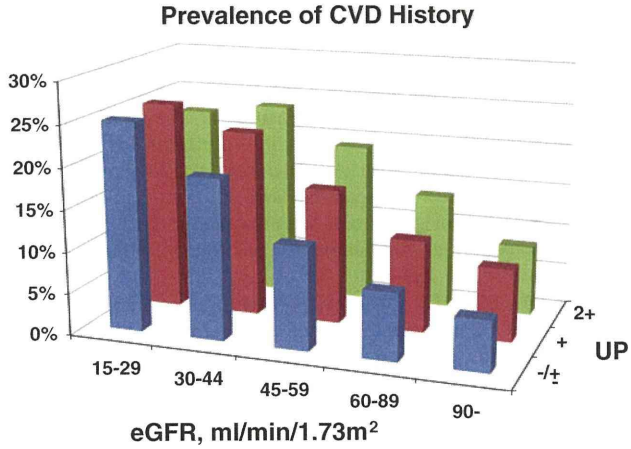

Fig. 2 Prevalence of history of cardiovascular disease (*CVD*) by the combination of eGFR and proteinuria. Prevalence of CVD was significantly ($P < 0.0001$) higher in every column except those with eGFR 15–29; not significant for proteinuria (+), and $P < 0.05$ for proteinuria ≥2+, when compared to the reference value of eGFR ≥90 and proteinuria minus or (±). *P* value was <0.02 for those with eGFR ≥90 and proteinuria ≥2+

Table 4 Mean (SD) levels of body mass index (BMI) and smoking rate in each sex based on the combination of eGFR and proteinuria

eGFR	Proteinuria	Men		Women	
		BMI (kg/m^2)	Smoker (%)	BMI (kg/m^2)	Smoker (%)
<15	Minus, ±	24.1 (2.6)	5.4	22.2 (3.0)	10.9
	1+	24.2 (2.4)	12.5	22.0 (3.4)	5.3
	≥2+	23.3 (2.8)	22.2	24.5 (4.7)	2.5
15–29	Minus, ±	23.6 (3.1)	15.0	23.6 (4.1)	8.0
	1+	24.5 (3.4)	7.0	23.5 (3.8)	6.5
	≥2+	24.2 (3.1)	18.4	25.3 (4.7)	6.0
30–44	Minus, ±	24.3 (2.9)	15.3	23.7 (3.8)	4.4
	1+	24.8 (3.5)	19.5	24.2 (4.5)	6.6
	≥2+	25.2 (3.2)	19.5	24.9 (4.4)	5.9
45–59	Minus, ±	24.1 (2.8)	15.8	23.2 (3.4)	3.9
	1+	24.7 (3.0)	20.6	24.2 (4.2)	5.7
	≥2+	25.2 (3.5)	24.9	25.1 (4.4)	5.7
60–89	Minus, ±	23.7 (3.0)	24.4	22.7 (3.4)	5.1
	1+	24.5 (3.4)	29.4	23.9 (4.3)	6.8
	≥2+	25.1 (3.8)	31.2	24.8 (4.8)	8.1
≥90	Minus, ±	23.4 (3.4)	38.8	22.7 (3.6)	7.2
	1+	24.2 (4.0)	46.5	24.2 (4.5)	8.3
	≥2+	25.0 (4.2)	39.5	25.0 (5.0)	9.4

Total number of participants was 332,174

SD standard deviation

increased prevalence of obesity. Although the prevalence of obesity (BMI ≥30 kg/m^2) is lower in Japan than in the USA [14], complications begin to increase in the Japanese after reaching a BMI of 25 kg/m^2.

Microalbuminuria is suspected when the dipstick test results for proteinuria are (±) and/or 1+ [15]. Routine measurement of microalbuminuria is not feasible for the universal screening of CKD, as the cost is much higher than that of a dipstick urine test for proteinuria. Japan has a long history of universal screening, including dipstick urine testing for both proteinuria and hematuria. A positive proteinuria test result has a strong predictive value for the development of ESRD.

The strengths of the present study are: the number of participants was sufficiently large. It is the first nationwide targeted screening program aimed at determining the prevalence of metabolic syndrome in Japan. People diagnosed with metabolic syndrome are entitled to receive instruction to modify their lifestyles and therefore the risk factors for CKD and CVD can be modified accordingly. The prevalence of metabolic syndrome and obesity, particularly in men, is increasing; therefore, the prevalence of CKD is increasing in Japan [16].The combined eGFR and dipstick proteinuria test results indicate that the prevalence of risk factors for CKD and CVD increasing. Future follow-up studies will provide the predictive value of this CKD stratification on CVD, ESRD, and mortality.

The present study has several limitations. It is a cross-sectional study. Single tests for dipstick proteinuria and serum creatinine might cause misclassification of the true prevalence of CKD. To confirm the existence of CKD, the test should be repeated annually, at least 3 months apart. The current estimation of GFR used in this study is precise (<60 ml/min/1.73 m^2); therefore, the proportion of those with moderately decreased GFR (<45 ml/min/1.73 m^2) seems to be high, 1.56%. We selected patients with data for both serum creatinine and dipstick urine test, which comprised approximately two-thirds of the total participants. A cost–benefit analysis on the best combination of screening tests remains to be performed in Japan. Details of CVD, such as subtype of stroke and heart disease, are not clear. Risk factors may differ among diseases. Information of past medical history, medications, and lifestyle were obtained from a questionnaire, which has not yet been validated. Finally, the elderly population, those aged ≥75 years, was not considered in the present screening. It remains to be determined whether or not risk stratification based on both eGFR and proteinuria is applicable in this age group. CKD also has a role in medical problems commonly seen in elderly people, such as malignancies, pneumonia, sepsis, dementia, and bone fractures.

In conclusion, the risk profiles of CKD and CVD are indicated by the new CKD classification based on eGFR and proteinuria levels in the newly developed screening system used in Japan. Although CKD stratification based on the combined eGFR and proteinuria results seems to be a useful predictor of CVD and mortality in the general

population in Japan, the validity of this finding has yet to be demonstrated in outcome studies, and would be useful for the international comparison of the incidence of ESRD [17].

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Conflict of Interest None.

References

1. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis. 2002;39:S1–S266.
2. An overview of regular dialysis treatment in Japan as of December 31, 2008. Japanese Society for Dialysis Therapy, Tokyo, Japan; 2009.
3. Jungers P, Zingraff J, Albouze P, Chauveau P, Page B, Hannedouche T, et al. Late referral to maintenance dialysis: detrimental consequences. Nephrol Dial Transplant. 1993;3:1089–93.
4. Iseki K, Ikemiya Y, Iseki C, Takishita S. Proteinuria and the risk of developing end-stage renal disease. Kidney Int. 2003;63: 1468–74.
5. Iseki K for the Okinawa Dialysis Study (OKIDS) Group. Analysis of referral pattern and survival in chronic dialysis patients in Okinawa, Japan (1993–1997). Clin Exp Nephrol. 2002;6:43–8.
6. Sunagawa H, Iseki K, Nishime K, Uehara H, Toma S, Kinjo K, et al. Epidemiologic analysis of diabetic patients on chronic dialysis. Nephron. 1996;74:361–6.
7. Chronic Kidney Disease Prognosis Consortium. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet. 2010;375:2073–81.
8. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, Yamagata K, et al. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis. 2009;53:982–92.
9. Imai E, Horio M, Yamagata K, Iseki K, Hara S, Ura N, et al. Slower decline of glomerular filtration rate in the Japanese general population: a longitudinal 10-year follow-up study. Hypertens Res. 2008;1:433–41.
10. Mak KH, Bhatt DL, Shao M, Hankey GJ, Easton JD, Fox KA, Topol EJ. Ethnic variation in adverse cardiovascular outcomes and bleeding complications in the Clopiodogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) study. Am Heart J. 2009;157:658–65.
11. Markus HS, Khan U, Birns J, Evans A, Kalra L, Rudd AG, et al. Differences in stroke subtypes between black and white patients with stroke: the South London Ethnicity and Stroke Study. Circulation. 2007;116:2157–64.
12. Yamagata K, Ishida K, Sairenchi T, Takahashi H, Ohba S, Shiigai T, et al. Risk factors for chronic kidney disease in a community-based population: a 10-year follow-up study. Kidney Int. 2007; 71:159–66.
13. Iseki K, Ikemiya Y, Kinjo K, Inoue T, Iseki C, Takishita S. Body mass index and the risk of development of end-stage renal disease in a screened cohort. Kidney Int. 2004;65:1870–6.
14. Kramer HJ, Saranathan A, Luke A, Durazo-Arvizu RA, Guichan C, Hou S, et al. Increasing body mass index and obesity in the incident ESRD population. J Am Soc Nephrol. 2006;17:1453–9.
15. Konta T, Hao Z, Takasaki S, Abiko H, Ishikawa M, Takahashi T, et al. Clinical utility of trace proteinuria for microalbuminuria screening in the general population. Clin Exp Nephrol. 2007;11:51–5.
16. Nagata T, Ninomiya T, Doi Y, Yonemoto K, Kubo M, Hata J, et al. Trends in the prevalence of chronic kidney disease and its risk factors in a general Japanese population: the Hisayama Study. Nephrol Dial Transplant. 2010;25:2557–64.
17. Caskey FJ, Cramer A, Elliott RF, Stel VS, Covic A, Cusumano A, et al. Global variation in renal replacement therapy for end-stage renal disease. Nephrol Dial Transplant. 2011; Epub.

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ORIGINAL ARTICLE

Cost-effectiveness of chronic kidney disease mass screening test in Japan

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Abstract
Background Chronic kidney disease (CKD) is a significant public health problem. Strategy for its early detection is still controversial. This study aims to assess the cost-effectiveness of population strategy, i.e. mass screening, and Japan's health checkup reform.
Methods Cost-effectiveness analysis was carried out to compare test modalities in the context of reforming Japan's mandatory annual health checkup for adults. A decision tree and Markov model with societal perspective were constructed to compare dipstick test to check proteinuria only, serum creatinine (Cr) assay only, or both.
Results Incremental cost-effectiveness ratios (ICERs) of mass screening compared with do-nothing were calculated as ¥1,139,399/QALY (US $12,660/QALY) for dipstick test only, ¥8,122,492/QALY (US $90,250/QALY) for serum Cr assay only and ¥8,235,431/QALY (US $91,505/QALY) for both. ICERs associated with the reform were calculated as ¥9,325,663/QALY (US $103,618/QALY) for mandating serum Cr assay in addition to the currently used mandatory dipstick test, and ¥9,001,414/QALY (US $100,016/QALY) for mandating serum Cr assay and applying dipstick test at discretion.
Conclusions Taking a threshold to judge cost-effectiveness according to World Health Organization's recommendation, i.e. three times gross domestic product per capita of ¥11.5 million/QALY (US $128 thousand/QALY), a policy that mandates serum Cr assay is cost-effective. The choice of continuing the current policy which mandates dipstick test only is also cost-effective. Our results suggest that a population strategy for CKD detection such as mass screening using dipstick test and/or serum Cr assay can be justified as an efficient use of health care resources in a

On behalf of The Japanese Society of Nephrology Task Force for the Validation of Urine Examination as a Universal Screening.

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population with high prevalence of the disease such as in Japan and Asian countries.

Keywords Chronic kidney disease · Cost-effectiveness · Dipstick test · Mass screening · Proteinuria · Serum creatinine

Introduction

A consensus has been established that chronic kidney disease (CKD) is a worldwide public health problem [1, 2]. The effectiveness of its early detection and treatment to prevent progression to end-stage renal disease (ESRD) and premature death from cardiovascular disease has become widely accepted [3], while the strategy of its screening is still under debate [4]. Whereas high-risk strategies such as routine screening for diabetes patients and as a part of initial evaluation of hypertension patients are pursued in Western countries [5, 6], some argue that population strategies, such as mass screening, could be adopted in Asian countries where CKD prevalence is high [7].

Japan has a long history of mass screening programme for kidney diseases targeting school children and adults since the 1970s. Both urinalysis and measurement of serum creatinine (Cr) level have been mandated to detect glomerulonephritis in annual health checkup provided by workplace and community for adults aged ≥40 years old since 1992 [8]. However, glomerulonephritis was replaced as the leading cause of ESRD by diabetic nephropathy in 1998, and the focus of mass screening policy for adults was shifted to control of lifestyle-related diseases. In 2008, the Japanese government launched a programme, Specific Health Checkup (SHC) and Specific Counselling Guidance, focusing on metabolic syndrome in order to control lifestyle-related diseases, targeting all adults between the ages of 40 and 74 years [9]. This is a combined programme of mass screening followed by health education or referral to physicians. During the process of this development of SHC, different types of screening test for kidney diseases were discussed in the health policy arena [10]. Abandonment of dipstick test to check proteinuria was initially proposed by the Ministry of Health, Labour and Welfare, which was opposed by nephrologists who emphasised the significance of CKD. As a consequence, serum Cr assay was alternatively dropped and dipstick test remained in the list of mandatory test items [11]. However, those found with proteinuria in SHC are not included in the health education programme nor referred to physicians in the following Specific Counselling Guidance that particularly targets metabolic syndrome. At the time, much attention was paid to a report from the USA which suggested the cost-ineffectiveness of mass screening for proteinuria [12], which encouraged the government to abandon dipstick test in their initial proposal.

From the viewpoint of CKD control, the current SHC and Specific Counselling Guidance are not adequate. Therefore, to present evidence regarding CKD screening test for the revision of SHC, which is due in 5 years from its start in 2008, the Japanese Society of Nephrology set up the Task Force for the Validation of Urine Examination as a Universal Screening. Since cost-effectiveness analysis provides crucial information for organising public health programmes such as mass screening, the task force conducted an economic evaluation as a part of their mission. This paper presents the value for money of CKD screening test demonstrated by the task force. The results have implications for CKD screening programmes not only in Japan but also for other populations with high prevalence of CKD such as in Asian countries.

Methods

We conducted cost-effectiveness analysis of CKD screening test in SHC with a decision tree and Markov modelling from societal perspective in Japan. In modelling, we carried out a deliberate literature survey to find the best available evidence from Japan, while reports from overseas were excluded. The PubMed database and Igaku Chuo Zasshi (Japana Centra Revuo Medicina), a Japanese medical literature database, were accessed with combinations of relevant terms such as CKD, health checkup etc. Additionally, we re-analysed our databases and carried out surveys where applicable.

Participant cohort

We assume that uptake of SHC does not change regardless of the choice of the test used for CKD screening, so we model a cohort of participants in SHC. Since the sex and age distribution of participants affects outcomes, we run our economic model by sex and age strata. Probabilities of falling into a sex and age stratum are adopted from a nationwide complete count report of SHC in 2008 [13]. Each value is shown in Table 1, and we estimate outcomes based on the prognosis of participants by initial renal function. We also run our economic model for 25 initial renal function strata defined by the combination of five levels of dipstick test results and five stages of CKD according to estimated glomerular filtration rate (eGFR) derived from serum Cr level. Probabilities of falling into an initial renal function stratum are calculated from the Japan Tokutei-Kenshin CKD Cohort 2008, which is a large cohort for the evaluation of SHC. Each value is shown in Table 1.

Table 1 Model assumptions

			Base-case value	Range tested in sensitivity analysis (%)	Source
Participant cohort					
Probability (%)					
Falling into sex and age stratum	Male	40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74	10.008, 9.280, 8.810, 9.783, 6.460, 5.721, 4.472	±50	[13]
	Female	40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74	6.291, 6.054, 6.137, 7.364, 6.836, 7.143, 5.643		
Falling into initial renal function stratum	−	Stage 1, stage 2, stage 3, stage 4, stage 5	11.660, 46.095, 28.627, 0.224, 0.029	±50	Japan Tokutei-Kenshin CKD Cohort 2008
	±	Stage 1, stage 2, stage 3, stage 4, stage 5	0.866, 3.771, 3.214, 0.056, 0.008		
	1+	Stage 1, stage 2, stage 3, stage 4, stage 5	0.325, 1.548, 1.779, 0.086, 0.013		
	2+	Stage 1, stage 2, stage 3, stage 4, stage 5	0.080, 0.385, 0.705, 0.095, 0.026		
	≥3+	Stage 1, stage 2, stage 3, stage 4, stage 5	0.027, 0.104, 0.204, 0.053, 0.020		
Decision tree					
Probability (%)					
Seeking detailed examination after screened as further examination required			40.0	±50	[15, 16] and expert opinion
Either eGFR <50 ml/min/1.73 m^2 or having comorbidity among stage 3 patients (advanced stage 3)			83.5	±50	Japan Tokutei-Kenshin CKD Cohort 2008
Starting CKD treatment after detailed examination	−	Advanced stage 3, stage 4, stage 5	48.9, 82.2, 96.0	±50	Delphi method survey of expert committee
	±	Advanced stage 3, stage 4, stage 5	51.7, 83.9, 97.1		
	1+	Stage 1, stage 2, early stage 3, advanced stage 3, stage 4, stage 5	25.6, 31.1, 46.7, 71.7, 92.2, 98.0		
	2+	Stage 1, stage 2, early stage 3, advanced stage 3, stage 4, stage 5	62.2, 68.3, 78.9, 93.2, 97.1, 99.8		
	≥3+	Stage 1, stage 2, early stage 3, advanced stage 3, stage 4, stage 5	93.2, 94.3, 97.1, 97.7, 99.9, 99.9		
Markov model					
Probability (%)					
From (1) screened and/or examined to (2) ESRD with no treatment by initial renal function	−	Stage 1, stage 2, stage 3, stage 4, stage 5	0.001, 0.004, 0.016, 0.154, 1.743	±50	Calculated from Okinawa database [18]
	±	Stage 1, stage 2, stage 3, stage 4, stage 5	0.019, 0.020, 0.036, 1.137, 5.628		
	1+	Stage 1, stage 2, stage 3, stage 4, stage 5	0.036, 0.024, 0.303, 3.527, 15.802		
	2+	Stage 1, stage 2, stage 3, stage 4, stage 5	0.080, 0.305, 1.170, 10.939, 31.409		
	≥3+	Stage 1, stage 2, stage 3, stage 4, stage 5	0.347, 0.933, 2.506, 13.824, 69.340		

Table 1 continued

				Base-case value	Range tested in sensitivity analysis (%)	Source
From (2) ESRD to (5) death by sex and age	Male	40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90		0.033, 0.034, 0.035, 0.036, 0.038, 0.039, 0.041, 0.042, 0.044, 0.045, 0.047, 0.048, 0.050, 0.052, 0.054, 0.056, 0.058, 0.060, 0.062, 0.065, 0.068, 0.071, 0.074, 0.078, 0.081, 0.084, 0.088, 0.092, 0.097, 0.101, 0.105, 0.111, 0.117, 0.123, 0.129, 0.135, 0.142, 0.148, 0.155, 0.160, 0.166, 0.176, 0.186, 0.196, 0.202, 0.208, 0.226, 0.229, 0.245, 0.288, 0.257	±50	Calculated from Japanese dialysis patient registry [21]
	Female	40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90		0.029, 0.030, 0.031, 0.032, 0.033, 0.034, 0.035, 0.036, 0.038, 0.039, 0.041, 0.042, 0.043, 0.045, 0.047, 0.049, 0.050, 0.052, 0.055, 0.057, 0.059, 0.062, 0.065, 0.068, 0.070, 0.074, 0.078, 0.080, 0.085, 0.089, 0.093, 0.097, 0.101, 0.105, 0.110, 0.115, 0.122, 0.127, 0.134, 0.138, 0.145, 0.151, 0.159, 0.162, 0.173, 0.185, 0.188, 0.198, 0.205, 0.219, 0.236		
From (1) screened and/or examined to (3) heart attack with no treatment by initial dipstick test result, sex and age	<1+	Male	40–44, 45–54, 55–64, 65–74, 75–84, ≥85	0.005, 0.041, 0.076, 0.132, 0.126, 0.068	±50	[22]
		Female	40–44, 45–54, 55–64, 65–74, 75–84, ≥85	0.019, 0.078, 0.130, 0.234, 0.275, 0.372		
	≥1+	Male	40–44, 45–54, 55–64, 65–74, 75–84, ≥85	0.000, 0.000, 0.018, 0.033, 0.112, 0.077		
		Female	40–44, 45–54, 55–64, 65–74, 75–84, ≥85	0.003, 0.010, 0.048, 0.079, 0.211, 0.224		
From (3) heart attack to (5) death by sex and age	1st year	Male	40–44, 45–54, 55–64, 65–74, 75–84, ≥85	2.8, 13.4, 13.0, 19.5, 33.7, 33.3	±50	[22]
		Female	40–44, 45–54, 55–64, 65–74, 75–84, ≥85	33.3, 0.0, 16.9, 25.0, 36.6, 45.8		
	2nd year	Male and female	40–44, 45–54, 55–64, 65–74, 75–84, ≥85	3.8, 3.8, 6.7, 19.5, 41.2, 100.0	±50	[24]
From (3) heart attack/(4) stroke to (2) ESRD				0.202	±50	[27]
From (1) screened and/or examined to (4) stroke with no treatment by initial dipstick test result, sex and age	<1+	Male	40–44, 45–54, 55–64, 65–74, 75–84, ≥85	0.026, 0.139, 0.264, 0.477, 0.738, 0.769	±50	[22]
		Female	40–44, 45–54, 55–64, 65–74, 75–84, ≥85	0.050, 0.202, 0.357, 0.655, 1.052, 1.540		
		Male	40–44, 45–54, 55–64, 65–74, 75–84, ≥85	0.014, 0.083, 0.124, 0.271, 0.508, 0.570		
		Female	40–44, 45–54, 55–64, 65–74, 75–84, ≥85	0.034, 0.133, 0.187, 0.382, 0.699, 0.905		
From (4) stroke to (5) death by sex and age	1st year	Male	40–44, 45–54, 55–64, 65–74, 75–84, ≥85	19.1, 14.3, 9.9, 10.6, 12.7, 18.2	±50	[22]
		Female	40–44, 45–54, 55–64, 65–74, 75–84, ≥85	13.6, 14.0, 13.7, 6.8, 14.8, 18.1		
	2nd year	Male	40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79, 80–84, ≥85	6.8, 8.2, 9.5, 12.6, 16.6, 23.3, 37.6, 61.9, 95.1, 100.0	±50	Calculated from Suzuki et al. [25, 26]
		Female	40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79, 80–84, ≥85	5.4, 6.4, 7.5, 9.0, 12.5, 18.4, 26.4, 40.1, 52.6, 71.7		

Table 1 continued

			Base-case value	Range tested in sensitivity analysis (%)	Source
From (1) screened and/or examined to (5) death by sex and age	Male	40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79, 80–84, 85–89, 90–94, 95–99, 100	0.002, 0.003, 0.004, 0.007, 0.010, 0.015, 0.024, 0.042, 0.070, 0.119, 0.196, 0.284, 0.397	±50	[28]
	Female	40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79, 80–84, 85–89, 90–94, 95–99, 100	0.001, 0.001, 0.002, 0.003, 0.004, 0.006, 0.010, 0.019, 0.036, 0.070, 0.132, 0.213, 0.327		
Effectiveness of treatment (%)					
Reduction of transition probabilities from (1) screened and/or examined to (2) ESRD with treatment of CKD			42.1	±50	[20]
Reduction of transition probabilities from (1) screened and/or examined to (3) heart attack with treatment of CKD			71.0	±50	[23]
Reduction of transition probabilities from (1) screened and/or examined to (4) stroke with treatment of CKD			69.3	±50	[23]
Quality of life adjustment					
Utility weight					
(1) Screened and/or examined	Stage 1, stage 2, stage 3, stage 4, stage 5		0.940, 0.918, 0.883, 0.839, 0.798	±20	[31]
(2) ESRD			0.658	±20	[32]
(3) Heart attack			0.771		
(4) Stroke			0.714		
Costing					
Annual cost per person (¥)					
Screening	Dipstick test only, serum Cr assay only, dipstick test and serum Cr		267, 138, 342	±50	Survey of health checkup service providers
Detailed examination			25,000	±50	Expert opinion
CKD treatment	Stage 1, stage 2, stage 3, stage 4, stage 5		120,000, 147,000, 337,000, 793,000, 988,000	±50	Expert opinion
ESRD treatment			6,000,000	±50	[33]
Heart attack treatment	1st year, 2nd year		2,780,000, 179,000	±50	[34]
Stroke treatment	1st year, 2nd year		1,000,000, 179,000	±50	[34]

Decision tree

Figure 1a shows our decision tree comparing a do-nothing scenario with a screening scenario. After the decision node, participants under the do-nothing scenario follow the Markov model shown in Fig. 1b. For those under the screening scenario, three types of screening test are considered: (a) dipstick test to check proteinuria only, (b) serum Cr assay only and (c) dipstick test and serum Cr assay. Other tests such as microalbuminuria and cystatin C [14] are not considered, because they are not available options in the context of this study.

Screened participants are portioned between CKD patients who undergo treatment and those who are left untreated through three chance nodes. The first chance node divides the participants between those who require further examination and those left untreated. Participants with (a) dipstick test only, ≥1+; with (b) serum Cr assay only, ≥stage 3; and with (c) dipstick test and serum Cr assay, either ≥1+ or ≥stage 3, are screened as requiring further examination. Those screened as requiring no further examination follow the Markov model. These are implemented by initial renal function stratum.

The second chance node divides participants screened as requiring further examination into those who seek detailed examination at health care providers and those who avoid any further examination. Its probability is assumed at 40.0% based on the literature [15, 16] and of the opinion of an expert committee set up for the purpose of this study, whose members are acknowledged in the "Acknowledgements" section. Those who avoid further examination follow the Markov model.

The third chance node divides participants who underwent further examination into those who undergo treatment of CKD and those left untreated. We derived these probabilities by initial renal function stratum with a Delphi survey of the expert committee. Regarding the strata of stage 3 CKD, a cut-off value of eGFR (50 ml/min/1.73 m^2) and comorbidity such as hypertension, diabetes and/or hyperlipidaemia are considered in order to depict the difference in clinical practice when recommending start of treatment [17]. We label early stage 3 CKD and advanced stage 3 CKD according to this criterion. Among stage 3 CKD patients, the probability of falling into advanced stage 3 CKD by either eGFR <50 ml/min/1.73 m^2 or having comorbidity is 83.5%, calculated from the Japan Tokutei-Kenshin CKD Cohort 2008. Each value is shown in Table 1. All participants follow the Markov model after their completion of detailed examination.

Markov model

The Markov model consists of five health states: (1) screened and/or examined, (2) ESRD, (3) heart attack, (4) stroke and (5) death. Transitions between these states are indicated by arrows. Although individuals follow various courses other than these five health states and indicated transitions, we model in this way based on available data and literature.

We set the span of staying in each state of the Markov model at 1 year. Annual transition probabilities from (1) screened and/or examined to (2) ESRD with no treatment by the initial renal function stratum are calculated from our database of screened cohort in Okinawa Prefecture [18] for this study, since there is no operational predictive model for progression of CKD to ESRD such as Tangri et al. [19] in Japan. Each value is shown in Table 1. Reductions of these transition probabilities brought about by treatment of CKD

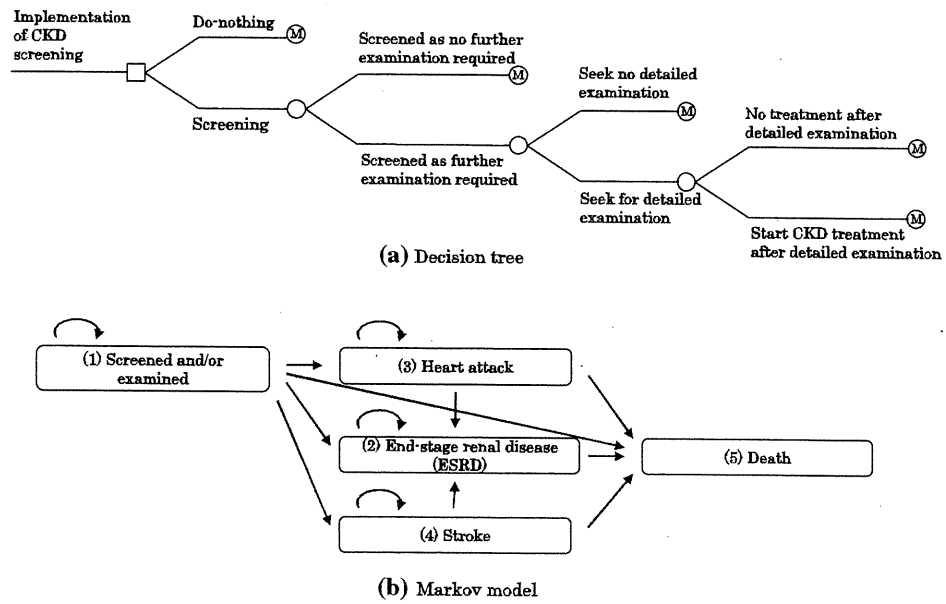

Fig. 1 Economic model. Ⓜ: Markov model

are set at 42.1% based on Omae et al. [20], who investigated the effectiveness of angiotensin-converting enzyme inhibitor in improving renal prognosis. This is a unique Japanese evidence of treatment effectiveness evaluating progression to ESRD which can be compared with our Okinawa cohort [18]. The subsequent transition probabilities to (5) death are calculated from the life expectancy of dialysis starters according to a complete count report of Japanese patients on dialysis [21] by sex and age. Each value is shown in Table 1.

Transition probabilities from (1) screened and/or examined to (3) heart attack with no treatment are adopted from an epidemiological study in Okinawa by Kimura et al. [22] by initial dipstick test result, age and sex. Each value is shown in Table 1. Reductions of these transition probabilities brought about by treatment of CKD are set at 71.0% based on the Hisayama study by Arima et al. [23]. The subsequent transition probabilities to (5) death are adopted from Kimura et al. [22] by age and sex for the first year, and from Fukiyama et al. [24] for the second year and thereafter. Each value is shown in Table 1.

Transition probabilities from (1) screened and/or examined to (4) stroke with no treatment are adopted from Kimura et al. [22] by initial dipstick test result, age and sex. Each value is shown in Table 1. Reductions of these transition probabilities brought about by treatment of CKD are set at 69.3% based on Arima et al. [23]. The subsequent transition probabilities to (5) death are adopted from Kimura et al. [22] by age and sex for the first year, and calculated from the Stroke Register in Akita of Suzuki [25, 26] for the second year and thereafter. Each value is shown in Table 1.

A transition probability from (3) heart attack and (4) stroke to (2) ESRD is adopted from an epidemiological study in Okinawa by Iseki et al. [27].

Transition probabilities from (1) screened and/or examined to (5) death are adopted from Vital Statistics of Japan 2008 [28] by age and sex. Each value is shown in Table 1.

We take a life-long time horizon so that the Markov cycle is repeated until each age stratum reaches 100 years old.

Quality of life adjustment

In order to estimate outcomes, use of quality-adjusted life years (QALYs) is recommended for economic evaluation of health care [29, 30]. QALYs are calculated as the sum of adjusted life-years experienced by a patient, where the adjustment is made by multiplying time by weights linked to the changing health state of the patient. The quality-adjustment weight is a value between 1 (perfect health) and 0 (death), which is one of the health-related quality of life measurements. Regarding (1) screened and/or examined, weights are assigned according to CKD stage based on initial renal function, using values adopted from Tajima et al. [31]. Weights for (2) ESRD, (3) heart attack and (4) stroke are cited from a past economic evaluation of antihypertensive treatment in Japanese context by Saito et al. [32].

Costing

From the societal perspective, costing should cover the opportunity cost borne by various economic entities in society. In the context of this study, costs borne by social insurers and patients are considered, since the cost of SHC is borne by social insurers and the cost of treatment is shared by social insurers and patients in Japan's health system. The amount of direct payments to health care providers by these entities is estimated as costs, while costs of sector other than health and productivity losses are left uncounted in this study. Cost items are identified along the decision tree and Markov model: screening, detailed examination, treatment of CKD, treatment of ESRD, treatment of heart attack and treatment of stroke. Each value is shown in Table 1.

Costs of screening were surveyed in five prefectures by inquiring health checkup service providers' price of adding CKD screening test to a test package that does not include renal function tests. Average price of those for (a) dipstick test to check proteinuria only, (b) serum Cr assay only and (c) dipstick test and serum Cr assay was ¥267 (US $3.0, with US $1 = ¥90), ¥138 (US $1.5) and ¥342 (US $3.8) per person, respectively. Cost of detailed examination is set at ¥25,000 (US $278) per person according to the national medical care fee schedule and a treatment model developed by the expert committee. Annual costs of CKD treatment per person are set at ¥120,000 (US $1,333) for stage 1 CKD, ¥147,000 (US $1,633) for stage 2 CKD, ¥337,000 (US $3,744) for stage 3 CKD, ¥793,000 (US $8,811) for stage 4 CKD and ¥988,000 (US $10,978) for stage 5 CKD, also from the national medical care fee schedule and a treatment model developed by the expert committee. Annual cost of ESRD treatment per person, ¥6,000,000 (US $66,667), is cited from a review of renal disease care in Japan by Fukuhara et al. [33]. Annual cost of heart attack treatment per person, ¥2,780,000 (US $30,889) for the first year and ¥179,000 (US $1,989) for subsequent years, are cited from a past economic evaluation of cardiovascular disease prevention in Japanese context by Tsutani et al. [34]. Similarly, annual costs of stroke treatment per person, ¥1,000,000 (US $11,111) for the first year and ¥179,000 (US $1,989) for subsequent years, are cited from Tsutani et al. [34] as well.

Discounting

Both outcomes and costs are discounted at a rate of 3% [30].

Policy options for economic evaluation

To draw significant policy implications from this economic evaluation, policy options from status quo need to be defined. Under the current SHC, the dipstick test to check proteinuria is mandatory, while serum Cr assay is not. However, some health insurers voluntarily provide serum Cr assay to participants in addition to SHC. We surveyed health insurers in five prefectures and found that 65.4% of them implement use of serum Cr assay. Also, we analysed the Japan Tokutei-Kenshin CKD Cohort 2008 and found that 57.3% of participants underwent use of serum Cr assay. Therefore, we define the status quo regarding screening test for CKD as 40% of insurers implementing dipstick test only and 60% implementing dipstick test and serum Cr assay.

Then we evaluate two policy options in this study: 'Policy 1: Requiring serum Cr assay', and 'Policy 2: Requiring serum Cr assay and abandoning dipstick test'. Policy 1 means mandating use of serum Cr assay in addition to the currently used dipstick test, so that 100% of insurers implement both dipstick test and serum Cr assay if policy 1 is taken. Policy 2 is considered based on two recent health policy contexts. One is the discussion aroused during the development of SHC in which requiring serum Cr assay only and abandoning dipstick test used in the former occupational health checkup scheme attracted substantial support. It is expected that such a policy option will be proposed in the revision of SHC. Another relates to the change in diagnosis criterion of diabetes [35], in which a blood test to check the level of haemoglobin A1c instead of a dipstick test to check urinary sugar level has become pivotal. Implementing dipstick test for checking proteinuria only bears scrutiny from the viewpoint of economic evaluation. We assume that 100% of insurers would stop providing dipstick test if policy 2 is adopted.

We calculate incremental cost-effectiveness ratios (ICERs) for these two policy options using our economic model. ICER is a primary endpoint of cost-effectiveness analysis, which is defined as follows:

$$\mathrm{ICER} = \frac{\text{Incremental cost}}{\text{Incremental effectiveness}} = \frac{\mathrm{Cost}_{\text{New policy}} - \mathrm{Cost}_{\text{Status quo}}}{\mathrm{Effectiveness}_{\text{New policy}} - \mathrm{Effectiveness}_{\text{Status quo}}}$$

This means the additional cost required to gain one more QALY under new policy.

Sensitivity analysis

Economic modelling is fundamentally an accumulation of assumptions adopted from diverse sources. Therefore, it is imperative to appraise the stability of the model. We perform one-way sensitivity analyses for our model assumptions. Assumed probabilities about the participant cohort, the decision tree and the Markov model are changed by ±50%. Reductions of transition probabilities brought about by treatment are also changed by ±50%. Utility weights for quality of life adjustments are changed by ±20%. Costs are changed by ±50%. Discount rate is changed from 0% to 5%. We also changed our assumption about status quo that 40% of insurers implement dipstick test only and 60% implement dipstick test and serum Cr assay by ±50% as well.

Results

Model estimators

Table 2 presents the model estimators. Under the do-nothing scenario, no patient is screened, with average cost of renal disease care per person of ¥2,125,490 (US $23,617) during average survival of 16.11639 QALY. When (a) dipstick test to check proteinuria only is applied, 832 patients out of 100,000 participants are screened, with additional cost of ¥7,288 (US $81) per person compared with the do-nothing scenario, for additional survival of 0.00639 QALY (2.332 quality-adjusted life days). When (b) serum Cr assay only is applied, 3,448 patients are screened with additional cost of ¥390,002 (US $4,333) per person compared with the do-nothing scenario, for additional survival of 0.04801 QALY (17.523 quality-adjusted life days). When (c) dipstick test and serum Cr assay are applied, 3,898 patients are screened with additional cost of ¥395,655 (US $4,396) per person compared with the do-nothing scenario, for additional survival of 0.04804 QALY (17.535 quality-adjusted life days).

Model estimators of ICERs were calculated as ¥1,139,399/QALY (US $12,660/QALY) for (a) dipstick test only, ¥8,122,492/QALY (US $90,250/QALY) for (b) serum Cr assay only and ¥8,235,431/QALY (US $91,505/QALY) for (c) dipstick test and serum Cr assay.

Cost-effectiveness

Table 3 presents the results of cost-effectiveness analysis. Regarding the status quo that 40% of insurers implement dipstick test only and 60% implement dipstick test and serum Cr assay, 2,837 patients out of 100,000 participants are screened, with average cost of screening and renal disease care per person of ¥2,365,798 (US $212,922) during average survival of 16.14777 QALY. Taking policy 1 that 40% of insurers currently using dipstick test only start use of serum Cr assay screens more patients (3,898).

Table 2 Model estimators

	No. of patients per 100,000 participants	Cost (¥)	Incremental cost (¥)	Effectiveness (QALY)	Incremental effectiveness (QALY)	Incremental cost-effectiveness ratio (¥/QALY)
Do-nothing	0	2,125,490		16.11639		
(a) Dipstick test only	832	2,132,778	7,288	16.12278	0.00639	1,139,399
(b) Serum Cr assay only	3,448	2,515,492	390,002	16.16440	0.04801	8,122,492
(c) Dipstick test and serum Cr assay	3,898	2,521,145	395,655	16.16443	0.04804	8,235,431

Table 3 Results of cost-effectiveness analysis

	No. of patients per 100,000 participants	Cost (¥)	Incremental cost (¥)	Effectiveness (QALY)	Incremental effectiveness (QALY)	Incremental cost-effectiveness ratio (¥/QALY)
Status quo	2,837	2,365,798		16.14777		
Policy 1: requiring serum Cr assay	3,898	2,521,145	155,347	16.16443	0.01666	9,325,663
Policy 2: requiring serum Cr assay and abandoning dipstick test	3,448	2,515,492	149,694	16.16440	0.01663	9,001,414

It costs more, but it gains more. Its incremental cost is ¥155,347 (US $1,726), and its incremental effectiveness is 0.01666 QALY (6.081 quality-adjusted life days), resulting in ICER of ¥9,325,663/QALY (US $103,618/QALY). Taking policy 2 that 40% of insurers currently using dipstick test only start use of serum Cr assay and abandon dipstick test screens more patients (3,448) compared with the status quo as well. It also costs more, but it gains more. Its incremental cost is ¥149,694 (US $1,663), and its incremental effectiveness is 0.01663 QALY (6.070 quality-adjusted life days), resulting in ICER of ¥9,001,414/QALY (US $100,016/QALY).

Stability of cost-effectiveness

One-way sensitivity analyses produce similar results not only between policy 1 and policy 2 but also among three model estimators of ICER. Therefore, we present a tornado diagram of policy 1 as an example in Fig. 2. Ten variables with large change of ICER are depicted. A threshold to judge cost-effectiveness is also drawn, which is according to World Health Organization's (WHO) recommendation, being three times gross domestic product (GDP) per capita [36]. Its value is ¥11.5 million/QALY (US $128 thousand/QALY) gain in 2009 in Japan.

The effectiveness of CKD treatment to delay progression to ESRD is found to be the most sensitive. Decreasing the effect by 50% increases ICER to ¥16,280,537/QALY (US $180,895/QALY). The effectiveness of CKD treatment to prevent stroke is also found to be the 10th largest change of ICER, but its range is limited.

The cost of treatment for stage 5 CKD is found to be the second most sensitive. Increasing the cost by 50% increases ICER to ¥14,404,335/QALY (US $160,048/QALY). The cost of ESRD treatment is found to be the fifth largest change, and the change is in the opposite direction; decreasing this increases ICER. Another cost item depicted is the cost of treatment for stage 3 CKD, which is found to be the sixth largest change.

The discount rate is found to be the third most sensitive. Discounting at a rate of 5% makes ICER ¥11,373,185/QALY (US $126,369/QALY). Since policy 1 can screen CKD patients without proteinuria by use of serum Cr assay, the prognosis of non-proteinuric stage 5 CKD without treatment is found sensitive as the fourth and the seventh largest change. The eighth largest change depicted relates to the prevalence of CKD in participating population, i.e. stage 2 CKD without proteinuria. The ninth largest change is utility weight for ESRD.

Taking the threshold to judge cost-effectiveness, one-way sensitivity analyses alter the interpretation of the results for only three variables: reductions of transition probabilities from (1) screened and/or examined to (2) ESRD with the treatment of CKD; cost of treatment for stage 5 CKD; and transition probability from (1) screened and/or examined to (2) ESRD with no treatment by initial renal function for stage 5 CKD without proteinuria.

Discussion

We conduct a cost-effectiveness analysis of CKD screening test in SHC. Facing the scheduled revision of mandatory test items, we appraise two possible policy options compared with the status quo that 40% of insurers implement dipstick test to check proteinuria only and 60% implement

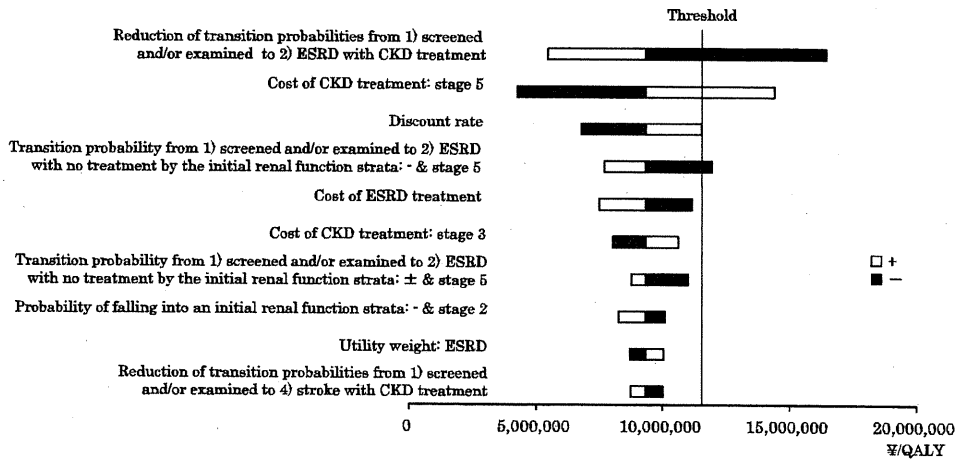

Fig. 2 Tornado diagram of policy 1. This tornado diagram shows ten variables which are found to be sensitive to the change in assumptions. Ten variables are presented, ordered according to the size of the change of ICER from top to bottom. The change of ICERs is represented by *white bars* when increasing the variable or by *black bars* when decreasing the variable from base-case value. The threshold to judge cost-effectiveness is 3 × GDP per capita (¥11.5 million/QALY gain)

dipstick test and serum Cr assay. Policy 1 is to mandate serum Cr assay in addition to the current dipstick test, so that 100% of insurers implement both dipstick test and serum Cr assay. Policy 2 is to mandate serum Cr assay and abandon dipstick test, so that 100% of insurers would stop providing dipstick test and switch to serum Cr assay. Our base-case analysis suggests that both policy options cost more and gain more. Estimated ICERs, are ¥9,325,663/QALY (US $103,618/QALY) for policy 1 and ¥9,001,414/QALY (US $100,016/QALY) for policy 2.

To interpret these ICERs, there is no established value of social willingness to pay for one QALY gain in public health programmes such as mass screening in Japan, although some suggest ¥5 million/QALY (US $56 thousand/QALY) for an innovative medical intervention [37]. We follow WHO recommendation in this study, which is three times GDP per capita [36]. Its value is ¥11.5 million/QALY (US $128 thousand/QALY) gain in 2009 in Japan. Given this threshold, both policy 1 and policy 2 are judged as cost-effective. Therefore, mandating serum Cr assay in SHC can be justifiable as an efficient allocation of finite resources for health. Between policy 1 and policy 2, the ICER of policy 2 is slightly more favourable than that of policy 1, while 450 more patients out of 100,000 participants are screened by adopting policy 1. If secondary prevention of CKD is emphasised as a policy objective in addition to efficiency, policy 1 is an acceptable option as well as policy 2.

Our model estimators have a policy implication, although estimated ICERs do not directly depict any marginal change in society. The ICER of (a) dipstick test only compared with the do-nothing scenario, ¥1,139,399/QALY (US $12,660/QALY), is remarkably favourable. This implies that mass screening with dipstick test only is cost-effective compared with abolishment of mass screening for kidney diseases altogether. Therefore, continuing the current policy, i.e. mandatory dipstick test, could be justifiable as an efficient resource allocation.

This contrasts with the reported cost-ineffectiveness of annual mass screening for adults using dipstick test to check proteinuria in the USA [12], although direct comparison cannot be made between the results of economic evaluations under different health systems. The difference could be attributable to the difference in the prevalence of proteinuria among screened population, with 5.450% being used in our model based on the Japan Tokutei-Kenshin CKD Cohort 2008, while 0.19% is assumed in the US study. Such epidemiological differences are known in terms of not only quantity but also in quality [7]. The prevalence of glomerulonephritis, especially IgA nephropathy, is higher in Asian countries including Japan compared with Western countries [10]. Also, the prevalence of renovascular disease such as ischaemic nephropathy, with which patients are often non-proteinuric until advanced stages of CKD, is lower in Asian countries [38]. The inclusion of heart attack and stroke into our model, which are excluded in the US model [12], may have also made the ICER more favourable.

There is a report of cost-ineffectiveness of population-based screening for CKD with serum Cr assay from Canada [39]. This Canadian model can be compared with our model estimators of (b) serum Cr only compared with the do-nothing scenario. Their health outcomes gain or incremental effectiveness is 0.0044 QALY, which is smaller than ours, 0.04801 QALY, while their incremental cost is C $463 (US $441, using US $1 = C $1.05), which is also smaller than ours, ¥390,002 (US $4,333). These differences probably reflect the difference in the prevalence of CKD between Canada and Japan. Regarding the efficiency of screening programme, our model estimator of ICER, ¥8,122,492/QALY (US $90,250/QALY), is slightly more favourable than that of Canada, C $104,900/QALY (US $99,905/QALY). However, the contradictory conclusion regarding cost-effectiveness is not due to this difference but rather the threshold taken. The Canadian study adopts lower value such

as C $20,000 to C $50,000/QALY (US $19,048 to US $47,619/QALY) following local practice [40].

Our sensitivity analysis suggests instability of the results in only three variables, so our findings are robust to a certain extent. The most sensitive variable is the effectiveness of CKD treatment delaying progression to ESRD: 42.1% reduction is adopted in our economic model according to the unique clinical evidence from Japan, whose agent is angiotensin-converting enzyme inhibitor. It is marginally larger than comparative values reported from Western countries. Reductions in the rate of GFR decline are 35.9% by Agodoa et al. [41], 39.8% by The GISEN Group [42] and 22.5% by Ruggenenti et al. [43]. However, we think our assumption of base-case value is reasonable in two accounts: in light of the indication of angiotensin receptor blockers [17], whose use is more tolerated than angiotensin-converting enzyme inhibitors [44], and the higher prevalence of glomerulonephritis including IgA nephropathy, being a primary renal disease for ESRD, in Japan [10], for which the effect of early treatment such as renin–angiotensin system (RAS) inhibition, an immunosuppression, reduces risk of ESRD by 60% [45].

In regards to the other sensitive variables, we think the prognosis of non-proteinuric stage 5 CKD without treatment does not greatly undermine our findings of base-case analysis, since the value is calculated from extended follow-up of an established database [18]. Uncertainty of the base-case value should be much less than the analysed ±50%. On the other hand, the cost of treatment for stage 5 CKD relates to one of the weaknesses of this study, as discussed in the following.

There are weaknesses in this study. The most significant one is that our economic model depicts the prognosis of CKD by initial renal function stratum. This approach is taken because of the limitation of epidemiological data, and it has little difficulty in estimating outcomes in terms of survival. However, it becomes problematic when it comes to costing. For example, a patient initially screened as stage 1 CKD stays at (1) screened and/or examined before transiting to the following health states such as (2) ESRD. This means that a patient skips over stage 2 CKD to 5 CKD before progressing to ESRD. To estimate the cost for this health state, the diversity of patients in terms of progression of the CKD stages should be taken into account. Our expert committee has developed treatment models to understand this problem. This type of uncertainty is larger in stage 1 CKD and smaller in stage 5 CKD, but the cost of stages 1–4 CKD are not found to be so sensitive in our sensitivity analysis. Also, we think that uncertainty of the cost of stage 5 CKD, the second most sensitive variable, is less than the analysed ±50%, and our findings based on the base-case analysis are plausible. The problem also affects quality of life adjustment, which tends to produce larger QALY outcomes.

Table 4 Recommendation of the Japanese Society of Nephrology Task Force for the validation of urine examination as a universal screening

Mandate use of serum Cr assay in addition to the current dipstick test in the next revision of SHC

Other weaknesses include our assumption of 100% adherence to treatment and so on. However, the most significant strength of this study is that our economic model depends totally on evidence from Japan only, which could justify our simplification in modelling on data availability basis. There is an opportunity for further refinement of our economic model, because a large-scale field trial evaluating the effect of multifactorial treatment including lifestyle modification for early-stage CKD [46] is ongoing in Japan, which will enable us to model progression of CKD with more rigorous clinical evidence [47].

In conclusion, we, the Japanese Society of Nephrology Task Force for the Validation of Urine Examination as a Universal Screening, recommend to mandate use of serum Cr assay in addition to the current dipstick test in the next revision of SHC, from the viewpoint of value for money and the importance of secondary prevention (Table 4). We think that continuation of current policy, in which dipstick test only is mandatory, is still a sensible policy option. Development of adequate Specific Counselling Guidance for screened participants is also recommended.

Whereas the primary objective of this study is to appraise policy options in Japanese context, it also demonstrates that good value for money can be expected from mass screening with dipstick test to check proteinuria in population with high prevalence; that is, a population strategy could be adopted for control of CKD. However, caution is needed when extrapolating this conclusion, since the scope of costing of our economic model does not cover the initial cost of launching mass screening. The model here is based on currently running SHC. The practice of annual mass screening for adults in Japan is quite exceptional, while such universal programmes are rarely found in other countries [48].

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Conflict of interest The authors have declared that no conflicts of interest exist.

References

1. Meguid El, Nahas A, Bello AK. Chronic kidney disease: the global challenge. Lancet. 2005;365:331–440.
2. Levey AS, Schoolwerth AC, Burrows NR, Williams DE, Stith KR, McClellan W, et al. Comprehensive public health strategies for preventing the development, progression, and complications of CKD: report of an expert panel convened by the Centers for Disease Control and Prevention. Am J Kidney Dis. 2009;53:522–35.
3. Levey AS, de Jong PE, Coresh J, El Nahas M, Astor BC, Matsushita K, et al. The definition, classification and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. Kidney Int. 2010;80:17–28.
4. Kiberd B. Screening for chronic kidney disease. BMJ. 2010;341:c5734.
5. de Jong PE, van der Velde M, Gansevoort RT, Zoccali C. Screening for chronic kidney disease: where does Europe go? Clin J Am Soc Nephrol. 2008;3:616–23.
6. Collins AJ, Vassalotti JA, Wang C, Li S, Gilbertson DT, Liu J, et al. Who should be targeted for CKD screening? Impact of diabetes, hypertension, and cardiovascular disease. Am J Kidney Dis. 2009;53:S71–7.
7. Chen N, Hsu CC, Yamagata K, Langham R. Challenging chronic kidney disease: experience from chronic kidney disease prevention programs in Shanghai, Japan, Taiwan and Australia. Nephrology (Carlton). 2010;15:31–6.
8. Imai E, Yamagata K, Iseki K, Iso H, Horio M, Mkino H, et al. Kidney disease screening program in Japan: history, outcome, and perspectives. Clin J Am Soc Nephrol. 2007;2:1360–6.
9. Kohro T, Furui Y, Mitsutake N, Fujii R, Morita H, Oku S, et al. The Japanese national health screening and intervention program aimed at preventing worsening of the metabolic syndrome. Int Heart J. 2008;49:193–203.
10. Yamagata K, Iseki K, Nitta K, Imai H, Iino Y, Matsuo S, et al. Chronic kidney disease perspectives in Japan and the importance of urinalysis screening. Clin Exp Nephrol. 2008;12:1–8.
11. Iseki K. Role of urinalysis in the diagnosis of chronic kidney disease (CKD). JMAJ. 2011;54:27–30.
12. Boulware LE, Jaar BG, Tarver-Carr ME, Brancati FL, Powe NR. Screening for proteinuria in US adults: a cost-effectiveness analysis. JAMA. 2003;290:3101–14.
13. Ministry of Health, Labour and Welfare. Heisei 20 nendo tokutei kenko shinsatokutei hoken shidono jisshi jyokyo ni tsuite. Tokyo: Ministry of Health, Labour and Welfare; 2010.
14. Peralta CA, Shlipak MG, Judd S, Cushman M, McClellan W, Zakai NA, et al. Detection of chronic kidney disease with creatinine, cystatin C, and urine albumin-to-creatinine ratio and association with progression to end-stage renal disease and mortality. JAMA. 2011;305:1545–52.
15. AkamaY Y, Kikuchi S, Sato K, Okada T, Yamaguchi T. Shokuiki teiki kenko shindan ni okeru seimitsu kensa jushin jyokyo–dai chukibo jigyojyo to shokibo jigyojyo no hikaku. Sangyoeiseigaku Zasshi. 2006;48:S60–1.
16. Tsuda K, Tsutsumi A, Kawakami N. Work-related factors associated with visiting a doctor for a medical diagnosis after a worksite screening for diabetes mellitus in Japanese male employees. J Occup Health. 2004;46:374–81.
17. Japanese Society of Nephrology. Clinical practice guidebook for diagnosis and treatment of chronic kidney disease 2009. Tokyo: Tokyo Igakusha; 2009.
18. Iseki K, Iseki C, Ikemiya Y, Fukiyama K. Risk of developing end-stage renal disease in a cohort of mass screening. Kidney Int. 1996;49:800–5.
19. Tangri N, Stevens LA, Griffith J, Tighiouart H, Djurdjev O, Naimark D, et al. A predictive model for progression of chronic kidney disease to kidney failure. JAMA. 2011;305:1553–9.
20. Omae K, Ogawa T, Nitta K. Therapeutic advantage of angiotensin-converting enzyme inhibitors in patients with proteinuric chronic kidney disease. Heart Vessels. 2010;25:203–8.
21. Japanese Society for Dialysis Therapy. An overview of regular dialysis treatment in Japan as of 31 December , 2005. Tokyo: Japanese Society for Dialysis Therapy; 2006.
22. Kimura Y, Takishita S, Muratani H, Kinjo K, Shinzato Y, Muratani A, et al. Demographic study of first-ever stroke and acute myocardial infarction in Okinawa, Japan. Intern Med. 1998;37:736–45.
23. Arima H, Tanizaki Y, Kiyohara Y, Tsuchihashi T, Kato I, Kubo M, et al. Validity of the JNC VI recommendations for the management of hypertension in a general population of Japanese elderly: the Hisayama study. Arch Intern Med. 2003;163:361–6.
24. Fukiyama K, Kimura Y, Wakugami K, Muratani H. Incidence and long-term prognosis of initial stroke and acute myocardial infarction in Okinawa, Japan. Hypertens Res. 2000;23:127–35.
25. Suzuki K. Stroke register in Akita: incidence and the burden of diseases. Nippon Ronen Igakkai Zasshi. 2008;45:169–71.
26. Suzuki K. Chiiki nosocchu hassho toroku wo riyo shita nosocchu iryo no shitu no hyoka ni kansuru kenkyu: Heisei 15 nendo—17 nendo sogo kenkyu hokokusho. Report of Health and Labour Sciences Research Grants (Contract No.: H16-KENKO-014). Tokyo: Ministry of Health, Labour, and Welfare; 2006.
27. Iseki K, Wakugami K, Maehara A, Tozawa M, Muratani H, Fukiyama K. Evidence for high incidence of end-stage renal disease in patients after stroke and acute myocardial infarction at age 60 or younger. Am J Kidney Dis. 2001;38:1235–9.
28. Ministry of Health, Labour and Welfare. Vital statistics of Japan 2008. Tokyo: Health and Welfare Statistics Association; 2010.
29. Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. Methods for the economic evaluation of health care programmes. 3rd ed. Oxford: Oxford University Press; 2005.
30. Gold RM, Siegel JE, Russel LB, Weinstein MC. Cost-effectiveness in health and medicine. New York: Oxford University Press; 1996.
31. Tajima R, Kondo M, Kai H, Saito C, Okada M, Takahashi H, et al. Measurement of health-related quality of life in patients with chronic kidney disease in Japan with EuroQol (EQ-5D). Clin Exp Nephrol. 2010;14:340–8.
32. Saito I, Kobayashi M, Matsushita Y, Mori A, Kawasugi K, Saruta T. Cost-utility analysis of antihypertensive combination therapy in Japan by a Monte Carlo simulation model. Hypertens Res. 2008;31:1373–83.
33. Fukuhara S, Yamazaki C, Hayashino Y, Higashi T, Eichleay MA, Akiba T, et al. The organization and financing of end-stage renal disease treatment in Japan. Int J Health Care Finance Econ. 2007;7:217–31.
34. Tsutani K, Igarashi A, Fujikawa K, Evers T, Kubin M, Lamotte M, et al. A health economic evaluation of aspirin in the primary

prevention of cardiovascular disease in Japan. Intern Med. 2007;46:157–62.
35. Seino Y. New diagnostic criteria for diabetes in Japan. Nippon Rinsho. 2010;68:2357–61.
36. Eichler HG, Kong SX, Gerth WC, Mavros P, Jönsson B. Use of cost-effectiveness analysis in health-care resource allocation decision-making: how are cost-effectiveness thresholds expected to emerge? Value Health. 2004;7:518–28.
37. Shiroiwa T, Sung YK, Fukuda T, Lang HC, Bae SC, Tsutani K. International survey on willingness-to-pay (WTP) for one additional QALY gained: what is the threshold of cost effectiveness? Health Econ. 2010;19:422–37.
38. Chrysochou C, Kalra PA. Epidemiology and natural history of atherosclerotic renovascular disease. Prog Cardiovasc Dis. 2009;52:184–95.
39. Manns B, Hemmelgarn B, Tonelli M, Au F, Chiasson TC, Dong J, et al. Population based screening for chronic kidney disease: cost effectiveness study. BMJ. 2010;341:5869.
40. Menon D, Stafinski T. Health technology assessment in Canada: 20 years strong? Value Health. 2009;12:S14–9.
41. Agodoa LY, Appel L, Bakris GL, Beck G, Bourgoignie J, Briggs JP, et al. Effect of ramipril vs amlodipine on renal outcomes in hypertensive nephrosclerosis: a randomized controlled trial. JAMA. 2001;285:2719–28.
42. GISEN The Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia). Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. Lancet. 1997;349:1857–63.
43. Ruggenenti P, Perna A, Gherardi G, Garini G, Zoccali C, Salvadori M, et al. Renoprotective properties of ACE-inhibition in non-diabetic nephropathies with non-nephrotic proteinuria. Lancet. 1999;354:359–64.
44. Schmieder RE, Ruilope LM, Barnett AH. Renal protection with angiotensin receptor blockers: where do we stand. J Nephrol. 2011;24:569–80.
45. Hotta O, Miyazaki M, Furuta T, Tomioka S, Chiba S, Horigome I, et al. Tonsillectomy and steroid pulse therapy significantly impact on clinical remission in patients with IgA nephropathy. Am J Kidney Dis. 2001;38:736–43.
46. Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. N Engl J Med. 2008;358:580–91.
47. Yamagata K, Makino H, Akizawa T, Iseki K, Itoh S, Kimura K, et al. Design and methods of a strategic outcome study for chronic kidney disease: frontier of renal outcome modifications in Japan. Clin Exp Nephrol. 2010;14:144–51.
48. Holland W. Screening for disease—consideration for policy. Euro Observer. 2006;8:1–4.

— 総　説 —

慢性腎疾患の早期発見と管理・加療の方法

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要旨：2009年末時点で我が国には290,661人の末期腎不全のために透析療法を受けている患者がいる。維持透析患者は年々増加しており，この慢性腎不全となり透析導入を要する慢性腎臓病（Chronic kidney disease; CKD）患者の腎機能悪化を少しでも抑制して，慢性腎不全患者の新たな発症を未然に防ぐことが急務である。しかもCKD患者は心臓血管病の強い危険因子であることが明らかとなり，腎不全対策だけでなく，心臓血管病対策としてもCKDの早期発見と予防対策が重要な課題となってきた。このようなCKDの発症・進展には，血圧異常，血流障害，糸球体の硬化病変，尿細管・間質の線維化などのいわゆるcommon pathwayが悪化要因として重要であり，これらの効率的な異常の是正により腎機能の悪化を抑制することがある程度は可能と考えられている。しかしながら最も効果的で有効な腎機能障害の進行抑制は，CKDに至った原疾患の治癒であることは間違いない。従って，CKDの診療にあたっては，常にCKDに至った原疾患が何かを念頭におき，対処することが求められる。

キーワード：慢性腎不全，心臓血管病，維持透析，危険因子

はじめに

CKDをはじめとする腎疾患は早期には自覚症状を欠き，症状出現時には高度腎障害まで進展していることが多く，早期発見のためには，検診での検尿検査や血清クレアチニン検査などのスクリーニングが診療の第一歩である。従来からわが国では検尿異常のみが初発徴候である糸球体腎炎の頻度が，欧米諸国に比べ高く[1]，腎疾患対策と言えば糸球体腎炎の早期発見，早期治療開始に焦点があてられてきた。このような背景から，1970年代から我が国では学校検尿に始まり，職域検尿，老人検尿など，全ての世代で検尿健診を実施する，生涯検尿体制が確立していた。しかしながら，最近の透析導入原疾患は糖尿病性腎症を代表とする生活習慣病関連の疾患が中心となり，原疾患構成が大きく変貌してきた。さらにはCKDの概念の普及に伴い，腎疾患を透析を要する末期慢性腎不全リスクというとらえ方以上に，心臓血管病発症リスクの高い病態であることも重視されるようになり，生活習慣病対策の柱の一つとしての重要性が認識されるようになってきた。本稿では，この世界的にも注目されているCKDについて，その早期発見法と，対処法についての考え方を概説する。

Kunihiro Yamagata

1）CKD活動の背景

CKD対策は2002年にK/DOQIによるCKDの定義[2]，2005年にはKDIGOにより，国際的にCKDの定義，腎機能の評価法などが決められ普及してきた[3]（**図1**）。我が国においては，日本腎臓学会が中心となり，慢性腎臓病対策協議会の設立，さらには全国においてCKDの概念普及のための様々な活動が実施されてきた。さらにCKD診療ガイドの刊行，日本人独自のeGFR推算式が作成され，我が国のCKD対策も順調に展開されている。この背景には，我が国の維持透析患者は年々増加を続けており（**図2**），透析療法が必要な末期腎不全患者では，維持透析治療がQOLを阻害すると同時に社会生活を送るのに多大な障害となっていること，その結果透析療法に要する医療費も当然ながら多大なものとなっていること，さらにこのような社会的，経済的な状況に加え，CKDが心臓血管病の発症リスクとしてきわめて重要であることが明らかとなり，腎臓専門医だけでなく，かかりつけ医や非腎臓専門医の腎疾患に対する認識が大きく変貌をとげてきたことがあげられる。また治療法がないといわれていた腎疾患に対する有効な治療方法についてのエビデンスが蓄積されてきたこと，さらに適切な時期の腎臓専門医とかかりつけ医と併診による治療が，その後の生命予後だけでなく，医療費抑制効果があることも要因としてあげられる[4]。このような中で，一般住民に対しての腎臓疾患についての認識を深めてもらい，検尿異常などの腎健診異常出現時やその後の経過観察などの対応を確実なものとして，CKDの早期発見を確実なものとする体制整備を行うことの重要性が再認識された（**図3**）。

2）CKDの早期発見のために

①CKDスクリーニング体制

わが国では法規的に慢性腎疾患の早期発見目的に検尿によるスクリーニング検査を1972年（昭和47年）より職域健診，1973年（昭和48年）より学校健診，1983年（昭和58年）より40歳以上の全住民に対して，老人保健法により年1回の定期健診の実施項目として施行してきた。さらに当初はBUN，1990年からは血清クレアチニン検査を40歳以上の全健診受診者に実施してきた。このようにわが国ではCKD早期診断のための検査項目のスクリーニングがCKDの概念が広まる前から可能であった。しかし，2008年以降はこの体制が大きく変更された。基本的には学校健診における検尿検査は継続され，そ

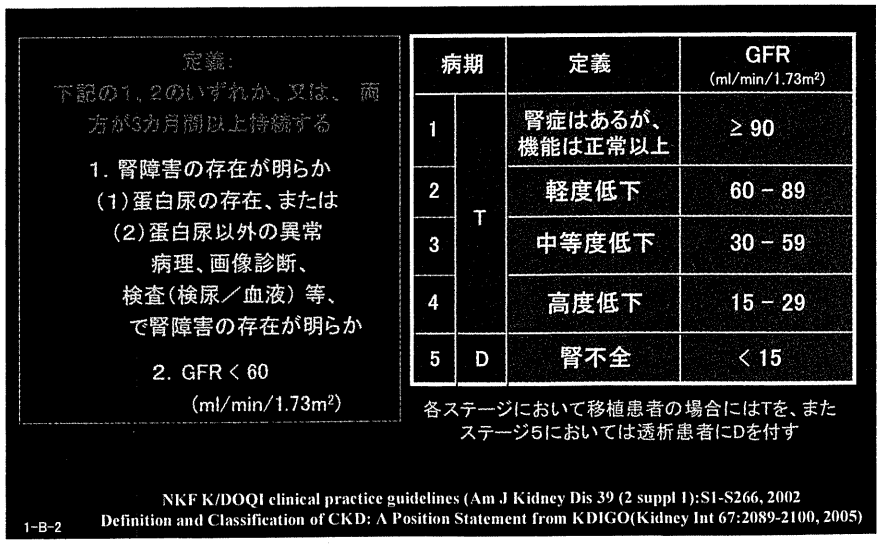

図1　K/DOQI-KDIGOガイドラインによる慢性腎臓病（CKD）の定義と病期（ステージ）分類

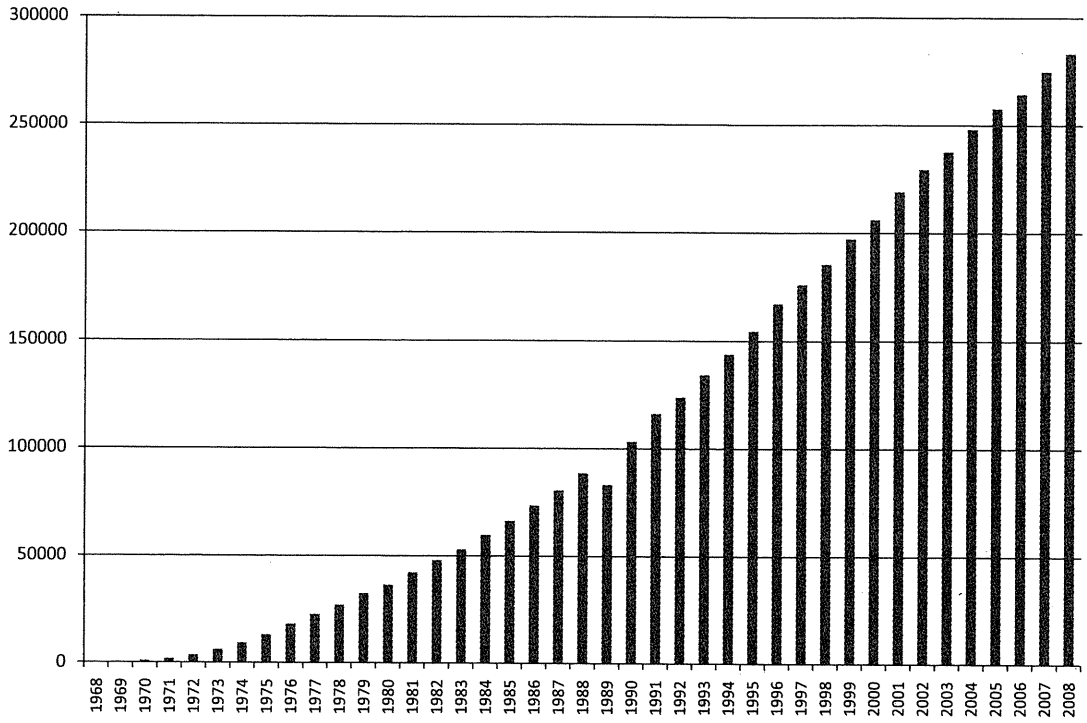

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図2　我が国の維持透析患者の年次推移

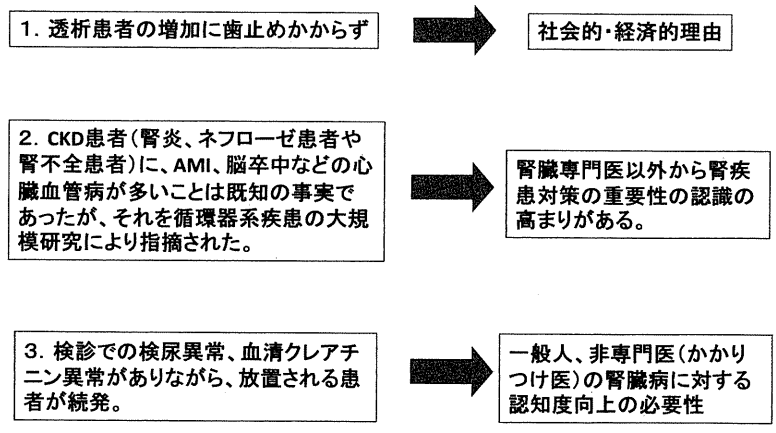

図3　CKDの概念普及の背景

れ以降の労働安全衛生法により規定されていた職域健診や老人保健法による老人基本審査は特定健診にて対応されることとなった。その結果として，我が国の腎健診における生涯検尿体制は，2008年以降，小児に始まり74歳までの検尿にとどまり，2007年をもって，生涯検尿の体制は終了となった。さらに，40歳以降の成人に実施されてきた血清クレアチニン検査は，健診での必須項目から除外された。また，75歳以降のいわゆる後期高齢者については，そもそも健診

そのものの対象から外れた。したがって，これらの患者は医療機関受診時に検尿検査や血清クレアチニン検査を実施することにより，初めて腎障害の有無のチェックが行われることとなる。CKDにおいては自覚症状出現後では，すでに病状が進行していることが多く，早期発見のためにはスクリーニング検査が必須である。

②CKDの発症リスク因子について

これまでの多くの疫学研究の結果や臨床所見から得られた，一般的なCKDの発症リスクとされるものを**表1**に示す[5]。CKD発症リスクには，高血圧，耐糖能障害，肥満，メタボリックシンドロームなどのように，可逆的で自己管理，加療により是正可能なものから，加齢，性別，既往症，低出生体重などの，非可逆的で対処不能なものがある。可逆的項目のうち，高血圧，耐糖能異常，脂質異常症の是正については，多くの前向き研究によりCKD発症予防が可能となることが示されている。

一方，このようなCKD発症リスクの高さ，重要度は，**図4**，**図5**に示すとおり各因子により異なる[6]。ただし，**図4**，**図5**に示した対象は，40歳以上の健診受診者で比較的健常な患者群である。蛋白尿出現のリスクについては，長期間の糖尿病や高血圧の罹病期間が反映され，すでにこれらの疾病と治療中の対象者についてより大きなリスクがあることが分かる。また腎機能が低下し，GFR＜60ml/min/1.73m^{2}となる危険因子は，尿所見異常者の腎機能悪化スピー

表1　CKD発症のリスク因子

可逆的な項目	非可逆的な項目
高血圧	加齢
耐糖能障害・糖尿病	男性
脂質異常症	腎疾患の家族歴
メタボリックシンドローム	急性腎不全後
肥満	尿路結石の既往
高尿酸血症	尿検査異常の既往
喫煙	
膠原病	
全身感染症	
尿道通過障害	
尿路結石	
前立腺肥大	

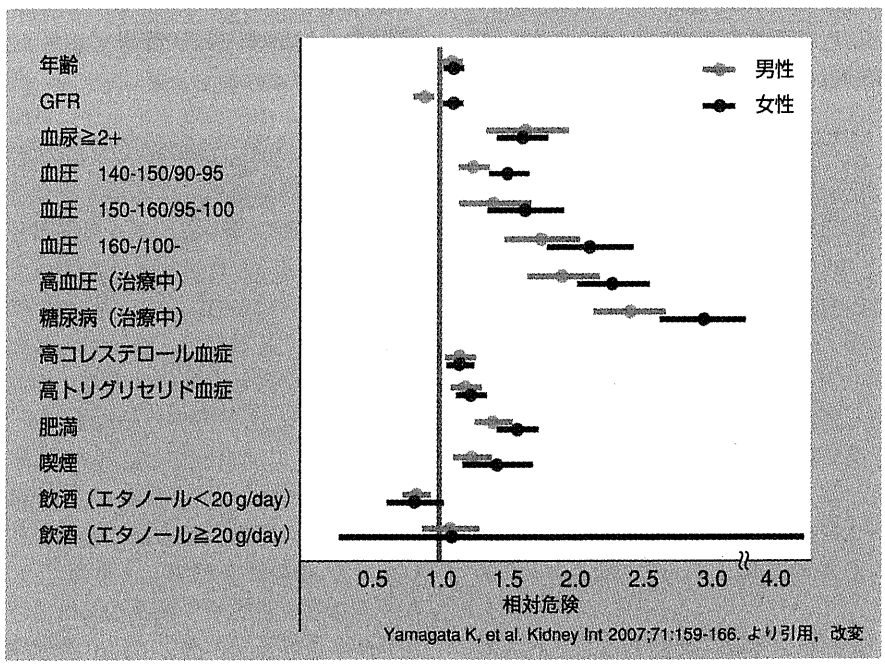

図4　10年間の経過観察中に蛋白尿（CKDステージ1 or 2）が出現するリスク

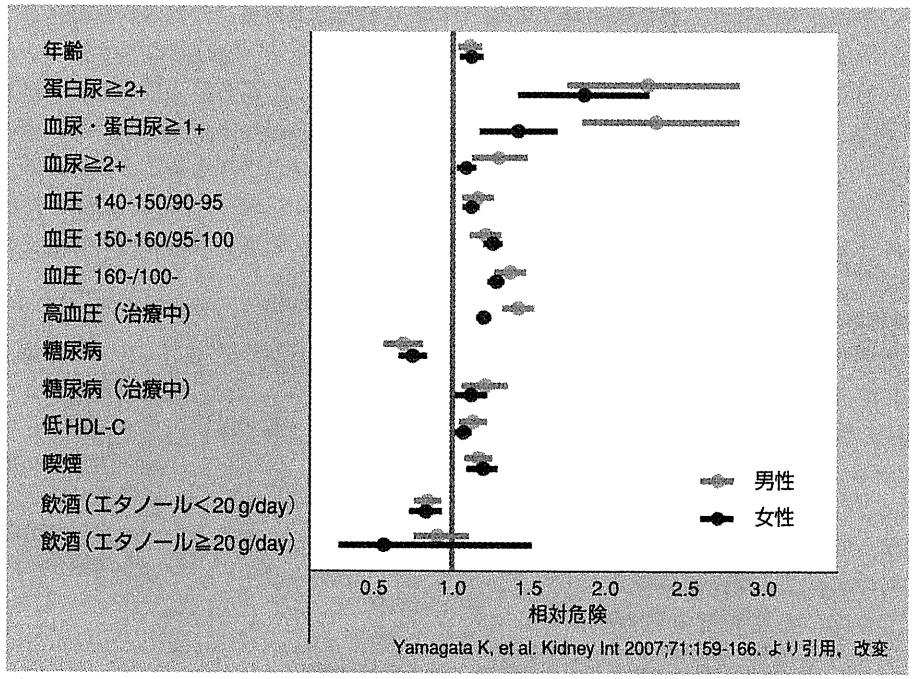

図5　10年間の経過観察中にCKDステージ3以上となるリスクファクター

ドの早さを反映し，尿蛋白陽性者が最もリスクが高いが，蛋白尿と同様，高血圧，糖尿病治療中，脂質異常症などがあげられる。また初期に過剰濾過状態となる患者が多いためなのか，健常人主体の軽症の耐糖能障害や糖尿病患者は，10年以内では腎機能維持される患者が多い。

3）CKDに至る原疾患の変遷

前項に示した蛋白尿出現，腎機能悪化というCKD発症について，もちろん何らかの具体的な腎臓そのものの異常，すなわち原腎疾患があり，その結果としてCKD発症に至る。そのようなCKDの原疾患について，末期慢性腎不全の状態である透析導入時の原疾患，腎臓を専門とする医療機関に受診中の患者の原疾患，検診受診で発見されるCKDの原疾患のそれぞれについて以下に検討する。

①透析導入患者の原疾患からみたCKDの原腎疾患

表2に，2009年1年間に透析を導入された患者の原疾患を示す[7]。最も多いのが糖尿病性腎症，次いで慢性糸球体腎炎，第3位が腎硬化症，第4位が嚢胞腎，第5位が急速進行性腎炎でこの順位は過去数年間不変である。また**図6**は主要原疾患である，糖尿病性腎症，腎硬化症，慢性糸球体腎炎の過去25年間の各年度導入患者に占める割合の推移を示す。糖尿病性腎症と腎硬化症による透析導入患者の比率が増加し，慢性糸球体腎炎による導入患者は減少を認めている。透析導入原疾患で見る限り，慢性糸球体腎炎による透析導入患者数の減少が顕著であるが，これは，特に小児期～若年成人での糸球体腎炎による透析導入減少があるためで，我が国の1970年代から進めてきた，学校検診，職域検診などの検尿検診の効果と考えられている[8]。一方，糖尿病性腎症ならびに腎硬化症については，生活習慣の変化，人口の高齢化とともに，着実に増加しており，慢性腎不全対策としても生活習慣病対策，メタボリックシンドローム対策の重要性の根拠となっている。急速進行性糸球体腎炎に関しては，透析導入患者数は未だ年々増加しており，高齢者に多い本疾患