17.4	136.64 ± 17.5
Diastolic	76.7 ± 10.9	77.3 ± 10.4	76.7 ± 10.7	76.4 ± 11.8	74.0 ± 11.6
CKD stage (%)					
Stage 1+2	40.3	49.1	47.4	17.7	20.4
Stage 3	37.6	35.7	31.1	57.6	28.3
Stage 4	13.4	10.3	14.5	15.8	21.6
Stage 5	8.7	4.9	7.0	8.9	29.7
Comorbidities (%)					
Cardiac disease	12.8	7.5	12.3	21.2	24.7
Stroke	6.5	3.5	5.9	11.9	12.7
Diabetes	27.4	15.5	18.0	34.2	100.0
Hypertension	77.1	72.8	70.6	93.7	89.4
Hyperlipidemia	42.6	44.6	36.8	42.2	51.6
Pharmacotherapy (%)					
ARB/ACEI	62.7	62.1	52.6	70.1	76.3
Statin	34.7	36.1	30.0	32.3	43.1
ESA	6.5	3.6	4.8	7.8	21.9
Steroid	25.3	32.9	36.2	2.8	2.1
Proteinuria (%)	49.6	47.3	41.2	49.8	78.9
Hemoglobin (g dl^{-1})	12.8 ± 2.1	13.2 ± 1.9	12.6 ± 2.0	12.7 ± 2.1	11.6 ± 2.3
Total cholesterol (mg dl^{-1})	197.6 ± 38.7	198.7 ± 35.9	203.5 ± 41.3	190.99 ± 39.9	190.4 ± 41.4
Smoker (%)	16.2	15.8	14.6	16.2	21.6
Renal biopsy proven (%)	62.7	81.0	53.5	20.8	24.9
					mean ± s.d.

Abbreviations: ARB/ACEI, angiotensin receptor blocker/angiotensin-converting enzyme inhibitor; BMI, body mass index; DN, diabetic nephropathy; ESA, erythropoiesis stimulating agent; HN, hypertensive nephropathy; ONs, other nephropathies; PRD, primary renal disease.

Data collection

Serum creatinine levels were measured using the enzyme assay method. Kidney function was determined using the formula for eGFR for Japanese individuals.[24] Positive results for urinary protein were identified using the dipstick test for spot urine or an autoanalyzer. Patients were considered to be positive for macroalbuminuria when the dipstick result was positive or greater, corresponding to a urinary protein level $>30\,mg\,dl^{-1}$.[25] Blood pressure was measured at local medical centers in outpatient clinics using an automatic sphygmomanometer based on the Korotkoff sound technique with the subject in a seated position. Information on medications at baseline and each patient's history of CVD, diabetes mellitus, hypertension and hyperuricemia were obtained from the medical records or from the results of blood examinations at registration. Subjects receiving lipid-lowering drugs or displaying serum cholesterol levels $>220\,mg\,dl^{-1}$ were considered to have hypercholesterolemia. Subjects with fasting glucose levels $>126\,mg\,dl^{-1}$ or non-fasting glucose levels $>200\,mg\,dl^{-1}$ or who used insulin or oral antihyperglycemic drugs were defined as having diabetes mellitus.

Data analysis

Associations between primary outcomes and either baseline kidney function or underlying renal disease were examined using Cox proportional hazard model analysis adjusted for confounding factors.

Data are shown as means ± s.d. A *P*-value <0.05 indicated statistical significance. All statistical analyses were conducted using STATA version 10.0 software (StataCorp LP, College Station, TX, USA).

RESULTS

During an observation period of 22.6 ± 11.9 months, 100 patients were lost because of a switch to other medical services or to the patient quitting due to social reasons, and the follow-up of 192 patients was ended because of the initiation of maintenance dialysis therapy. There were 115 cases of CVD events (37 cases of stroke) and 44 cases of all-cause death (Table 2).

Table 2 Number of events

CKD stage	*CVD*	*Stroke*	*Death*	*ESRD*
Primary renal disease				
CKD1+2	2	1	1	—
CKD3	7	2	6	2
CKD4	2	1	2	8
CKD5	—	—	1	40
Hypertensive nephropathy				
CKD1+2	4	—	1	1
CKD3	12	8	6	—
CKD4	7	4	3	6
CKD5	3	2	3	24
Diabetic nephropathy				
CKD1+2	4	3	—	1
CKD3	7	1	3	1
CKD4	8	—	5	18
CKD5	10	3	4	54
Other nephropathies				
CKD1+2	2	7	2	—
CKD3	3	4	3	3
CKD4	6	1	4	9
CKD5	1	—	—	25

Abbreviations: CKD, chronic kidney disease; CVD, cardiovascular disease; ESRD, end-stage renal disease (dialysis induction).

In terms of CVD events and all-cause mortality, significant increases in hazard ratios were seen with increasing CKD stage using univariate analysis (Figure 1); however, these trends disappeared after multivariate adjustment (Table 3a). Significant differences in hazard ratios were seen with respect to underlying renal diseases using univariate analysis, and these differences were significant even after adjusting for confounding factors including eGFR (Table 3b).

Dialysis was started only for those patients who had a CKD stage 4 to 5 at the time of entry (Figure 2; CKD1+2: 0.2%, CKD3: 0.6%,

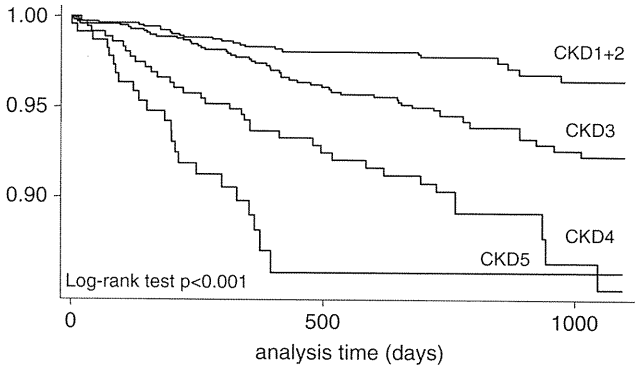

Figure 1 Event-free survival for cardiac disease, apoplexy and all cause of death for patients at different chronic kidney disease (CKD) stages.

Table 3a Risk for endpoints of CVD, stroke and death by CKD stage in all patients

				Univariate analysis		*Multivariate analysis*[a]	
CKD stage	*CVD*	*Stroke*	*Death*	*HR*	*95% CI*	*HR*	*95% CI*
CKD 1+2	12	11	4	1.00		1.00	
CKD 3	29	15	18	2.21	1.37–3.55	1.06	0.64–1.77
CKD 4	23	6	14	4.39	2.62–7.36	1.76	1.00–3.12
CKD 5	14	5	8	7.47	4.22–13.24	2.29	1.17–4.49

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease (such as angina pectoris, acute myocardial infarction and congestive heart failure); HR, hazard ratio.
[a]Adjusted for age, gender, hemoglobin, positive for proteinuria, systolic blood pressure, body mass index, presence of hyperlipidemia, presence of diabetes, prescription of steroid, smoker, history of cardiovascular disease or stroke, use of RAS (renin–angiotensin system) inhibitors.

Table 3b Risk for endpoints of CVD, stroke and death by underlying renal diseases in all patients

				Univariate analysis		*Multivariate analysis*[a]	
Underlying renal disease	*CVD*	*Stroke*	*Death*	*HR*	*95% CI*	*HR*	*95% CI*
PRD	11	4	10	1.00		1.00	
ONs	12	12	9	3.17	1.78–5.62	2.22	1.22–4.05
HN	26	14	13	7.12	4.18–12.14	3.33	1.82–6.09
DN	29	7	12	10.88	6.29–18.84	5.93	2.80–12.52

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; DN, diabetic nephropathy; HN, hypertensive nephropathy; HR, hazard ratio; ONs, other nephropathies; PRD, primary renal disease.
[a]Adjusted for age, gender, hemoglobin, positive for proteinuria, systolic blood pressure, body mass index, presence of hyperlipidemia, presence of diabetes, prescription of steroid, smoker, history of cardiovascular disease or stroke, use of RAS (renin–angiotensin system) inhibitors and estimated GFR (glomerular filtration rate).

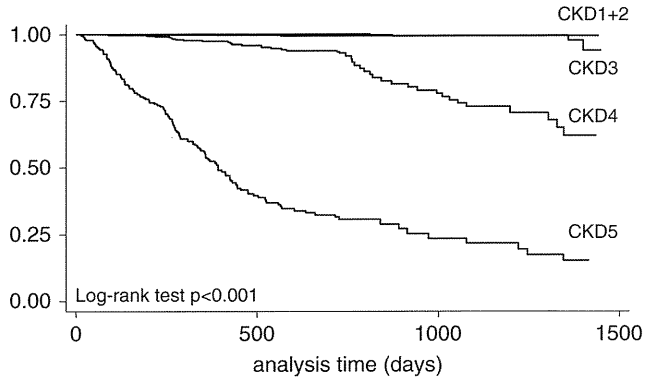

Figure 2 Event-free survival for progression to end-stage renal disease (dialysis induction) for patients at different chronic kidney disease (CKD) stages.

Table 4 Risk of progression to ESRD (dialysis induction) by underlying renal disease

Underlying		*Univariate analysis*		*Multivariate analysis*[a]	
Renal disease	*ESRD*	*HR*	*95% CI*	*HR*	*95% CI*
PRD	50	1.00		1.00	
ONs	37	1.43	0.94–2.19	1.11	0.70–1.76
HN	31	1.09	0.70–1.71	1.13	0.69–1.88
DN	74	5.25	3.66–7.53	1.25	0.68–2.28

Abbreviations: CI, confidence interval; DN, diabetic nephropathy; ESRD, end-stage renal disease; HN, hypertensive nephropathy; HR, hazard ratio; ONs, other nephropathies; PRD, primary renal disease.
[a]Adjusted for age, gender, hemoglobin, positive for proteinuria, systolic blood pressure, body mass index, presence of hyperlipidemia, presence of diabetes, prescription of steroid, smoker, history of cardiovascular disease or stroke, use of RAS (renin–angiotensin system) inhibitors and estimated GFR (glomerular filtration rate).

CKD4: 11.4%, CKD5: 61.1%), and no significant differences were observed with respect to underlying renal diseases after adjusting for confounding factors, including eGFR (Table 4).

DISCUSSION

This study aimed to clarify the impact of underlying renal diseases on CVD events and death before the initiation of dialysis treatment by analyzing the outcomes of 2692 CKD outpatients from 11 nephrology clinics. After 22.6 months of follow-up, there was a significant difference in the frequencies of CVD events and mortality among groups of patients with different underlying renal diseases, even after adjusting for possible confounding factors including kidney function. These findings showed that patients with HN represent a high-risk group, except for diabetic nephropathy patients, followed by ONs and PRD. In contrast, in terms of chronic dialysis induction, no significant differences were observed based on underlying renal diseases.

Both traditional and non-traditional mechanisms underlie the increased risk of CVD among CKD patients. Traditional factors include hypertension, diabetes, hyperlipidemia and smoking, whereas non-traditional factors include specific factors related to the uremic milieu, such as fluid overload, calcium/phosphate abnormalities, anemia, malnutrition, enhanced inflammation and oxidative stress, and the accumulation of uremic toxins.[26–34] Therefore, subjects with vasculopathy demonstrated by traditional factors are thought to undergo accelerated vascular damage along with progression of the CKD stage. Hypertension is a predominant risk factor for CVD in the general population, and it is logical that long-standing exposure to pathological conditions such as hypertension may have resulted in an increased frequency of CVD and mortality among non-diabetic subjects with HN. Several factors could have contributed to the better CVD outcomes in the group with PRD. First, half of the patients with PRD had immunoglobulin A nephropathy; glucocorticoid therapy does not increase the risk of CVD for these patients.[34] Blood pressure was also more adequately controlled in these patients than in patients in the other groups (Table 1). In addition, prevalent vasculopathy was not predominant in pre-dialysis PRD patients, as has been indicated for pediatric patients.[35,36] These results indicate that CKD staging cannot be applied on its own to predict which subjects are at high risk of CVD without taking into account the type of underlying renal disease. These results also suggest that individuals with HN should be the primary targets of CVD prevention measures among non-diabetic CKD patients.

In contrast, the present study revealed that the differences among underlying renal diseases did not have any influence on the frequency of the induction of dialysis after adjusting for confounding factors, including eGFR. In addition, dialysis induction was limited to subjects with CKD5. This result may confirm the clinical notion that CKD5 is the primary criterion for dialysis induction, as recommended in published guidelines.[37–39]

In the present study, several clinical issues that might have biased the analytical results must be considered. First, because all of the included patients were recruited from nephrology clinics, our patient selection may have introduced a bias toward relatively better medical compliance among those patients with modifiable factors, including the uremic milieu and blood pressure. Second, among patients with hypertension or diabetes, patients who had presented with proteinuria before entry into the study and who had responded to medical treatment thereafter were excluded from the study unless their eGFR was $<60\,ml\,min^{-1}$ per $1.73\,m^2$. Thus, the patients with diabetes or HN included in the present study may have been relatively resistant to conventional therapies. This resistance may have made their outcomes relatively worse, even though we adjusted for positive findings for proteinuria. Finally, data on microalbuminuria were not available in the present study. Because the clinical significance of microalbuminuria has been well demonstrated, further study is needed to determine the effect of microalbuminuria in these patients.

In conclusion, the present study demonstrated that patients with HN are at increased risk of CVD events and death among non-diabetic CKD patients, which highlights the clinical significance of HN.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

This study was supported by a grant from Astellas Pharm, Inc. The authors express special thanks to Mrs. Makiko Nakayama and Jun Sakaino for their assistance with the study.

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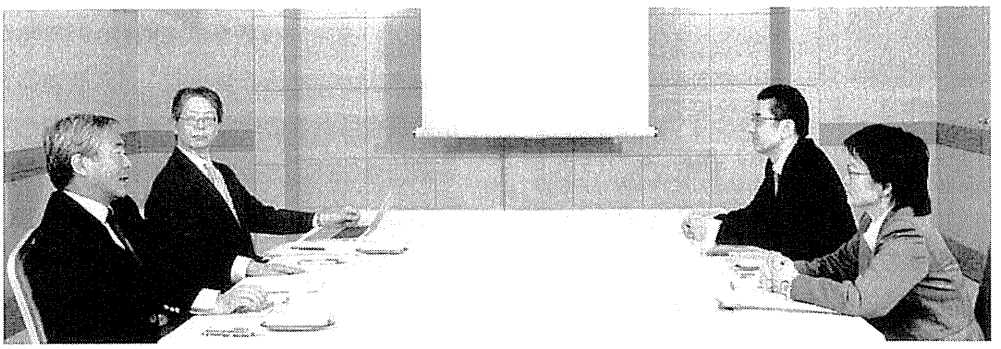
《座談会》

これからの静岡県のCKD治療戦略を考える



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磯﨑　泰介（社会福祉法人　聖隷福祉事業団　総合病院　聖隷浜松病院　腎臓内科/腎センター）

藤垣◆本日は，静岡県東部，中部，西部の基幹病院の腎臓内科の先生にお集まりいただき，CKD早期発見/治療を達成するための問題点，とくに腎専門医と一般内科医との認識の違いを議論することで，これからの静岡県におけるCKD治療戦略を考えたいと思います．

従来，慢性の経過をたどる腎疾患は治療法のないものとして考えられていましたが，早期発見/診断により，進行の抑制から臨床的寛解まで期待できることがわかり，その患者数の多さ，末期腎不全への進展，そして心血管イベントの合併抑制という観点から，CKDへの対策が全世界的に叫ばれています．

わが国では，かかりつけ医と腎専門医の病診連携によるCKD対策促進のために，2007年9月にCKD診療ガイドが出版され，CKDの概念はかなり定着したものと思われます．CKD治療においては，地域単位での対策と実践が最重要と考えられますので，かかりつけ医と腎専門医の連携は欠かせません．

CKDの早期発見のために

藤垣◆CKDとは，蛋白尿などの腎障害の存在を示す所見，もしくは，糸球体濾過量（GFR）60 m*l*/min/1.73 m^2未満の状態が3ヵ月以上持続する状態と定義されます．また，GFRのレベルによるCKD病期分類がなされ，病期ごとの対策が推奨されています．

CKDの診断と管理・治療のための検査オーダーの必須項目として，尿試験紙法による尿蛋白定性と尿潜血反応，随時尿における尿蛋白定量とクレアチニン（Cr）定量，そして血清Cr値があります．腎専門医と一般内科医ではCKD早期発見のための認識に違いがあると思いますが，CKD診断の検査項目と実施状況，そしてCKD診断検査実施のタイミング，また，eGFR算出の重要性の認識などについて，各地区での実情やご意見をうかがいたいと思います．はじめに，静岡東部地区の米村先生，こ

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の点に関していかがでしょうか.

米村◆一般の先生方のなかには，今までの慢性腎不全がCKDという名称に変わったという認識しかなく，CKDが動脈硬化性疾患のリスクであるということをあまり認識されていない方も多いのではないでしょうか．一般の先生方におけるCrや検尿の検査項目や実施状況はわかりませんから，潜在的なCKD患者数も正確に把握できていないと思います.

藤垣◆中部地区の森先生，いかがでしょう.

森◆一般内科を受診されていて，腎機能が低下している患者さんを人間ドックの先生が見つけ出し，当院に紹介してくれていますが，それはCKD患者全体の氷山の一角で，われわれはその氷山の一角を診療しているにすぎないと考えています．やはりCKDの患者数にはかなり目こぼしがあるのではないでしょうか.

ただ，CKDのキャンペーンによって，周知度は上がっていると思います．静岡地区で送られてくる患者さんのデータはほとんどeGFRが算出してありますので，一般内科医の先生方の更なるCKDへの理解が重要になると思います.

藤垣◆県西部の磯崎先生，いかがでしょうか.

磯崎◆CKDの定義からもわかるように，腎障害の所見がある群，eGFRが低下し慢性腎不全の状態となった群，それぞれをわれわれは相手にしています．検尿異常やCrの軽度上昇の所見で，早期介入をおこなうことでステージの進行を根本的に阻止できる症例が，現在のCKDでは周知徹底されていない可能性があり，われわれ腎臓内科医も注意する必要があります.

CKD診療ガイドでは蛋白尿2+以上または尿潜血・尿蛋白がともに1+以上で専門医への紹介を推奨していますが（**図1**）[1]，1999年からの11年間での腎生検327例を解析したところ，後者の紹介は比率として多くはありません．つまり，慢性腎炎で遭遇する頻度が最も高いIgA腎症の発見は少し遅れている印象を受けます.

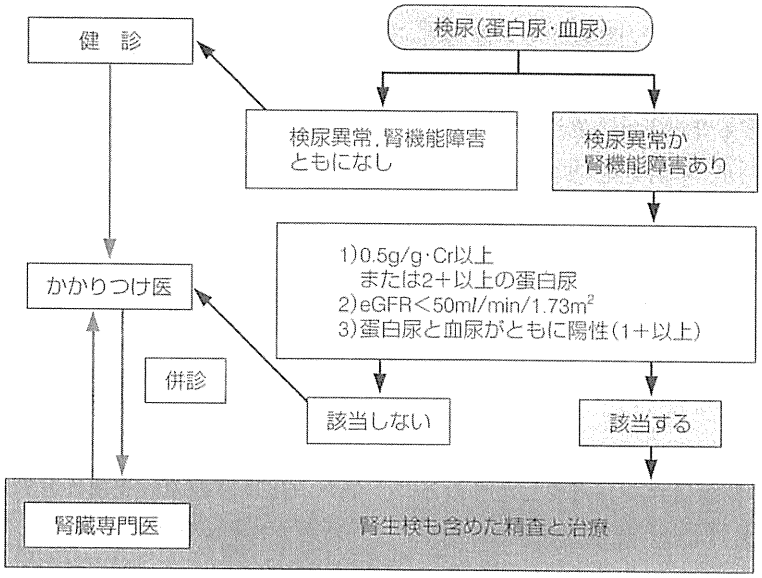

図 1. CKDの診療連携システム案
（日本腎臓学会編，2009[1]より引用）

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藤垣◆eGFRは，各検査会社，基幹病院内の検査室など，かなりのところで自動的に算出し報告されていますが，問題はそれを一般内科医の方が認識されているかということです．さらに，CKDの対策にあたり尿蛋白/Cr比という概念が導入されているわけですが，CKDの検査値に対する一般内科医の認識はいかがでしょうか．

米村◆eGFRに関しては先生方によって温度差があります．ただし，eGFRには問題点もあり，高齢者で筋肉量の少ない人は高値を示し，筋肉量のある若い人では低めになるなど筋肉量による影響を受けます．eGFRは指標として現時点では最も簡便な方法だと思いますが，やはり完全なものではないので，それ以外の方法も考慮するべきだろうと思います．たとえば当院では全例24時間蓄尿をし，クレアチニン・クリアランス（CCr）を算出しています．

また，開業の先生方は蛋白尿のCr比の概念をあまりご存じないようで，尿蛋白2+や3+という状態で紹介されてくる患者さんが非常に多いですね．

森◆私の施設でもやはり尿蛋白/Cr比の概念なしで患者さんを紹介されることが多いです．当院の病診連携のチャート中には，随時のCr定量と蛋白の定量を書く項目を作ってあるのですが，連携のなかで開業医の先生に尿蛋白/Cr比の重要性を認識していただきたいと考えています．

磯﨑◆私は紹介状で「次回は蓄尿してCCrをみます」とか「蛋白尿をみさせていただき，0.5 g/g·Cr以上あれば腎生検しますよ」とお伝えすることで，そのかかりつけ医にCKD診断の道筋を示すことができればと考えています．また，当院では「腎臓いきいき手帳」というものを作り，それに蓄尿も含めたすべてのデータを記載し，かかりつけ医の先生との連携パスのかわりに使用しています．これは，実際にeGFRと蓄尿のCCrを併記することによって，その違いに注目してもらうことを目的としています．

CKD治療における実践的な病診連携のあり方

藤垣◆さて，わが国の成人人口におけるCKD患者数は約1,330万人と推計され，この数多い患者さんを的確に診療していくためには，かかりつけ医と腎専門医との病診連携が欠かせません．ここでは腎専門医への紹介タイミングや腎専門医の立場からの実践的な病診連携についてのご意見をうかがいたいと思います．まず森先生のご施設での病診連携についてはいかがでしょうか．

森◆基本的には，CKD診療ガイドに沿った形の連携をめざしていますが，ご高齢の方ではeGFR 50 ml/min/1.73 m^{2}以下ですと，ほとんどが紹介の適応となってしまい，大変なことになります．しかし，eGFR 30 ml/min/1.73 m^{2}以下ですと心疾患などの合併症が非常に多くなりますので，eGFR 40 ml/min/1.73 m^{2}以下での紹介をお願いしています．実際，当院に紹介される患者さんでは悪性腫瘍を含め合併症が多く見つかります．その後ずっと病診連携でフォローするかどうかは各症例に応じて決定しています．

藤垣◆CKDの患者さんを腎専門医に紹介するタイミングを計る指標として，半数以上の一般内科医がeGFRをあげています（**図2**）[2]．しかし，CKDの基準をeGFR60ml/min/1.73 m^{2}以下としますと高齢者のCKDは膨大な数になりますから，ここ1年間世界の趨勢をみても，高齢者のeGFRの判断基準をどうするかは議論の的になっています．

磯﨑先生はかかりつけ医の先生との病診連携，院内連

【森　典子先生】

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携ともに積極的にやっておられますが，その点に関していかがでしょうか．

磯﨑◆浜松市の医師会は連携に非常に積極的で，2007年から浜松医科大学の第一内科と急性期病院である当院と医師会の3者で，CKD浜松地区病診連携委員会を立ち上げました．浜松地区のかかりつけ医のうち，当院では約40%の200人くらいの先生と連携しています．

この11年間で，連携先，紹介患者数ともに大幅に増加していますが，専門医の人数はほとんど変わりませんから紹介の患者さんを全部引き受けることは困難です．そこで当院ではスクリーニング，生活習慣指導，処方薬などを決めた後，相当数の患者さんを逆紹介しています．そして当院では定期的に，生活習慣指導や検査をフォローアップして，双方向的連携をおこなっています．

また，腎機能の低下とともに，腎専門医への来院の期間を短くすることで，患者さんへも病態の進行度を理解していただいています．腎機能が2割を切るCKDステージ4から5への移行段階では，腎専門医が透析導入を考慮し，患者さんと相談しながら治療をおこなうことで透析導入に向けて心と体の準備をしながら，円滑に透析導入していくシステムを作っています．

藤垣◆従来，専門医とかかりつけ医の双方向連携という考え方はなかったかと思いますが，森先生のご施設ではいかがですか．

森◆当院では，原則全例紹介制の外来ですので，今はかかりつけ医の先生を主体にする患者さんがほとんどです．専門医では専門医でしかできないことをしてお返しするというスタンスで，患者さんにもご理解いただいています．

かかりつけ医の先生が連携によってCKD診療への理解を深め，実臨床に活かすことができればよいのですが，

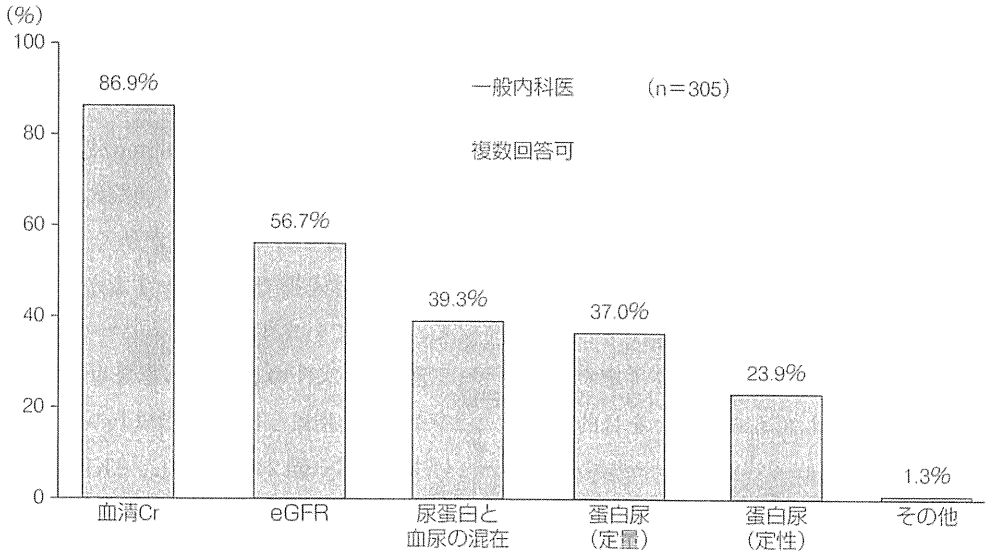

図2．CKD患者を腎専門医に紹介する際に参考にする指標
対象：一般内科医（「内科」を第一標榜とし，20床未満の医療機関に勤務し，かつ高血圧症症例を月10例以上診察している医師）
腎専門医（腎臓内科を第一標榜とし，かつ透析患者が全症例の半分以下である医師）
（槇野博史，2010[2]より引用）

実際は症例ごとに患者さんの背景は異なりますのでなかなかむずかしいかと思います．ですので，私の場合処方や検査について毎回具体的にお願いをしています．多少，手間がかかりますが，医師会の先生方の腎臓診療に対する理解度や知識を向上していただくための，基幹病院の宿命として多少の負担はいたし方ないと思います．

藤垣◆かかりつけ医の先生および患者さん双方がメリットを感じるような病診連携のあり方というのが必要であるということですね．

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【磯﨑泰介先生】

高血圧合併CKDの降圧治療

藤垣◆高血圧はCKDの原因かつ増悪因子ですので，CKD治療の中心は降圧療法です．高血圧合併CKD診療では，厳格な降圧目標として130/80 mmHg未満が設定され，第一選択薬にレニン・アンジオテンシン（RA）系抑制薬の使用が推奨されています．また，多くの場合多剤併用が必要となること，降圧と同時に蛋白尿の減少をめざすことが基本とされています．

RA系抑制薬によるCKD進行抑制は蛋白尿減少効果に依存するとされ，尿蛋白減少が十分でない場合には最大投与量までの増量が推奨されています．実際ロサルタンでは，50 mgから100 mgへ増量することで，降圧に関係なく尿中アルブミンの更なる減少が報告されています[3]．

一方，RA系抑制薬への追加薬として，第二選択薬はCa拮抗薬と利尿薬が推奨されています（**図3**）[4]．たとえばGFR30ml/min以上ある場合にサイアザイド系利尿薬を処方することで，ナトリウム（Na）再吸収抑制，循環血液量の減少，末梢血管抵抗の減少による降圧が期待されます．副作用としての低カリウム（K）血症，耐糖能低下，高尿酸血症は，少量の利尿薬であればあまり問題にならないとのデータもあります．

CKDやその背景疾患であるメタボリックシンドローム，糖尿病，高齢の患者では，食塩感受性が高く，RA系抑制薬と利尿薬の併用は理にかなっているといえ，夜間高血圧を改善する効果も認められています．さらに，2

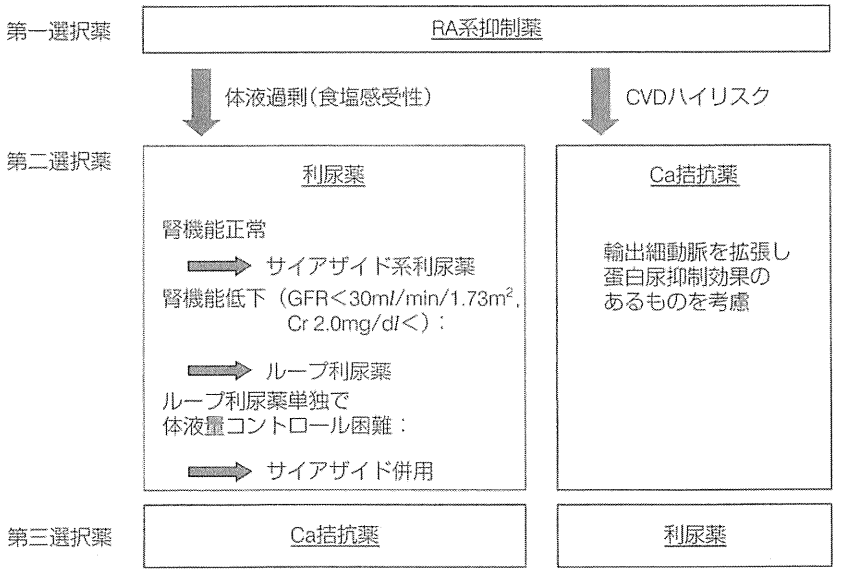

図3．CKDの高血圧治療の進め方
（日本腎臓学会・日本高血圧学会編，「CKD診療ガイド高血圧編」[4]より引用）

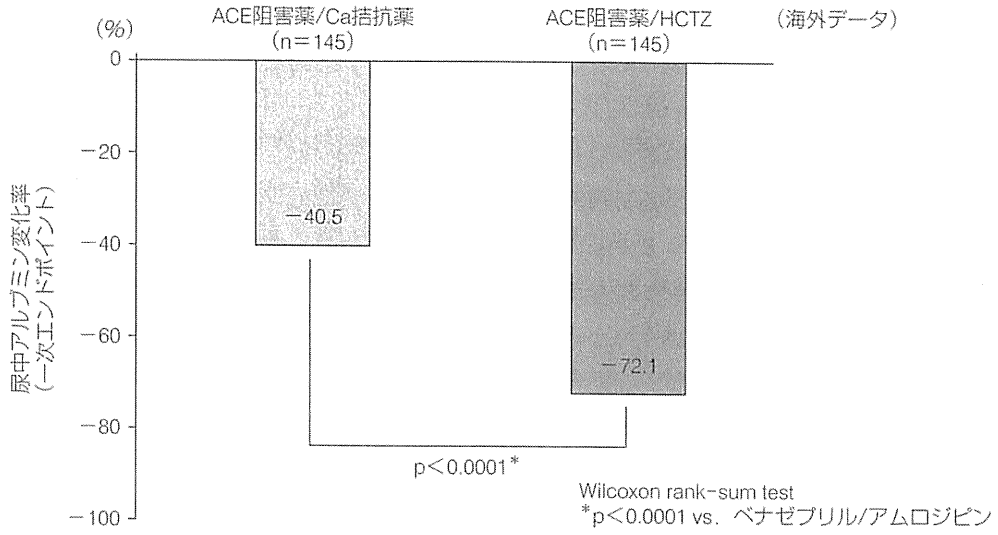

図 4. RA 系抑制薬/利尿薬による腎保護効果
対象：2 型糖尿病を合併した高血圧症患者 294 例
方法：ベナゼプリル 20 mg/アムロジピン 5 mg またはベナゼプリル 20 mg/ヒドロクロロチアジド（HCTZ）12.5 mg から治療を開始し，130/80 mmHg に達しない場合は増量，または他の降圧薬を追加し 52 週間投与した．
一次エンドポイント：尿中アルブミン/Cr 比，降圧効果，アルブミン尿の正常化
（Bakris GL *et al*, 2008[5] より引用）

型糖尿病を合併しアルブミン尿を有する高血圧患者を対象とした GUARD 試験（Gauging Albuminuria Reduction with Lotrel in Diabetic Patients with Hypertension）では，RA 系抑制薬と少量利尿薬を長期間投与することにより，腎障害の指標である尿中アルブミン量の約 72% の低下がみられています．アルブミン尿の減少効果は，RA 系抑制薬と少量利尿薬併用群で，Ca 拮抗薬アムロジピン併用群よりも有意に大きく，腎保護効果がすぐれる可能性が示唆されています（**図 4**）[5]．

近年，利尿薬の有用性の再認識とともに，ARB と利尿薬との配合剤が使用できるようになりましたが，高血圧合併 CKD の治療における RA 系抑制薬の増量，利尿薬・Ca 拮抗薬を追加すべきケースなどについて先生方のご意見をお願いしたいと思います．

米村◆ARB は CKD 治療の第一選択薬として勧められていますが，使用には二つの条件があると私は考えています．血清 K が 4.8 mEq/*l* 以下であるということが一つ．もう一つは，紹介された患者さんや，腎機能の悪い患者さんに対しては必ず CT で腎臓のボリュームや，下部尿路，腎動脈起始部の石灰化を確認し，狭窄の有無をしっかりみるということです．

藤垣◆K の値ですと，かかりつけ医の先生も測定すればすぐにわかるということですが，その他の項目に関しては，なかなか見極めがむずかしいと思います．そのへんはかなりハードルが高いですね．磯崎先生はいかがでしょうか．

磯﨑◆当院では CT まではやっておりませんが，初診で全例にエコーをおこない狭窄がなければ，RA 系はファーストチョイスで使います．また，K の値ももちろん考慮しますが，K が上がった場合，消化管出血やアシドーシスなど薬以外で K を上げる要因の有無を判断したうえで，食事療法で K 制限をかけるなどしてできるだけ RA 系抑制薬を続行するようにします．

藤垣◆森先生のご施設では，どのような治療をされていますか．

森◆当院にいらっしゃるのは全例紹介患者さんですし，人間ドックからいらっしゃる患者さんもかかりつけ医をもっておりますので，すでに RA 系抑制薬が処方されていることが多いです．ですから，われわれのところではそちらを増量するか，あるいは Ca 拮抗薬か利尿薬を併用するかというところを判断して，かかりつけ医の先生にお返しするような形になっています．

藤垣◆先生のところでは，蛋白尿を減らすために，血圧に関係なくARBを増量することはありますか．

森◆しばしばありますね．

藤垣◆高食塩摂取の状態では，血圧だけではなく内皮細胞障害への影響なども示唆されていますね．CKD治療には長期のフォローアップが必要であり，厳格に降圧することが重要であると考えられます．磯﨑先生，どうでしょうか．

磯﨑◆2004年に，当科を外来受診している糖尿病性腎症60人の血圧と食塩感受性を調べました．収縮期血圧を130～140 mmHgにコントロールするのに必要な降圧薬の平均投与数は2.4剤でした．糖尿病性腎症ではとくに，血圧のコントロールに難渋することが多いといえます．

その方々の蓄尿を調べますと，収縮期血圧と食塩摂取量にはきれいな相関関係がみられ，食塩感受性による収縮期血圧への影響は明らかでした．したがって，利尿薬によるNaの排出は有用であると考えられます．また，糖尿病性腎症では，インスリン抵抗性や浮腫を伴うことが非常に多く，こうした例では少量の利尿薬を積極的に使用する必要があります．

藤垣◆CKD合併高血圧では処方される降圧薬の種類が多い傾向にありますが，ARB/HCTZの合剤も臨床で使用できるようになっています．CKDでは降圧薬以外の薬剤も多く処方されており，薬剤数が減ることによる服薬コンプライアンスの向上というメリットなども考えられます．CKD患者さんに合剤を使用する場合，留意すべき点はございますか．

森◆合剤への切り替えの際には，残薬をおもちの患者さんの場合，前の薬剤と一緒に服用してしまう可能性もあるので注意が必要ですね．

磯﨑◆とくに腎専門医では，ステージが進んで体液管理・血圧管理がむずかしい患者さんを相手にすることが多く，調節することが多いので合剤の処方は慎重になると思います．ただし，かかりつけ医レベルでは，ステージが比較的若く腎機能も比較的予備力がある人を診察されることが多いので，剤数を増やすことなくそういう方の治療ができるという点がメリットだと考えます．

そのうえで，先ほどの季節性の問題や摂食量，体液量を考慮して，臨機応変な処方が必要になるのではないでしょうか．専門医とかかりつけ医の先生で密な連携をすることが大事だと考えます．

藤垣◆そうですね．合剤に関しては，われわれ腎専門医もその効果的な使い方を考える必要があるということでしょうか．

本日は，基幹病院の腎臓内科の立場から，静岡各地，施設の事情なども交えて議論していただきました．

基本的には，どの場所で発生したCKD患者さんも，今ある医療を平等に受けることができるということが，われわれの願いかと思います．本日の議論が，静岡県でのCKD対策をどのように考えるかということのきっかけとなれば幸いです．本日はどうもありがとうございました．

（2010年10月　静岡）

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提供：MSD株式会社

Clin Exp Nephrol (2011) 15:535–538
DOI 10.1007/s10157-011-0446-9

ORIGINAL ARTICLE

Measurements of serum cystatin C concentrations underestimate renal dysfunction in pediatric patients with chronic kidney disease

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Received: 24 January 2011 / Accepted: 24 March 2011 / Published online: 21 April 2011

Abstract
Background In our clinical experience, cystatin C (CysC) concentrations are not as high as expected in patients with chronic kidney disease (CKD) and high-stage renal dysfunction. We therefore investigated whether measurements of serum CysC result in an underestimation of renal dysfunction in pediatric patients with CKD.
Methods Glomerular filtration rate (GFR) was estimated from serum creatinine (Cr) concentration, using the equation Cr-GFR (%) = [0.30 × body length (m)/serum Cr] × 100; and from serum CysC concentration, using the equation Cys-GFR (%) = (0.70/serum CysC) × 100. We investigated the relationship between GFR estimated by these 2 equations. Patients aged 2–12 years were assorted into 5 groups, based on GFR-Cr categories of <12.5, ≥12.5 to <25, ≥25 to <50, ≥50 to <75, and ≥75%, and GFR-CysC/GFR-Cr ratios were compared in these 5 groups.
Results The median GFR-CysC/GFR-Cr ratio in groups of patients with GFR-Cr of <12.5, ≥12.5 to <25, ≥25 to <50, ≥50 to <75, and ≥75% were 2.28, 1.48, 1.22, 1.18 and 0.98, respectively, with statistically significant differences between any two groups ($p < 0.001$).
Conclusion Measurements of serum CysC concentrations lead to underestimation of renal dysfunction in pediatric patients with CKD.

Keywords Serum cystatin C level · Pediatric chronic kidney disease · CKD · Renal dysfunction

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Introduction

Glomerular filtration rate (GFR) reflects kidney function, and is measured by renal clearance techniques. Inulin clearance is the gold standard for evaluating kidney function, but it cannot be measured easily. Therefore, various other methods are used to determine kidney function.

We previously observed a significant positive correlation between serum creatinine (Cr) concentration and body length in children aged 1–12 years, with body length (m) × 0.30 yielding a value similar to the reference serum Cr concentration [1]. An equation for estimated GFR (eGFR) has been used to assess the relationships among body length, glomerular filtration rate (GFR), and serum Cr concentration, using the equation eGFR (ml/min/1.73 m^2) = κ × body length (cm)/serum Cr value (mg/dl) [2], where the constant κ was assumed to be unvaried in children aged 2–12 years. This equation indicates that at constant body length, GFR is in reciprocal proportion to serum Cr concentration. Serum Cr concentration can be determined as body length (m) × 0.30 if GFR is 100%, therefore eGFR (%) = [0.30 × body length (m)/serum Cr] × 100.

We have also found that reference serum cystatin C (CysC) concentrations gradually decrease during the year after birth, with slightly higher concentrations in 1 year olds (0.76 ± 0.10 mg/L) than in children aged ≥2 years (0.70 ± 0.09 mg/L), and serum CysC concentrations are

relatively constant in children aged ≥2 years [3]. The reciprocal of CysC concentration may therefore correlate with GFR as well or better than the reciprocal of serum Cr [4]. Thus, eGFR may be derived from serum CysC concentration using the equation eGFR (%) = (0.70/serum CysC) × 100. In our clinical experience, however, CysC levels are not as high as expected in chronic kidney disease (CKD) patients with high-stage renal dysfunction. We therefore investigated whether measurements of serum CysC concentrations result in an underestimation of renal dysfunction in pediatric CKD patients.

Materials and methods

We included a total of 199 children (114 males and 85 females), aged 2–12 years, who had been admitted to or attended the outpatient clinic of Aichi Children's Health and Medical Center between December 2003 and February 2008 for CKD, but had not undergone dialysis or renal transplantation.

Patients from whom consent was not received for inclusion of specimens in a clinical report were excluded. Data on serum Cr values, serum CysC values, and body length measured in daily laboratory tests were reviewed.

Serum Cr concentrations were determined by an enzymatic method, using a Hitachi 7170S automated analyzer (Hitachi High-Technologies Corp.) with Accuras Auto antibody (Shino-Test Corp.). The coefficients of inter- and intra-assay variance were satisfactory (1.31 and 1.80%, respectively).

Serum CysC concentrations were also determined using the Hitachi 7170S automated analyzer and a latex agglutination turbidimetric method (Mitsubishi Chemical Medience Corp.). The coefficients of inter- and intra-assay variance were satisfactory (1.14 and 1.25%, respectively).

We utilized two equations for eGFR [1–4]. In children aged 1–12 years, body length (m) × 0.30 yielded a value similar to the reference serum Cr concentration measured enzymatically [1]. Since the reciprocal of serum Cr correlated with GFR [2, 5, 6], we utilized an equation for eGFR derived from serum Cr

$$\text{Cr - GFR}\ (\%) = [0.30 \times \text{body length (m)}/\text{serum Cr}] \times 100.$$

We also found that normal children aged ≥2 years have relatively constant serum CysC concentrations (0.70 ± 0.09 mg/L) [3]. Since the reciprocal of CysC correlated with GFR [4], we utilized an equation for eGFR derived from serum CysC

$$\text{Cys - GFR}\ (\%) = (0.70/\ \text{serum CysC}) \times 100.$$

The relationship between values obtained from these two equations was plotted by scattergram. Patients were assorted into five CKD stage groups by Cr-GFR, i.e., Cr-GFR <12.5, ≥12.5 to <25, ≥25 to <50, ≥50 to <75, and ≥75%, thought to be approximately equal to an international CKD stage classification, and the GFR-CysC/GFR-Cr ratio was compared among these 5 groups.

Spearman's rank correlation and Mann–Whitney's U test were used for statistical comparisons, and $p < 0.01$ was regarded as statistically significant.

Results

The demographic and clinical characteristics, including any underlying illnesses, of the patients are shown in Table 1. The correlation between GFR-Cr and GFR-CysC in all subjects was compared with a line with a slope of 1.0 that passed through the origin (Fig. 1). In CKD patients with high-stage renal dysfunction, the GFR-CysC levels were generally higher than this line. We therefore compared GFR-CysC/GFR-Cr ratios in five groups of patients at different CKD stages, as assessed by GFR-Cr percentages (Table 2). We found that the median GFR-CysC/GFR-Cr in pediatric patients with GFR-Cr <12.5, ≥12.5 to <25, ≥25 to 50, ≥50 to <75, and ≥75% were 2.28, 1.48, 1.22, 1.18 and 0.98, respectively, with significant differences between any two groups ($p < 0.001$). The

Table 1 Patient characteristics

	Total (n = 199)
Male, n (%)	114 (60.0)
Age (years), median (range)	7 (2–12)
Underlying illness, n (%)	
Vesicoureteral reflux	27 (13.6)
Renal hypoplasia/dysplasia	23 (11.6)
Hydronephrosis	17 (8.5)
Minimal change nephritic syndrome	16 (8.0)
Nephritis	14 (7.0)
IgA nephropathy	11 (5.5)
Neurogenic bladder	9 (4.5)
Reflux nephropathy	9 (4.5)
Megaureter	8 (4.0)
Focal segmental glomerulosclerosis	7 (3.5)
Alport's syndrome	6 (3.0)
Hematuria syndrome	4 (2.0)
Henoch–Schönlein purpura nephritis	4 (2.0)
Autosomal recessive polycystic kidney disease	3 (1.5)
Branchio-oto-renal syndrome	3 (1.5)
Membranoproliferative glomerulonephritis	3 (1.5)
Membranous nephropathy	2 (1.0)
Nephronophthisis	2 (1.0)
Others	31 (15.6)

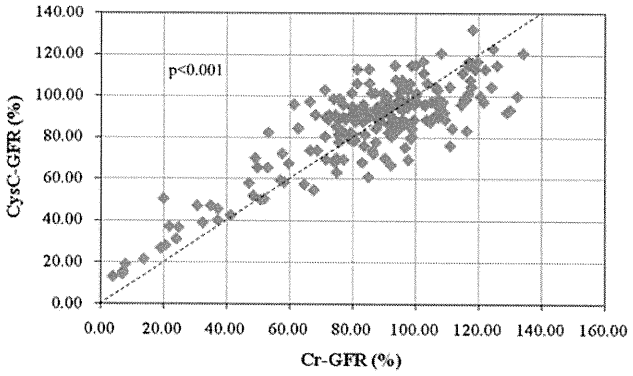

Fig. 1 Correlation between GFR-Cr and GFR-CysC in all subjects. The *dashed line* represents a line with a gradient of 1.0 passing through the origin

Table 2 GFR-CysC/GFR-Cr in five CKD stage groups by GFR-Cr categories

GFR-Cr	*n*	Median (GFR-CysC/GFR-Cr)
<12.5%	4	2.28
≥12.5 and <25%	7	1.48
≥25 and <50%	10	1.22
≥50 and <75%	28	1.18
≥75%	150	0.98

Significant difference between any two groups ($p < 0.001$)

relationships between GFR-Cr strata and GFR-CysC/GFR-Cr are shown in box-and-whisker plots in Fig. 2. The boxes are drawn around the quartile values, and the whiskers extend from each quartile to the smallest and largest observed values. The GFR-CysC/GFR-Cr ratio exceeded 1.0 more often in CKD patients with high-stage renal dysfunction.

Discussion

True measurements of GFR using the inulin clearance method are impractical as a regular monitoring tool. This method is complicated, requiring timed urine collections and frequent blood samplings. It is difficult to obtain timed urine collections from young children because of the physiological immaturity of their bladder function, and this method is even more difficult in children with bladder dysfunction. Therefore, easy, reproducible and precise surrogate methods are needed to measure GFR.

It is necessary to set standard serum Cr and CysC measurements for the medical care of pediatric CKD patients. We previously reported a significant positive correlation between serum Cr concentration and body length in children aged 1–12 years, showing that body

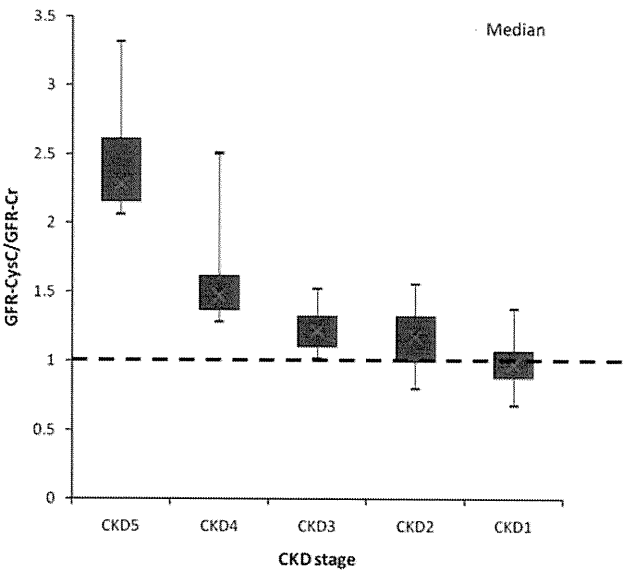

Fig. 2 Relationships between GFR-Cr strata and GFR-CysC/GFR-Cr. *Box-and-whisker* plots of the relationships between GFR-Cr strata and GFR-CysC/GFR-Cr, with significant differences between any two groups ($p < 0.001$). The *boxes* are drawn around the quartile values, and the *whiskers* extend from each quartile to the smallest and largest observed values

length (m) × 0.30 yielded a value similar to the reference serum Cr [1]. In addition, we reported that reference serum CysC concentrations gradually decrease during the year after birth, with slightly higher concentrations in 1 year old children (0.76 ± 0.10 mg/L) than in children aged ≥2 years (0.70 ± 0.09 mg/L) [3].

Although the correlation between reciprocal serum CysC concentration and GFR was reported equivalent to the correlation between serum Cr and GFR, we observed clinically that CysC concentrations were not as high as expected in CKD patients with high-stage renal dysfunction. We therefore determined whether measurements of serum CysC concentrations underestimate renal dysfunction in pediatric CKD patients.

Since the reciprocal of serum Cr has been found to correlate with GFR [2, 5, 6], we defined Cr-GFR (%) as [0.30 × body length (m)/serum Cr] × 100 in children aged 1–12 years. If we assume that the reciprocal of CysC is correlated with GFR, we could define Cys-GFR (%) as (0.70/serum CysC) × 100 at the age of 2 years or over. We compared these two estimated GFR equations by scattergram and by examining the GFR-CysC/GFR-Cr ratio in five groups of patients with CKD stages defined by GFR-Cr. We found that the GFR-CysC/GFR-Cr ratio exceeded 1.0 more often in CKD patients with high-stage renal dysfunction and that there were significant differences between any two groups. If we assume a simple reciprocal relationship between CysC and GFR, serum CysC concentrations lead to underestimations of renal

dysfunction compared with serum Cr in pediatric patients with CKD. At present, the reasons that serum CysC concentrations levels are not as high as expected in CKD patients with high-stage renal dysfunction are unclear. It has been reported that elevation of the serum CysC level slowed down for high-stage adult CKD patients. The existence of non-renal clearance of CysC is indicated and the magnitude is about 20 ml/min/1.73 m^2 in humans [7], which may explain the results in this study.

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Clin Exp Nephrol (2011) 15:694–699
DOI 10.1007/s10157-011-0452-y

ORIGINAL ARTICLE

Age, gender, and body length effects on reference serum creatinine levels determined by an enzymatic method in Japanese children: a multicenter study

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Received: 8 March 2011 / Accepted: 6 April 2011 / Published online: 21 April 2011

Abstract
Background Enzymatic methods have recently been used to measure creatinine (Cr) instead of the Jaffe method. Therefore, it is necessary to determine the reference serum Cr value for these enzymatic methods to evaluate renal function in Japanese children.
Methods To determine reference values of serum Cr in Japanese children, 1151 children (517 male, 634 female) aged between 1 month and 18 years had their serum Cr values measured by an enzymatic method. To be included in the study the children had to be without kidney disease, urogenital disease, infectious disease, inflammatory disease, dehydration, muscular disease, anomaly syndrome, cardiovascular disease, malignant disease, hypertension, liver or pancreas disease, or pregnancy.
Results The medians of reference values increased gradually with age, i.e., 0.30 mg/dl at 4 years old and 0.41 mg/dl at 10 years old. In adolescence, they increased significantly more rapidly in males than in females. We found a linear regression equation capable of estimating the reference value of serum Cr in children aged 2–11 years, and quintic regression equations capable of estimating the reference values of serum Cr in male and female children of all ages.
Conclusion The reference serum Cr levels determined by an enzymatic method related to age, gender, and body length, and our linear and polynomial equations showing the relationship between body length and serum Cr level will be applicable for screening of renal function in Asian as well as Japanese children.

Keywords Reference serum creatinine level · Japanese children · Enzymatic method · Body length · eGFR

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Introduction

Serum creatinine (Cr) levels are generally proportional to muscle mass and inversely proportional to renal function. Therefore, they are lower in infancy, and increase gradually with growth. Schwartz et al. [1] expressed the relationship between body length, glomerular filtration rate (GFR), and serum Cr level as estimated GFR (eGFR; ml/min/1.73 m^2) $=\kappa \times$ body length (cm)/serum Cr value (mg/dl). The coefficient κ is 0.33 in preterm infants under 1 year old, 0.45 in full-term infants under 1 year old, 0.55 in children 2–12 years old, and 0.55 and 0.70 in females and males over 12 years old [1–4].

This formula is clinically useful as it allows estimation of the normal serum Cr level from the patient's body length. This equation utilizes the Jaffe method to measure Cr; however, enzymatic methods have recently been used to measure Cr, making the above formula no longer applicable. In 2009, the updated Schwartz formula was reported as follows: eGFR (ml/min/1.73 m^2) $= 0.413 \times$ body length (cm)/serum Cr value (mg/dl) by enzymatic Cr determination in children 7.7–14.3 years old [5].

It would be beneficial to obtain a reference serum Cr value by an enzymatic method in Japanese children according to sex and age for renal function evaluation in routine practice. We also attempted to derive a formula to estimate reference serum Cr values in Japanese children as a function of body length, based on the Schwartz formula: i.e., normal serum Cr value (mg/dl) = $k \times$ body length (m) in subjects aged 2–11 years, and to derive polynomial formulae to estimate reference serum Cr values as functions of body length in males and females between 1 month and 18 years old.

Materials and methods

A total of 1151 children (517 male and 634 female) between the ages of 1 month and 18 years presenting at the facilities of the members for the Committee of Measures for Pediatric Chronic Kidney Disease (CKD) and Tokyo Health Service Association between 2008 and 2009 were included in the study. The children had to be without kidney disease, urogenital disease, infectious disease, inflammatory disease, dehydration, muscular disease, anomaly syndrome, malignant disease, hypertension, cardiovascular disease, liver or pancreas disease, or pregnancy. The study was approved by the local ethics boards, and written informed consent was obtained from the parents of each subject.

Data regarding serum Cr values and body lengths measured at the same time were reviewed.

With the exception of 1 male and 2 females at the age of 1 month, and 1 male and 1 female at the age of 18 years, the subjects were divided into the following groups based on age: $\geq$3 to <6 months ($n = 18$; 16 male, 2 female), $\geq$ 6 to < 9 months old ($n = 19$; 15 male, 4 female), $\geq$ 9 months to <1 year old ($n = 31$; 17 male, 14 female), 1 year old ($n = 70$; 33 male, 37 female), 2 years old ($n = 73$; 40 male, 33 female), 3 years old ($n = 88$; 48 male, 40 female), 4 years old ($n = 81$; 43 male, 38 female), 5 years old ($n = 96$; 47 male, 49 female), 6 years old ($n = 102$; 43 male, 59 female), 7 years old ($n = 85$; 38 male, 47 female), 8 years old ($n = 56$; 18 male, 38 female), 9 years old ($n = 36$; 18 male, 18 female), 10 years old ($n = 44$; 12 male, 32 female), 11 years old ($n = 58$; 19 male, 39 female), 12 years old ($n = 69$; 15 male, 54 female), 13 years old ($n = 68$; 30 male, 38 female), 14 years old ($n = 57$; 17 male, 40 female), 15 years old ($n = 37$; 15 male, 22 female), and 16 years old ($n = 57$; 30 male, 27 female). Reference intervals (2.5 percentile and 97.5 percentile) of serum Cr against age were calculated in children between the age of 3 months and 11 years, and against sex and age between 12 and 16 years old. In addition, reference intervals for serum Cr were calculated in children relative to body length every 10 cm. In subjects aged 2–11 years, the relationship between body length and serum Cr level was determined by linear regression analysis according to the report of Uemura [6]. In all subjects, the relationship between body length and serum Cr level was determined by polynomial regression analysis in males and females, respectively. We expressed reference serum Cr level as a quintic equation of body length. In mathematics, a quintic equation is a polynomial equation of degree 5. We chose a quintic equation as a polynomial expression of theoretical changes in serum Cr level with growth in childhood. Age-related changes in serum Cr level have 4 phases with growth where the level decreases gradually up to around 1 year while renal function is developing, increases gradually before puberty while muscle mass is increasing, increases markedly according to the rapid increase in muscle mass in adolescence, and plateaus in adulthood. Therefore, we speculated that there were 4 inflection points in the developmental curve of reference serum Cr level.

Serum samples were stored at −70°C until serum Cr was measured at SRL Inc (Tokyo, Japan). The serum level of Cr was determined by an enzymatic method using a Bio Majesty automated analyzer (JCA-BM8060; JEOL Ltd, Tokyo, Japan) with Pureauto S CRE-L (Sekisui Medical Co., Ltd, Tokyo, Japan). The coefficient of variation was satisfactory (2.08%).

All analyses were conducted using Microsoft Excel 2007 and a statistical software package (JMP 8; SAS Institute Inc, Cary, NC, USA). We conducted linear and polynomial regression analyses to evaluate factors influencing Cr levels. We used Wilcoxon analysis to compare differences in serum Cr levels between the sexes. In all analyses, $P < 0.01$ was taken to indicate statistical significance.

Results

We examined the correlations between serum Cr concentration and age in all subjects divided according to sex (Fig. 1). Scattergrams showed that reference serum Cr concentrations increased gradually with age, and the increase was more marked in males than females in adolescence. We reviewed the median, 2.5 percentile, and 97.5 percentile of serum Cr reference value in each age group regardless of sex between 3 months and 11 years, because no significant differences were found between males and females in these age groups (Table 1). The median of the reference value increased gradually with age, i.e., 0.30 mg/dl at 4 years old and 0.41 mg/dl at 10 years old. In addition, we reviewed serum Cr reference value equally between 12 and 16 years old in males and females