Table 3 Model estimators of budget impact

Year	Budget impact: total additional expenditure (¥, million)				Additional expenditure for screening (¥, million)				Additional expenditure for curative care (¥, million)			
	Dipstick test only	Serum Cr assay only	Dipstick test and serum Cr assay	Status quo	Dipstick test only	Serum Cr assay only	Dipstick test and serum Cr assay	Status quo	Dipstick test only	Serum Cr assay only	Dipstick test and serum Cr assay	Status quo
1st (2012)	79	2,505	2,517	1,542	16	8	20	18	64	2,497	2,497	1,524
2nd (2013)	−96	3,295	3,308	1,946	16	8	20	18	−112	3,287	3,288	1,928
3rd (2014)	−278	3,972	3,985	2,280	16	8	20	18	−294	3,964	3,965	2,262
4th (2015)	−454	4,561	4,574	2,563	16	8	20	18	−470	4,553	4,554	2,545
5th (2016)	−615	5,089	5,103	2,815	16	8	20	18	−631	5,081	5,083	2,797
6th (2017)	−755	5,572	5,586	3,049	16	8	20	18	−771	5,564	5,566	3,031
7th (2018)	−872	6,025	6,039	3,274	16	8	20	18	−887	6,017	6,019	3,256
8th (2019)	−964	6,453	6,467	3,494	16	8	20	18	−979	6,445	6,447	3,476
9th (2020)	−1,032	6,861	6,875	3,712	16	8	20	18	−1,048	6,853	6,855	3,693
10th (2021)	−1,079	7,261	7,275	3,933	16	8	20	18	−1,094	7,252	7,255	3,915
11th (2022)	−1,105	7,660	7,675	4,162	16	8	20	18	−1,120	7,652	7,655	4,144
12th (2023)	−1,114	8,060	8,076	4,399	16	8	20	18	−1,129	8,052	8,056	4,380
13th (2024)	−1,109	8,456	8,472	4,638	16	8	20	18	−1,124	8,448	8,452	4,620
14th (2025)	−1,092	8,845	8,861	4,878	16	8	20	18	−1,108	8,837	8,841	4,860
15th (2026)	−1,067	9,235	9,251	5,122	16	8	20	18	−1,083	9,227	9,231	5,104

Cr creatinine

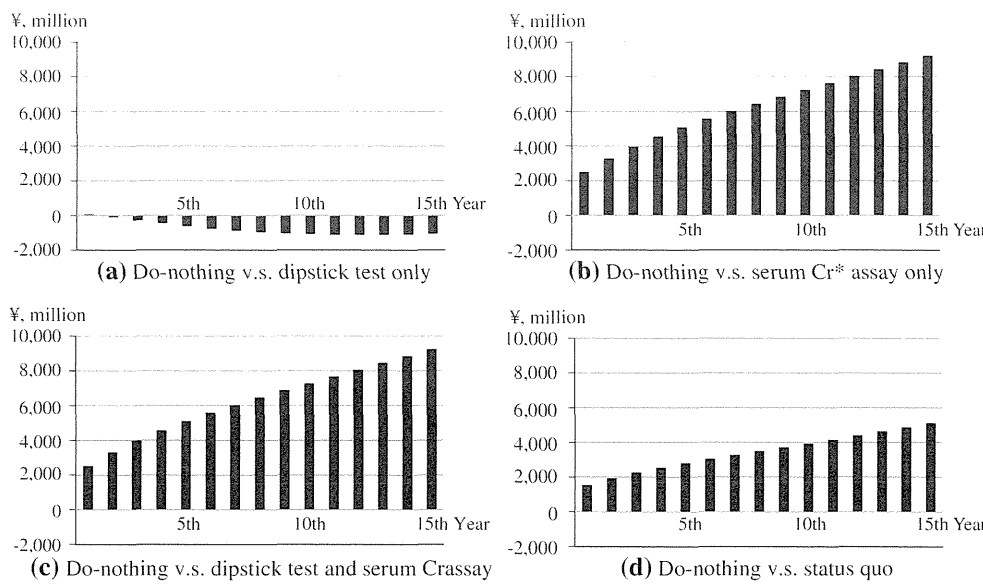


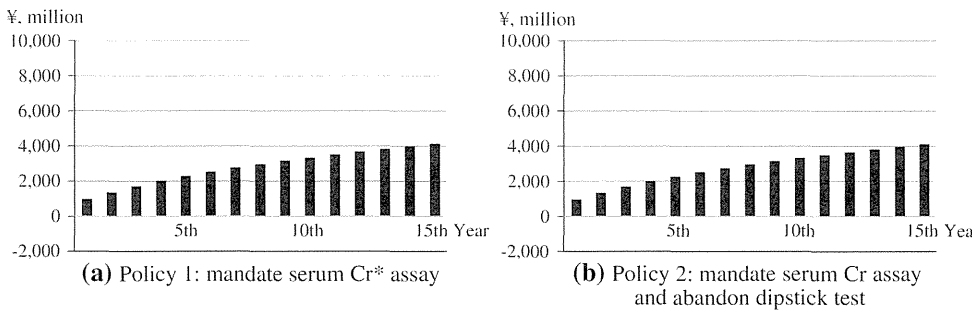
Fig. 2 *Black bars* depict annual budget impacts of mass screening compared with do-nothing scenario. Negative budget impacts on (**a**) imply that the continuation of current policy which mandates dipstick test only would contain medical care expenditure. **a** Do-nothing versus dipstick test only. **b** Do-nothing versus serum Cr assay only. **c** Do-nothing versus dipstick test and serum Cr assay. **d** Do-nothing versus status quo. *Cr* creatinine

serum Cr assay in addition to the dipstick test (Policy 1), and mandate serum Cr assay and abandon dipstick test (Policy 2), both positive and increasing budget impacts are found in the fifteen-year time frame. Although there is no established rule for interpreting the results of budget impact analysis, estimated values of ¥963 million (US$9.63 million) to ¥4,129 million (US$41.29 million) per year over fifteen years are considerable amounts of money of limited resources. These amount to 0.0026 to 0.011 % of national medical care expenditure in 2010 [22], and 0.068 and 0.29 % of the annual increase between 2009 and 2010, ¥1,413,500 million (US$14,135 million), respectively. Our case study exemplifies a situation where budgetary constraints, or affordability, matters to the use of

Table 4 Results of budget impact analysis

Year	Budget impact: total additional expenditure (¥, million)		Additional expenditure for screening (¥, million)		Additional expenditure for curative care (¥, million)	
	Policy 1: mandate serum Cr assay	Policy 2: mandate serum Cr assay and abandon dipstick test	Policy 1: mandate serum Cr assay	Policy 2: mandate serum Cr assay and abandon dipstick test	Policy 1: mandate serum Cr assay	Policy 2: mandate serum Cr assay and abandon dipstick test
1st (2012)	975	963	2	−10	973	973
2nd (2013)	1,362	1,349	2	−10	1,360	1,359
3rd (2014)	1,705	1,692	2	−10	1,704	1,702
4th (2015)	2,011	1,998	2	−10	2,010	2,008
5th (2016)	2,287	2,274	2	−10	2,285	2,284
6th (2017)	2,537	2,523	2	−10	2,535	2,533
7th (2018)	2,765	2,751	2	−10	2,763	2,761
8th (2019)	2,973	2,958	2	−10	2,971	2,969
9th (2020)	3,164	3,149	2	−10	3,162	3,159
10th (2021)	3,342	3,328	2	−10	3,341	3,338
11th (2022)	3,513	3,498	2	−10	3,511	3,508
12th (2023)	3,677	3,662	2	−10	3,675	3,672
13th (2024)	3,833	3,818	2	−10	3,832	3,828
14th (2025)	3,983	3,967	2	−10	3,981	3,977
15th (2026)	4,129	4,113	2	−10	4,127	4,123

Cr creatinine



(a) Policy 1: mandate serum Cr* assay

(b) Policy 2: mandate serum Cr assay and abandon dipstick test

Fig. 3 *Black bars* depict annual budget impacts associated with suggested mass screening policy reforms which mandate the use of serum Cr assay. Positive budget impacts on both panels imply that the reforms would result in the increase of medical care expenditure. **a** *Policy 1* mandate serum Cr assay. **b** *Policy 2* mandate serum Cr assay and abandon dipstick test. *Cr* creatinine

cost-effective interventions which have been judged as worth using according to social willingness to pay for new intervention.

The most impressive finding of this study, however, is the decreasing additional expenditures of dipstick test only scenario, which become negative in just its second year. This suggests that the mandatory dipstick test under current practice would contain medical care expenditure, i.e. 'decreasing annual national medical costs'. In other words, this is a valuable evidence that prevention saves life as well as money. And requiring dipstick test instead of serum Cr assay as a mandatory test item in SHC in 2008 may have been a sensible choice.

Due caution is needed to interpret the results of our budget impact analysis, since they depend on crucial assumptions. Positive budget impacts are found to be attributable to additional expenditure for curative care; however, for example, the analysis does not take medical advancement or health system development into account. In the coming 15 years, innovative therapeutic agents to prevent progression to ESRD are expected [23–26], and community-based CKD control intervention under collaboration between general practitioners and nephrologists is under study [27]. More prevention of ESRD should bring significant reduction in budget impact, since treatment of ESRD is most costly. With regard to the mass screening test, other

tests such as microalbuminuria or cystatin C could be an option in the middle to long run [24], which would fundamentally change the background of this analysis.

In the policy arena, the revision of SHC after its first five-year period was made in 2012, in which the continuation of current policy was chosen. And our study is in accord with keeping dipstick test in the mandatory test list. Further economic evaluation incorporating medical advancement or health system development is necessary for the future development of SHC and the next revision of CKD mass screening.

Acknowledgments This work was supported by Health and Labour Sciences Research Grants for "Research on the positioning of chronic kidney disease (CKD) in Specific Health Check and Guidance in Japan" (H20-circulatory(lifestyle)-ippan-008), "Design of the comprehensive health care system for chronic kidney disease (CKD) based on the individual risk assessment by specific health checkup" (H24-intractible(renal)-ippan-006), and a grant for strategic outcome study project for renal disease (H19-renal disease-senryaku-001), the Ministry of Health, Labour and Welfare of Japan.

Conflict of interest The authors have declared that no conflict of interest exists.

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Clin Exp Nephrol (2013) 17:255–260
DOI 10.1007/s10157-012-0692-5

ORIGINAL ARTICLE

Annual incidence of persistent proteinuria in the general population from Ibaraki annual urinalysis study

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Received: 5 June 2012 / Accepted: 23 August 2012 / Published online: 13 September 2012

Abstract
Background For a definitive diagnosis of chronic kidney disease, at least 2 consecutive positive results of proteinuria with an interval of >3 months are required. However, most previous reports were based on single-screening data.
Patients and methods The subjects in this study were participants in an annual health examination held in Ibaraki, Japan, between 1993 and 2003. The follow-up duration with serial urinalysis for 3 years of patients who were negative for proteinuria in the initial year was 330,614 person-years in males and 687,381 person-years in females among 81,854 male and 155,256 female subjects. We evaluated the incidence and risk factor for the incidence of proteinuria and persistent proteinuria.
Result The annual incidence of proteinuria and persistent proteinuria was 1.31 and 0.33 % in males and 0.68 and 0.14 % in females. Among the subjects without hypertension and diabetes, the annual incidence was 0.81 and 0.16 % in males and 0.37 and 0.06 % in females, respectively. Risk analysis indicated that hypertension in males [hazard ratio (HR) 2.052] and females (2.477), diabetes in males (3.532) and females (3.534) and reduced renal function in males (3.097) and females (2.827) were significant positive risks for development of persistent proteinuria.
Conclusion By annual urinalysis screening of the general population, 1 out of 303 male subjects and 1 out of 725 female subjects developed persistent proteinuria every year. Subjects with diabetes, hypertension and reduced renal function had a 2 or 3 times higher risk for the incidence of persistent proteinuria in both males and females.

Keywords Urinalysis · Chronic kidney disease · Persistent proteinuria · Risk factors

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Introduction

At present, it is considered that the worldwide population of patients with end-stage renal disease (ESRD) will continue to increase as a result of more patients requiring renal replacement therapy (RRT). Moreover, we know that chronic kidney disease (CKD) is a risk factor of not only progression to ESRD, but also the development of cardiovascular diseases (CVD) [1–3]. Therefore, we should promote reducing the incidence of CKD to save quality of life in the general population and economic loss due to the increasing number of ESRD patients.

In Japan, annual urinalysis screening programs were introduced for every schoolchild in 1973, for every working adult in 1972, and for residents >40 years of age in 1982 under the auspices of local governments and the Ministry of Health, Labor and Welfare of Japan [4]. However, Boulware et al. [5] reported that annual urinalysis screening for proteinuria is not cost-effective unless selectively directed toward a high-risk group such as older persons and persons with hypertension, or conducted at an infrequent interval. However, Kondo et al. [6] reported that

annual screening of proteinuria with dipsticks was cost-effective for the Japanese population. One reason for the opposite views on urinalysis screening comes from the difference in the prevalence of proteinuria among races [7–9]. In particular, the prevalence of proteinuria is high in the Japanese general population [4, 10] and in Asians generally [7]. Chronic glomerulonephritis (CGN) has been found to be a more frequent underlying renal disease for ESRD in Asians than in Caucasians [11, 12]. Most CGN patients have no symptoms at the early stage of the disease, and the only method for early detection is urinalysis [13]. The reduced number of new ESRD patients with CGN might be caused by early detection and early referral to nephrologists due to the annual urinalysis screening program in Japan [14, 15]. Proteinuria also accelerates a decline in the glomerular filtration rate (GFR) [16], and proteinuria is the strongest predictor of CKD stage progression [17].

Therefore, to explain the effectiveness of annual urinalysis screening, we had to elucidate the annual incidence of proteinuria and persistent proteinuria in the general population and focus on people without high risk of proteinuria such as hypertension and diabetes. To date, however, because most previous reports were based on single-screening data, we had no precise evidence of the incidence of persistent proteinuria for a period of more than 3 months, which is a required for a definitive diagnosis of CKD in the general population.

In this study, from the result of the annual health examination held in Ibaraki, Japan, we estimated the annual incidence of proteinuria and persistent proteinuria among the Japanese general population and among the population with or without diabetes, hypertension or reduced renal function. This analysis might provide clues for future screening policy for urinary abnormalities to reduce the number of CKD patients.

Subjects and methods

The participants in the annual health examination held in Ibaraki, Japan between 1993 and 2003 comprised 152,569 males and 267,594 females (age range 40–98 years (median 61 years). Among them, 63,728 males and 103,381 females did not receive serial urinalysis for 3 years, 5,174 males and 4,368 females had proteinuria at their initial urinalysis, and 1,813 males and 4,589 females had missing data. The prevalence of proteinuria in our subjects, i.e., a positive result for proteinuria in their first urine examination, was 3.4 % (5,174/152,569) in males and 1.6 % (4,368/267,594) in females. After we excluded those subjects, the study population comprised 81,854 male and 155,256 female subjects.

To diagnose persistent proteinuria, data obtained with an interval of >3 months is required by definition [18]. The incidence of persistent proteinuria in this study was defined as positive for proteinuria by consecutive annual urinalysis. The subjects were followed up until persistent proteinuria was recorded during the 10-year follow-up duration; their follow-up duration was 330,614 person-years in males and 687,381 person-years in females (Fig. 1).

We defined diabetes as subjects who were taking oral hypoglycemic or insulin treatment, subjects with fasting blood sugar ≥126 mg/dl or random blood sugar ≥200 mg/dl. Subjects having systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg or taking antihypertensive medication were defined as hypertensive [19]. Estimated GFR (eGFR) was calculated from the simplified equation developed from the MDRD study [20] as follows: eGFR (ml/min/1.73 m^2) = 186.3 × (serum creatinine)$^{-1.154}$ × age$^{-0.203}$ × (0.742 for female subjects) without adjusting for Japanese covariant factors and we separated the subjects to normal renal function (eGFR ≥60 ml/min/1.73 m^2) and reduced renal function (eGFR <60 ml/min/1.73 m^2). These co-morbid conditions of the initial year were applied for the analysis.

Hypercholesterolemia was defined as total cholesterol (T-Cho) ≥220 mg/dl, low high-density lipoprotein cholesterol (HDL-C) as ≤35 mg/dl, and hypertriglyceridemia was defined as triglycerides (TG) ≥250 mg/dl.

Alcohol intake was defined as total alcohol consumption in grams per day calculated from questions on the number of glasses of wine, beer, fortified wines, sake, and liqueurs/

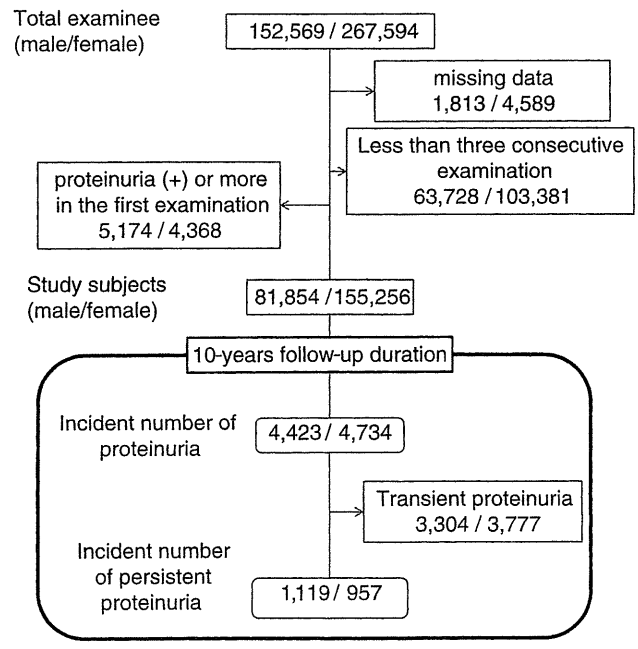

Fig. 1 Number of examinee and study subjects and their male:female ratio are shown

spirits per day. One glass of any alcoholic beverage was assumed to contain 10 g of alcohol. The total alcohol consumption was then classified into four categories—no alcohol consumption, occasional alcohol consumption, <20 g/day, and >20 g/day. Smoking habits were classified into three categories—non-smoker, previous smoker or current smoker.

Proteinuria was tested using dipstick (Ames Hemacombisticks; Bayer-Sankyo Ltd., Tokyo, Japan). A test result of '1+' or more was defined as positive. Serum creatinine concentration was measured by a modified Jaffe method (Creatinine-HR; Wako Pure Chemicals Industries, Ltd., Osaka, Japan) using an autoanalyzer (Hitachi 7350; Hitachi Ltd., Tokyo, Japan or RX-20; JEOL Ltd., Tokyo, Japan). Measurements of blood glucose, T-Cho, TG, and HDL-C were measured using an autoanalyzer (Hitachi 7350; Hitachi Ltd).

Statistical methods

To compare males and females and to compare subjects with presence and absence of hypertension, diabetes or reduced renal function, we applied the chi-squared test. The primary outcome for the analysis was the development of persistent proteinuria during the follow-up period. Variables were age, diabetes, hypertension and renal function (eGFR <60 ml/min), hypercholesterolemia (−, +), low HDL-C (−, +), hypertriglyceridemia (<150 mg/dl, 150−299 mg/dl, ≥300 mg/dl), obesity (−, +), cigarette smoking (never, previous smoker and current smoker with <1 pack/day and >1 pack/day), alcohol consumption (never, occasional drinker, alcohol consumption <20 g/day and alcohol consumption ≥20 g/day). Hazard ratios of proteinuria and persistent proteinuria development by sex were estimated by using Cox regression model after confirming the proportionality in each model (SAS software, version 8.3, SAS Institute Inc., CA, USA). A p value of <0.05 was considered statistically significant.

Result

Table 1 shows baseline characteristics of the study subjects. Male subjects were significantly older, more frequently with hypertension and diabetes, and less frequently with reduced renal function.

During the entire observation period, 4,423 male and 4,734 female subjects were newly positive for proteinuria and the annual incidence of proteinuria was 1.31 % in males and 0.689 % in females (Fig. 2a). Among them, 1,119 males and 957 females had continued to be positive for proteinuria. Consequently, the incidence of persistent proteinuria was 0.33 % in males and 0.14 % in females (Fig. 2a); 74.7 % (3,304/4,423) in males and 79.8 % (3,777/4,734) in females had transient proteinuria.

From the above results, 1 out of 303 male subjects and 1 out of 725 female subjects developed persistent proteinuria every year in our study subjects. The incidence of proteinuria and the incidence of persistent proteinuria were both significantly higher in males.

When separating the subjects by co-morbid conditions, the annual incidence of proteinuria among the subjects without hypertension and diabetes was 0.83 % in males and 0.37 % in females (Fig. 2b). Moreover, the annual incidence of persistent proteinuria was 0.16 and 0.06 %, respectively, and 1 out of 632 male subjects and 1 out of 1,626 female subjects developed persistent proteinuria every year.

The annual incidence of proteinuria and persistent proteinuria in the subjects with hypertension, diabetes or reduced renal function was significantly higher than the incidence without each condition. Meanwhile, the annual incidence of persistent proteinuria in males with each co-morbid condition was significantly higher than the incidence without it (Fig. 3a). In females, the annual incidence of proteinuria was highest in subjects with diabetes followed by reduced renal function and hypertension and each of them was also significantly higher than the incidence without each condition (Fig. 3b).

We then analyzed the risk factors for the incidence of proteinuria and persistent proteinuria. Significant risk factors for the incidence of proteinuria were age, hypertension, diabetes, reduced renal function, obesity, low HDL-C, hypertriglyceridemia, and heavy smoker (current smoker >1 pack/day) in male subjects. In females, we found the same trend in risk factors for the incidence of persistent proteinuria as in males except for low HDL, hypertriglyceridemia and alcohol consumption (Table 2). Low HDL was not a significant risk for the incidence of persistent proteinuria in females, whereas hypertriglyceridemia (≥300 mg/dl) was a higher risk factor in females than in males. For smoking habit, a significant risk for incidence of persistent proteinuria was observed in both previous and current smoker in males.

Discussion

Diabetic nephropathy, CGN, and hypertensive nephropathy are three universal major primary renal diseases leading to ESRD. For the purpose of early detection of diabetic nephropathy or hypertensive nephropathy, selective screening of patients with diabetes or hypertension might be preferable. However, we should take into account that the prevalence and incidence of ESRD due to CGN are

Table 1 Baseline characteristics of the subjects divided by sex

	Males		Females	
Subjects in the study (*N*)	81,854		155,256	
Age[a]	60.2	9.7	56.8	10.2*
Follow-up duration (person-years)	330,614		687,381	
Non-hypertensive, non-diabetic[b]	36,567	44.7 %	89,360	57.6 %*
Non-hypertensive, diabetic[b]	2,410	2.9 %	2,171	1.4 %*
Hypertensive, non-diabetic[b]	39,115	47.8 %	60,301	38.8 %*
Hypertensive, diabetic[b]	3,762	4.6 %	3,424	2.2 %*
GFR <60 ml/min/1.73 m^2 [b]	4,272	5.20 %	9,643	6.2 %*
Total cholesterol (mg/dl[a])	196.5	34.1	209.9	35.2*
HDL-C (mg/dl[a])	52.8	14.6	58.4	14.5*
TG (mg/dl[a])	151.6	100.4	131	78.4*
Body mass index[a]	23.4	2.9	23.4	3.2
Smoking				
Current[b]	38,847	47.5 %	9036	5.9 %*
Previous[b]	24,103	29.4 %	1,219	0.8 %*
Alcohol consumption				
Occasional[b]	12,019	14.7 %	13,857	8.9 %*
Ethanol <20 g/day[b]	39,135	47.8 %	6,854	4.4 %*
Ethanol >20 g/day[b]	4,468	5.5 %	192	0.1 %*

* $p < 0.05$

[a] Mean, SD

[b] *N* (%)

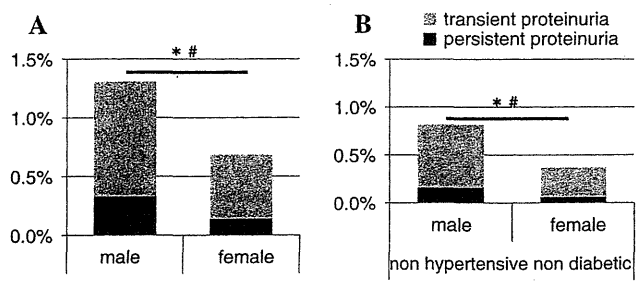

Fig. 2 The annual incidence of proteinuria and persistent proteinuria. *Black and gray bar* indicates the annual incidence of persistent proteinuria and transient proteinuria, respectively. A total of *stacked bars* mean annual incidence of proteinuria. The incidence of proteinuria and persistent proteinuria in males and females with any comorbid conditions (**a**) or without hypertension and diabetes (**b**) was demonstrated. Statistical significant value between males and females was indicated as: *asterisks* the incidence of proteinuria and *ash symbols* persistent proteinuria

different among races and geographic areas [4, 21–25]. Moreover, early detection of asymptomatic CGN without hypertension or diabetes strongly depends on urinalysis performed when screening the general population.

For a definitive diagnosis of CKD, at least 2 consecutive positive results of proteinuria with an interval of >3 months are required. To date, there has been no report on the annual incidence of persistent proteinuria in the general population.

In the present study, the incidence of persistent proteinuria in the general population was one-quarter of the incidence of proteinuria with an estimated 3,298 cases per million per year (1 patient per 303 person-years) in males and 1,379 cases per million per year (1 patient per 725 person-years) in females.

Previously, Brantsma et al. reported that the annual incidence of microalbuminuria was 1.02 % in both genders [26]. By using urine dipsticks we found an annual incidence of proteinuria of 1.20 % in males and 0.64 % in females. Furthermore, the incidences of proteinuria in our study were 37–81 times higher than in previous reported incidences in the non-hypertensive and non-diabetic population [0.01 % (0.001–0.1 %)] [5, 27]. In Japan, because of the high annual incidence of proteinuria among the non-hypertensive and non-diabetic population including CGN, frequent universal urinalysis screening might be preferable. As well as the incidence of proteinuria, the incidence of persistent proteinuria was higher in subjects with hypertension, diabetes or reduced renal function than in subjects without these conditions in both genders. Among incident proteinuria, 74.7 % of males and 79.8 % of females had transient proteinuria. Using 24-h urinary albumin excretion, albuminuria was diminished in 27.8 % of the subjects for a median follow-up duration of 4.2 years [26]. Using dipstick urinalysis, we have higher false positive results due to urine concentration or other non-pathological conditions. However, it is important to know aging, hypertension, diabetes, reduced renal function, obesity, dyslipidemia and smoking habit were strong risk factors for developing persistent proteinuria in both males and females. Further studies are needed to confirm the effect of controlling those factors on the incidence of both proteinuria and persistent proteinuria in a large population.

Our study has the advantage of a large sample size and availability of serial data. Moreover, this is the first report to show the incidence of persistent proteinuria in a community-based frequent follow-up study. However, it also has several limitations. Firstly, the participants of this study were from a community-based general population, but there was a lack of subjects aged <40 years old. Secondly, there was no data about detailed underlying renal diseases in our subjects.

In conclusion, our study aimed to determine the incidence of persistent proteinuria and its risk factors, and this is the first report to show the incidence of persistent proteinuria in the general population. As a result, the annual incidence of persistent proteinuria was 0.33 % in males and 0.14 % in females. The incidence of persistent proteinuria among the hypertensive, diabetic or reduced renal function

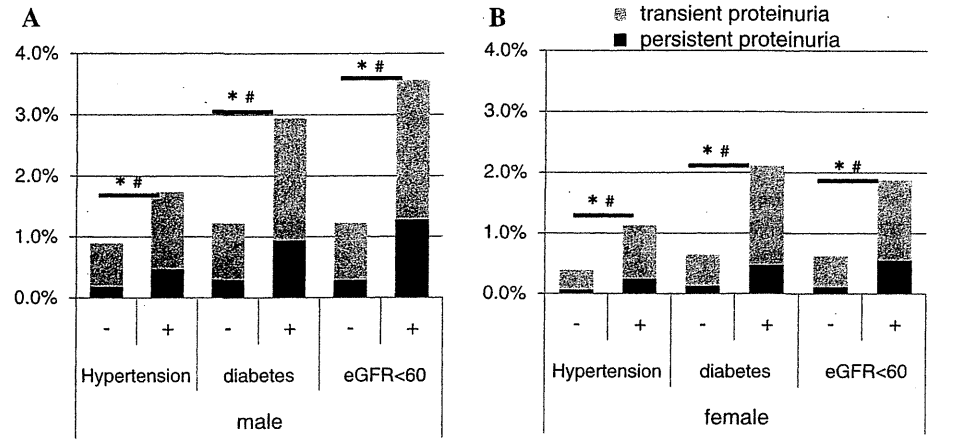

Fig. 3 The different annual incidence between the presence and absence of co-morbid conditions. *Black and gray bar* indicates the annual incidence of persistent proteinuria and transient proteinuria. A total of *stacked bars* mean annual incidence of proteinuria. Every co-morbid condition was significantly higher than without it (**a**, **b**). In any condition >20 % in males (**a**) and >16 % in females (**b**) with proteinuria in the 2nd year had persistent positive results for proteinuria. Statistical significant value between presence and absence of co-morbid conditions was indicated as: *asterisks* the incidence of proteinuria and *ash symbols* persistent proteinuria

Table 2 Multivariate analysis of predictors for developing persistent proteinuria

Predictors at first year	Male			Female		
	HR	95 % CI	*p*	HR	95 % CI	*p*
Age	1.03	1.022–1.04	<0.0001*	1.024	1.016–1.032	<0.0001*
Non-hypertensive, non-diabetic	1.00					
Non-hypertensive, diabetic	3.532	2.627–4.75	<0.0001*	3.534	2.338–5.341	<0.0001*
Hypertensive, non-diabetic	2.052	1.761–2.39	<0.0001*	2.477	2.116–2.898	<0.0001*
Hypertensive, diabetic	5.216	4.239–6.42	<0.0001*	5.62	4.315–7.319	<0.0001*
GFR <60 ml/min/1.73 m^2	3.097	2.637–3.64	<0.0001*	2.827	2.392–3.340	<0.0001*
Body mass index >25	1.511	1.332–1.71	<0.0001*	1.649	1.446–1.880	<0.0001*
Total cholesterol ≥220 mg/dl	1.075	0.934–1.24	0.3105	1.103	0.968–1.258	0.1401
HDL-C <35 mg/dl	1.387	1.144–1.68	0.0009*	1.008	0.729–1.393	0.9609
TG 150–299 mg/dl	1.25	1.096–1.43	0.0009*	1.449	1.261–1.666	<0.0001*
TG >300 mg/dl	1.249	0.992–1.57	0.0583	1.815	1.41–2.336	<0.0001*
Previous smoking	1.26	1.07–1.49	0.0058	1.537	0.765–3.091	0.2273
Current smoking <1 pack/day	1.48	1.09–2.02	0.0134*	1.419	0.934–2.157	0.1014
Current smoking >1 pack/day	1.44	1.23–1.7	<0.001*	1.44	0.97–2.137	0.0707
Occasional drinker	0.99	0.82–1.19	0.891	0.816	0.603–1.104	0.1879
Ethanol <20 g/day	0.85	0.74–0.97	0.0195*	1.012	0.71–1.442	0.9486
Ethanol >20 g/day	0.91	0.68–1.21	0.5067			

95 % CI 95 % confidence interval

* $p < 0.05$

population was much higher than among the normal population. By annual urinalysis screening of the general population, we detected that 1 out of 303 male subjects and 1 out of 725 female subjects developed CKD due to persistent proteinuria every year in Japan.

Acknowledgments The authors would like to thank the staff of Ibaraki Health Service Association, especially Mr. Ryuji Yamashita and Dr. Iwao Yamaguchi. This study was supported in part by a Grant-in-Aid for Strategic Outcome Study project for chronic kidney disease and Research on the Positioning of Chronic Kidney Disease in Specific Health Check and Guidance in Japan from the Ministry of Health, Labor and Welfare of Japan.

Conflict of interest None declared.

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CKD 進行の危険因子

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要　旨

・CKD 進行の危険因子は生活習慣，食事内容，高血圧，蛋白尿・アルブミン尿，糖尿病，脂質異常症，高尿酸血症，腎障害をきたしやすい薬剤，とさまざまであり，それぞれの因子の対策を組み合わせて包括的に診療することで，進行を抑制することが可能である。

・CKD 進行の危険因子には生活習慣にかかわる要素が多く含まれるため，持続したリスク排除を行うためには，CKD の進行に寄与する危険因子を一般市民や医療従事者が熟知し，チームで継続指導にあたることが大切である。

はじめに

慢性腎臓病(chronic kidney disease；CKD)の治療の第一の目的は，末期腎不全へ至ることを阻止する，あるいは末期腎不全へ至る時期を遅らせることである。第二の目的は，合併症である心血管病(cardiovascular disease；CVD)の新規発症を抑制する，あるいは既存の CVD の進展を阻止することである。これらの目的達成のためには，CKD の進行に寄与する危険因子を一般市民や医療従事者が熟知し，その因子を抑えることが肝要である。

本稿では，CKD 進行の危険因子とその病態について要点を解説する。各因子の治療方法についてはこの後の稿を参照されたい。

生活習慣

CKD における生活習慣の改善は，食事療法・薬物療法と並んで有効かつ重要であり，CKD 患者が正しい知識を身につけられるよう医療サイドが指導していくことが大切である。

1 肥満

茨城県の健診受診者を 10 年間調査した研究では，CKD の新規発症および悪化の危険因子が示されている(**図1, 2**)[1]。この中で BMI(body mass index)25 以上の肥満は CKD の発症および悪化の危険因子であった。他にも BMI が 25 以上になると尿蛋白の出現率および末期腎不全の危険が高まることが報告されている[2,3]。過剰な脂肪組織は交感神経系やレニン-アンジオテンシン系を刺激し，糸球体の hyperfiltration や腎での Na 再吸収を増加させ，蛋白尿や腎障害を引き起こすことが

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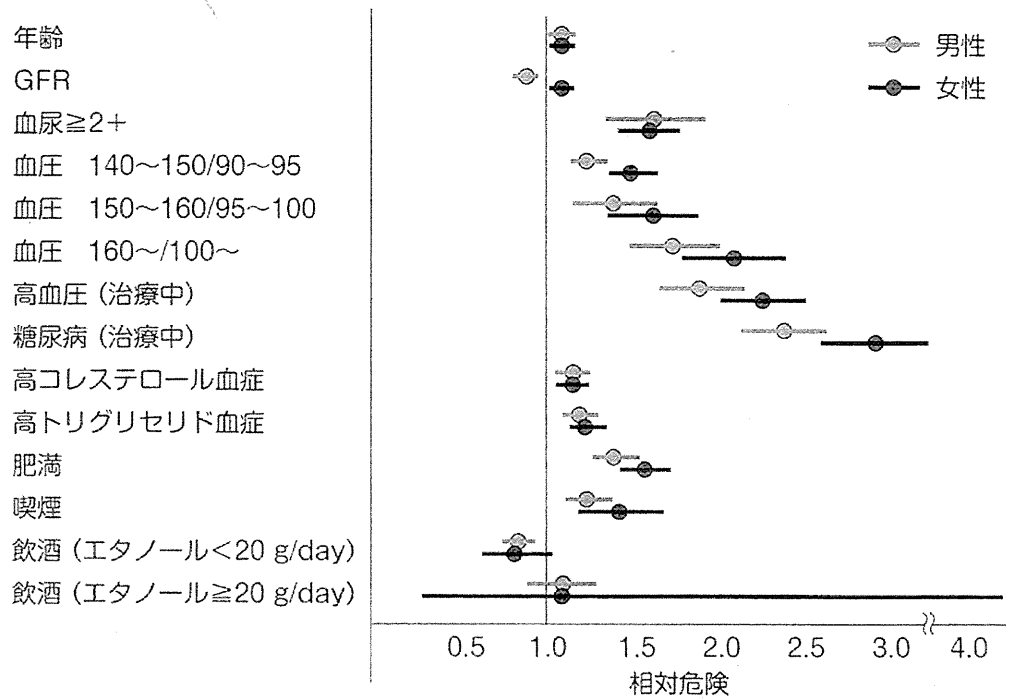


図1　10年間の経過観察中に蛋白尿(CKDステージ1あるいは2)が出現する危険因子[1)]

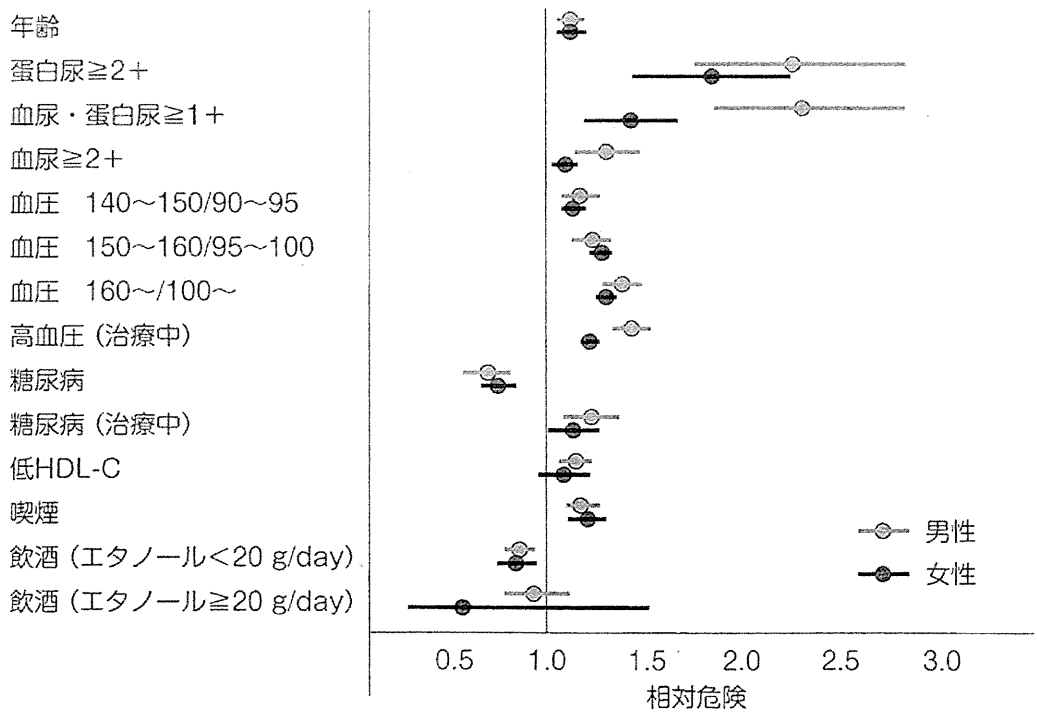


図2　10年間の経過観察中にCKDステージ3以上が出現する危険因子[1)]

推測されている。

2 喫煙

喫煙が腎障害を引き起こす要因には，ニコチンによる脈拍や血圧の上昇のほか，喫煙による腎血管の収縮，腎血流の低下など血行動態への影響に加えて，ニコチンによるメサンギウム細胞の増殖やフィブロネクチンの増加，TGF-β_1産生増加に

よる腎線維化の促進，カドミウムや鉛の曝露による腎毒性などがあげられる。喫煙は CKD の発症および悪化の危険因子であり[1]，IgA 腎症においても喫煙は用量依存性に腎機能低下を有意に悪化する危険因子であることが報告されている[4]。

3 アルコール摂取量

エタノール 20 g/日以上を超える飲酒は，CKD の発症および悪化の危険因子となる可能性が示唆されている[1]。連日多量の飲酒が GFR 60 未満の発症と相関関係にあるとの報告もある[5]。過度の飲酒は血圧上昇，高尿酸血症，中性脂肪上昇，糖尿病の危険因子も高まることから，CKD の発症・増悪防止のためにも控える必要がある。

4 脱　水

脱水は腎血流減少による腎機能低下の危険因子となるため，その予防と対処が必要でなる。高熱による多量の不感蒸泄や，下痢，嘔吐による消化管からの体液の喪失，食欲不振による経口摂取の低下などが脱水の原因となる。特に高齢者では動脈硬化により腎血流の低下をきたしやすく，CVD を合併している場合はその増悪にも注意する必要がある。降圧薬や利尿薬を服用している CKD 患者に脱水が重なると腎機能低下が助長されることもあるため，その際は投薬量の調整が必要となる。

5 運　動

CKD の各病期を通して，過労を避け，十分な睡眠や休養を取ることは必要であるが，倦怠感が著明な場合や全身浮腫，心不全を呈する場合を除き，安静を強いる必要はない。運動量は個々の腎機能などに合わせて調節する。肥満は CKD の危険因子であり，肥満解消のための運動を適切に指導する。

食事管理

1 食　塩

CKD 患者では食塩の過剰摂取により高血圧をきたしやすい。また，GFR が低下した状態では食塩の過剰摂取により細胞外液量の増加を招き，浮腫，心不全，肺水腫の原因ともなる。CKD の病態に合わせた適正な食塩摂取量の指導が必要である。

2 たんぱく質

過度のたんぱく質摂取は糸球体の hyperfiltration を促進し，腎機能低下時にはたんぱく質の代謝産物が尿毒素物質として蓄積することもある。このため，たんぱく質も CKD の病期に合わせた摂取量の指導が必要である。

高血圧

CKD と高血圧は密接な関係があり，血圧の上昇により腎機能の悪化をもたらし，また腎機能が悪化すると血圧がさらに上昇するという悪循環が生じる。Multiple Risk Factor Intervension Trial (MRFIT)では，332,514 人の男性を平均 16 年間観察し，814 人が末期腎不全に至った。その中で高血圧が末期腎不全に至る強い危険因子であり，収縮期血圧および拡張期血圧が上昇すると末期腎不全になりやすいことが報告されている(**図 3**)[6]。また，CKD の患者は血圧が高いほど脳卒中，心筋梗塞，総死亡危険因子が高くなり，その傾向は腎機能低下群でさらに顕著となる[7]。

蛋白尿，アルブミン尿

蛋白尿，アルブミン尿の増加は CKD の進展因子となり，また CVD の発症や死亡の危険因子にもなる。蛋白尿，アルブミン尿の原因となる CKD の原疾患の治療を行うとともに，蛋白尿，アルブ

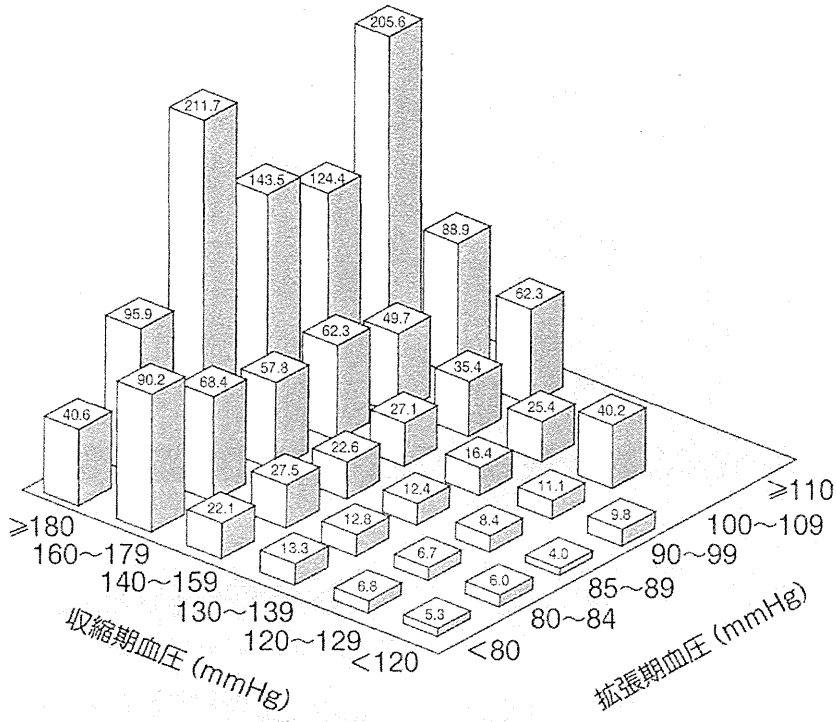


図3　末期腎不全の10万人・年あたりの年齢調整済み発症率[6]

ミン尿減少効果を有するRAS阻害薬の投与が有効である。

糖尿病

新規透析導入の原疾患の第1位は糖尿病性腎症であり，CKD対策の重要課題である。糖尿病性腎症の発症・進展抑制には，厳格な血糖管理と血圧管理の双方が重要である。これは糖尿病を合併する他のCKD患者においても同様である。また，糖尿病性腎症の進展とともに大血管障害の合併危険因子も高まるため，肥満，脂質異常症，喫煙などの危険因子管理も合わせて行う。

脂質異常症

脂質異常症はCKDの発症，進行およびCVD発症の危険因子である。健常人において，総コレステロール値が高値になるほど，15年後にCr 1.5 mg/dl以上になる相対危険度は高くなる(**図4**)[8]。CKD患者にスタチンを投与すると蛋白尿の軽減効果や腎機能の低下抑制が期待されている。

高尿酸血症

高尿酸血症は末期腎不全の危険因子であり，男性では7.0 mg/dl以上，女性では6.0 mg/dl以上でリスクが高まる(**図5**)[9]。腎機能低下により尿酸排泄が低下するため，さらに高尿酸血症の頻度が高まる。肥満や飲酒，喫煙も高尿酸血症の原因となるため，包括的なリスク管理が必要である。

薬　剤

CKD患者においては，腎障害をきたす薬物の投与は極力避ける。やむを得ず投与する場合は，腎機能の細やかなモニタリングが必要である。**表**にCKD患者において注意すべき薬剤を示す[10]。

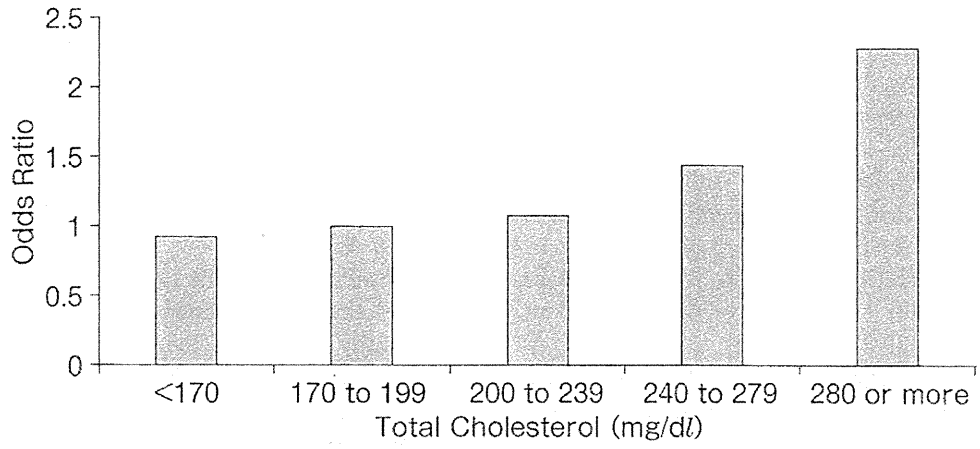
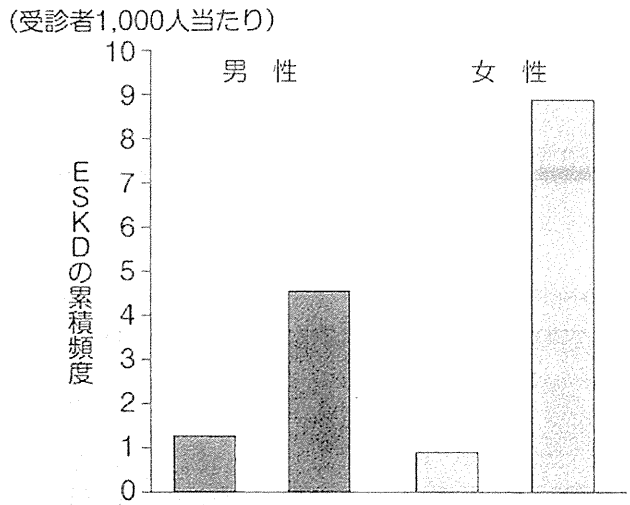


図 4　総コレステロールと腎機能低下の相対危険度[8]



血清尿酸値 (mg/dl)	<7.0	≧7.0	<6.0	≧6.0
健診受診者	15,617	7,332	21,795	3,433
ESKD患者数	19	34	19	31

図 5　血清尿酸値による ESKD の累積頻度[9]

特に腎血流が低下しやすい高齢者，脱水状態，糖尿病の患者や，利尿薬の投与中の患者に腎障害をきたす薬剤を投与すると，腎障害の危険がさらに増大することを熟知しておくべきである。

表　CKD 患者において注意すべき薬剤[10]

- NSAIDs(腎血流低下，間質性腎炎，急性尿細管壊死，ネフローゼ症候群)
- アムホテリシン B(尿細管壊死，腎血流低下，尿細管アシドーシス)
- シスプラチン(尿細管壊死)
- シクロスポリン(腎血流低下，慢性尿細管・間質性腎炎)
- アミノ配糖体(尿細管壊死)，イホスファミド(尿細管壊死)
- ヨード系造影剤(腎血流低下，急性尿細管壊死)
- メトトレキサート(閉塞性腎不全，尿細管壊死)
- マイトマイシン C(糸球体障害，溶血性尿毒症症候群)
- リチウム(腎性尿崩症)，D-ペニシラミン(糸球体障害)
- フィブラート(横紋筋融解症)
- ゾレドロネート(尿細管壊死)，パミドロネート(ネフローゼ症候群)

おわりに

CKD 進行の危険因子はさまざまであり，それぞれの因子の対策を組み合わせて包括的に診療することで，進行を抑制することが可能である。また，持続したリスク排除を行うためには，医療従事者がチームで継続指導にあたることが大切である。

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CKD患者の専門医への紹介・フォローアップ基準

斎藤知栄*　山縣邦弘*

SUMMARY

CKD患者はわが国においても膨大な数の患者数が存在し，その診療にはかかりつけ医・非腎臓専門医と腎臓専門医との密接な診療連携をおこなう必要がある．「CKD診療ガイド2012」では，最新のCKD重症度分類に準じて，CKD患者を専門医に紹介するタイミングや，CKD患者のフォローアップ，腎臓専門医への通院頻度について解説されており，これまでより実情に即したCKD診療のフォローアップや医療連携のあり方が示されている．

KEY WORDS

かかりつけ医，腎臓専門医，医療連携，FROM-J

はじめに

わが国における慢性腎臓病（chronic kidney disease：CKD）の推計人口は2005年の時点で約1,300万人であり，20歳以上の約8人に1人がCKDであることになる[1]．このように国民病ともいえる多くのCKD患者の診療はかかりつけ医・非腎臓専門医と腎臓専門医が医療連携をおこない協働してあたることで，CKD患者の初期診療から専門的診療まで幅広く対応することが可能となる．以上の理念から，かかりつけ医を対象とした「CKD診療ガイド」が日本腎臓学会より2007年に作成され，2009年に改訂された．「CKD診療ガイド」には，かかりつけ医・非腎臓専門医が腎臓専門医へ紹介するタイミングや，フォローアップの頻度や検査項目などが記載されており，診療の現場で活用されてきた．

本稿では，CKD患者を専門医へ紹介するタイミングと，CKD患者のフォローアップについて，「CKD診療ガイド2012」で改訂された点をふまえて紹介する．

1．CKD患者を専門医に紹介するタイミング

かかりつけ医・非腎臓専門医では，CKD患者を診療する際には，尿検査（蛋白尿，血尿）と血清クレアチニン（Cr）濃度の双方の評価が必要である．さらに尿蛋白陽性例においては，随時尿で尿蛋白濃度，尿Cr濃度を測定し，尿蛋白を尿蛋白濃度/尿Cr濃度で算出したg/g・Crで表すことで定量化した評価ができ望ましい．

腎臓専門医へ紹介するタイミングは，つぎのいずれかに該当する場合である．

1）高度の蛋白尿

「CKD診療ガイド2012」[2]では，CKDの重症度分類に蛋白尿区分が加わり，A3では高度蛋白尿として尿蛋白濃度/尿Cr濃度が0.5 g/g・Cr以上，糖尿病患者においては顕性アルブミン尿として尿アルブミン濃度/尿Cr濃度が300 mg/g・Cr以上と定義されている（**図1**）．尿蛋白濃度の定量がおこなわれていない場合は，尿蛋白2+以上がおよそ高度蛋白尿に該当する．これまでの多

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原疾患	蛋白尿区分			A1	A2	A3
糖尿病	尿アルブミン定量（mg/日） 尿アルブミン/Cr比（mg/g·Cr）			正常	微量アルブミン尿	顕性アルブミン尿
				30未満	30～299	300以上
高血圧 腎炎 多発性嚢胞腎 移植腎 不明 その他	尿蛋白定量（g/日） 尿蛋白/Cr比（g/g·Cr）			正常	軽度蛋白尿	高度蛋白尿
				0.15未満	0.15～0.49	0.50以上
GFR区分（ml/分/1.73 m²）	G1	正常または高値	≧90		*1	紹介
	G2	正常または軽度低下	60～89		*1	紹介
	G3a	軽度～中等度低下	45～59	50～59	40歳未満は紹介*2	紹介
				40～49	40～69歳も紹介*2	
	G3b	中等度～高度低下	30～44	30～39	70歳以上も紹介*2	紹介
	G4	高度低下	15～29		紹介	紹介
	G5	末期腎不全	＜15		紹介	紹介

3ヵ月以内に30%以上の腎機能の悪化を認める場合は腎臓専門医へ速やかに紹介すること．
*1 血尿と蛋白尿の同時陽性の場合には紹介
*2 尿所見正常の場合，腎臓専門医への紹介は，安定した70歳以上の患者ではeGFR40ml/分/1.73 m²としてもよい

図 1. 腎臓専門医への紹介基準
（日本腎臓学会編，2012[2]より引用）

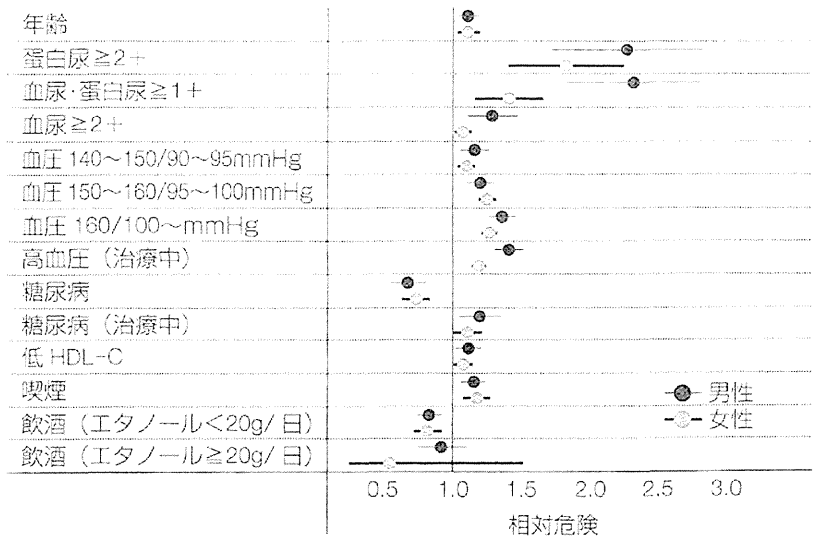

図 2. 10年間の経過観察中にCKDステージ3～5となる危険因子
（Yamagata K *et al*, 2007[3]より改変引用）

くの疫学研究から，尿蛋白の程度が強いほど腎機能悪化のリスクが上昇することが明らかであった（**図2**）[3]．高度蛋白尿あるいは顕性アルブミン尿を呈する場合は，今後腎機能が悪化するおそれがあるため，腎生検を含めた精査を腎臓専門医でおこなう必要がある．

2）蛋白尿と血尿がともに陽性

蛋白尿1＋以上および血尿1＋以上とともに陽性の場合も，やはり将来の腎機能悪化の危険因子である（**図2**）[3]．IgA腎症を含めた増殖性糸球体腎炎などの進行性糸球体腎炎である可能性が高く，腎生検を含めた精査を考慮すべきであり，腎臓専門医への紹介をおこなう．

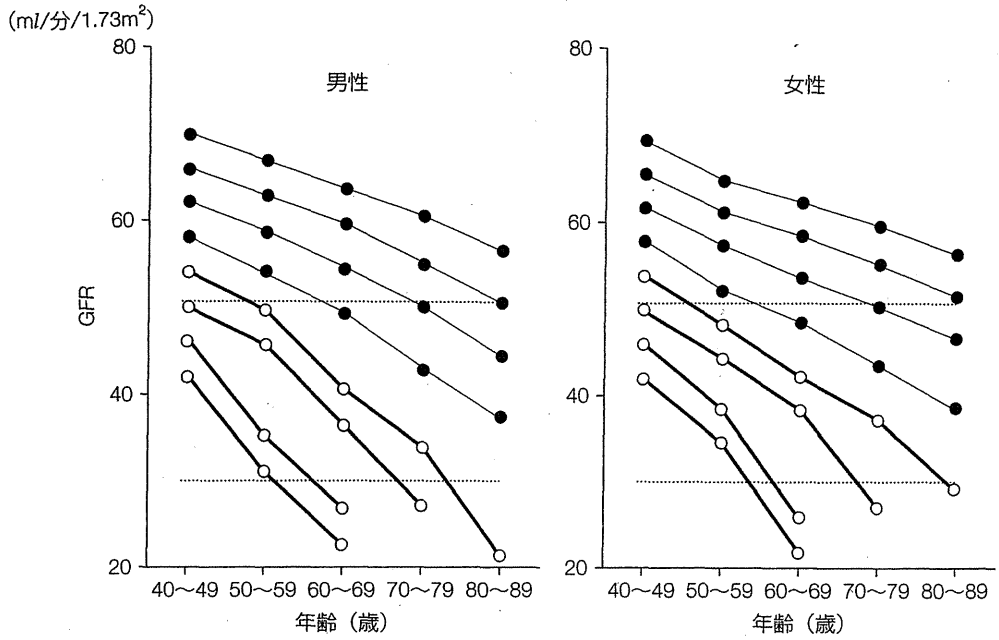

図 3. 加齢に伴う腎機能（GFR）低下のシミュレーション
GFR 50 ml/分/1.73 m²未満の患者（——）は2倍以上の速さで腎機能が低下する．
（Imai E *et al*, 2008[4]より改変引用）

3）GFR 50 ml/分/1.73 m²未満

わが国における疫学調査では，eGFRが50 ml/分/1.73 m²未満において，将来的に腎不全レベルまで腎機能が低下するリスクが高まる（**図3**）[4]．一般人でeGFR 60 ml/分/1.73 m²以上70 ml/分/1.73 m²未満の群の腎機能低下率を基準にした場合，eGFR 50 ml/分/1.73 m²未満の群では2倍以上のスピードで腎機能低下が進行することが明らかであり，一方，70歳以上ではeGFR 40 ml/分/1.73 m²未満から腎機能低下スピードが速まる．

20歳以上の日本人で，eGFRが50 ml/分/1.73 m²未満の一般住民は約317万人（3.07%）と推定されており，このCKD群は腎機能悪化が予想されるために，腎臓専門医に紹介する．

70歳以上ではGFR 40 ml/分/1.73 m²未満から腎機能低下のリスクが高まるため，安定した70歳以上のCKD患者では，かかりつけ医の判断により腎臓専門医への紹介基準をGFR 40 ml/分/1.73 m²未満としてもよい．一方，若年者（40歳未満）では，GFR 60 ml/分/1.73 m²未満であれば，長期の腎予後も考慮し，腎臓専門医への紹介を考慮すべきである．また，上記基準を満たさなくとも各指標が悪化を示すときは，診察の頻度を上げるなど十分注意して診療にあたる．このように「CKD診療ガイド2012」では年齢に応じた腎機能の紹介基準が考慮されている．

4）その他

最近出現した血尿および蛋白尿で，CRP陽性などの炎症所見を有する場合は，急速進行性糸球体腎炎の可能性があるため，3ヵ月を待たずに腎機能（eGFR）を評価する．

3ヵ月以内に30%以上の腎機能の悪化を認めるなど進行が速い場合は，腎臓専門医へ速やかに相談し治療方針を決定する．

血尿の場合，初回陽性時には画像検査や尿細胞診などで尿路系の異常の有無の確認をおこなう．結果によっては泌尿器科的検索がさらに必要であり，専門医への紹介も考慮する．

2．CKD患者のフォローアップ

1）CKD患者のフォローアップのポイント

CKD患者のフォローアップで重要なことは，CKDの進行を遅らせることと，合併症であるCVDの発症を防

表 1. かかりつけ医における CKD 患者のフォローアップ検査項目

実施間隔：ステージ G1～G2：3～6ヵ月ごと
ステージ G3～G5：1～3ヵ月ごと

検査項目：ステージ G1～G2：蛋白尿定性または蛋白尿定量（g/gCr），血尿，血清 Cr，eGFR
＊糖尿病患者のみ FBS，HbA1c，尿アルブミン（3ヵ月ごと）
ステージ G3～G5：蛋白尿定性または蛋白尿定量（g/gCr），血尿，血清 Cr，eGFR，BUN，UA，Alb，Na，K，Cl，Ca，P，Hb，
＊糖尿病患者のみ FBS，HbA1c，尿アルブミン（3ヵ月ごと）

血圧測定：毎診察時
胸部 X 線/ECG：適宜

（日本腎臓学会編，2012[2]より引用）

原疾患		蛋白尿区分		A1	A2	A3
糖尿病		尿アルブミン定量（mg/日） 尿アルブミン/Cr 比（mg/g·Cr）		正常	微量アルブミン尿	顕性アルブミン尿
				30 未満	30～299	300 以上
高血圧 腎炎 多発性嚢胞腎 腎移植 不明 その他		尿蛋白定量（g/日） 尿蛋白/Cr 比（g/g·Cr）		正常	軽度蛋白尿	高度蛋白尿
				0.15 未満	0.15～0.49	0.50 以上
GFR 区分（ml/分/1.73 m²）	G1	正常または高値	≧90	≦12	≦6	≦3
	G2	正常または軽度低下	60～89	≦12	≦6	≦3
	G3a	軽度～中等度低下	45～59	≦6	≦3	≦3
	G3b	中等度～高度低下	30～44	≦3	≦3	≦3
	G4	高度低下	15～29	≦3	≦3	1
	G5	末期腎不全	＜15	1	1	1

図 4. 腎臓専門医への受診間隔（月）（かかりつけ医へは随時）
（日本腎臓学会編，2012[2]より引用）

ぐことである．

CKD の進行は，食事療法，生活指導および薬物療法で遅らせることが可能である．一方，CKD 患者の各ステージからの末期腎不全への移行は，ステージが進むと増加する．各ステージにおける診療の有効性を随時チェックし，eGFR の低下や蛋白尿の増加を認める場合は治療法の見直しや，腎臓専門医への紹介の必要性も検討する．

経過中に CKD の急性増悪を認める場合，過労，脱水，感染の合併や薬剤投与によるものを考慮する．これらの因子が除去されても改善がない場合は腎臓専門医へ紹介する．

腎臓専門医へ紹介した後も，同じ治療方針に沿って，かかりつけ医・非腎臓専門医と腎臓専門医が連携して治療をおこなう．

成人における CKD 患者のフォローアップの目安を**表 1** に示す．また腎臓専門医と連携して治療をおこなう際の腎臓専門医への受診間隔（月）を**図 4** に示す．

2）各病態のフォローアップ

糖尿病による CKD では，血糖管理を HbA1c 6.9%（NGSP 値）未満とする．ただし腎機能が低下すると腎臓でのインスリン異化が低下し，血糖管理は改善するが低血糖をきたすおそれがあり，注意が必要である．また糖尿病では CVD の頻度が高く，無症状であっても心電図や心エコーなど心臓の評価をおこなう．

蛋白尿陽性患者では，蛋白尿を定期的に尿蛋白濃度/尿 Cr 濃度で評価する．糖尿病患者においては尿アルブミン濃度/尿 Cr 濃度で評価する．蛋白尿が多いほど CKD 進行速度が速く，蛋白尿を減らす治療が必要である．

高血圧による CKD では，血圧の厳格な管理が必要で

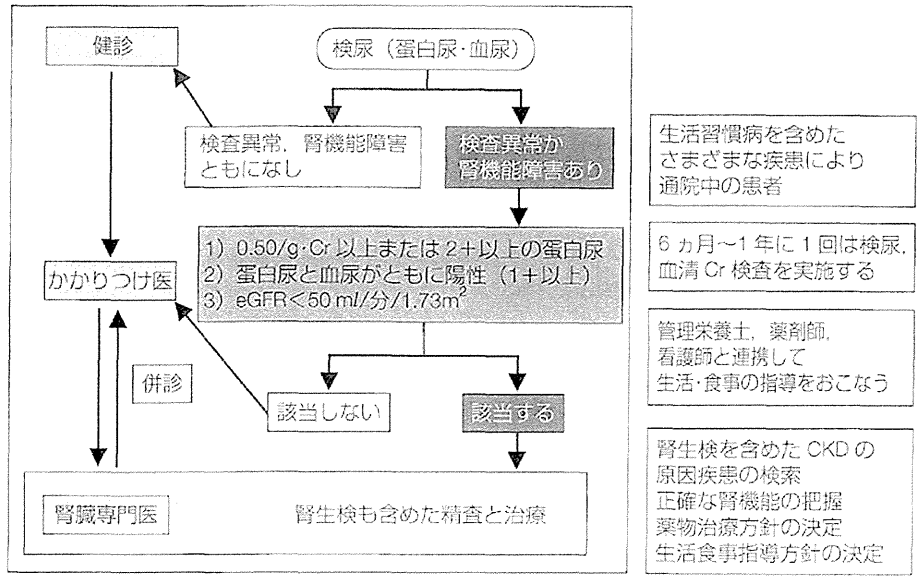

図 5. CKD患者の専門医との連携体制案
（日本腎臓学会編，2012[2]より引用）

ある．腎硬化症では尿所見が乏しいため，腎機能（eGFR）で定期的に評価をおこなう．また腎硬化症はCVDを含む動脈硬化性病変の合併も多く，眼底検査，脈波伝播検査，頸動脈超音波検査などで動脈硬化の程度を評価することが望ましい．

ステージG3以上では高カリウム血症が出現しやすく，時に心室性不整脈など致死的な合併症を引き起こすことがある．定期的に血清カリウムを評価するとともに，カリウムを多く含む食事摂取がないか，またRA系抑制薬などの投薬により血清カリウム値の上昇をきたしていないかを注意深く観察する．

ステージG3以上では腎性貧血をきたす可能性がある．貧血の定期的な評価をおこなうとともに，腎性貧血以外に消化管出血や鉄欠乏性貧血など他の貧血の要素がないか確認する．腎性貧血に対してはエリスロポエチンの投与が必要である．

3．CKD患者の医療連携

CKD診療ガイドは，かかりつけ医がCKDの診療をおこなうために，そして，かかりつけ医と腎臓専門医の連携体制を構築するために作成され，現在の「CKD診療ガイド2012」に引き継がれている．CKD患者の専門医との連携体制案を**図5**に示す．

厚生労働省は2007年度の戦略研究のテーマとして腎臓病を採択し，腎臓病の重症化防止のための方策として，かかりつけ医/非腎臓専門医と腎臓専門医の連携を促進するための診療システムの有用性を検討する研究「腎疾患重症化予防のための戦略研究（Frontier of Renal Outcome Modification in Japan：以下FROM-J）」が開始された[5]．FROM-JではCKD診療ガイドに準拠して診療にあたる介入A群と，介入A群の内容に加えて参加者への受診促進支援，CKD診療目標の達成度をかかりつけ医へフィードバックし，管理栄養士による生活・食事指導をおこなう介入B群，の2群を設定し，その効果を比較検討する．主要評価項目にはかかりつけ医と腎臓専門医の連携率として，紹介率および逆紹介率が設定されている．全国より49医師会，491名のかかりつけ医，2,417名のCKD患者が参加しており，2008年10月より介入開始し，現在は成果の精査および解析がおこなわれている．

FROM-Jはまさしく，CKD診療ガイドを柱として，かかりつけ医のCKD診療と，かかりつけ医と腎臓専門医との医療連携を支援するCKD診療連携システムの有用性の検証を目的としている．CKD診療ガイドがもたらすCKD診療の有効な連携方法の確立が腎臓病重症化