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ORIGINAL ARTICLE

Budget impact analysis of chronic kidney disease mass screening test in Japan

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Abstract
Background Our recently published cost-effectiveness study on chronic kidney disease mass screening test in Japan evaluated the use of dipstick test, serum creatinine (Cr) assay or both in specific health checkup (SHC). Mandating the use of serum Cr assay additionally, or the continuation of current policy mandating dipstick test only was found cost-effective. This study aims to examine the affordability of previously suggested reforms.
Methods Budget impact analysis was conducted assuming the economic model would be good for 15 years and applying a population projection. Costs expended by social insurers without discounting were counted as budgets.
Results Annual budget impacts of mass screening compared with do-nothing scenario were calculated as ¥79–¥−1,067 million for dipstick test only, ¥2,505–¥9,235 million for serum Cr assay only and ¥2,517–¥9,251 million for the use of both during a 15-year period. Annual budget impacts associated with the reforms were calculated as ¥975–¥4,129 million for mandating serum Cr assay in addition to the currently used mandatory dipstick test, and ¥963–¥4,113 million for mandating serum Cr assay only and abandoning dipstick test.
Conclusions Estimated values associated with the reform from ¥963–¥4,129 million per year over 15 years are considerable amounts of money under limited resources.

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

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The most impressive finding of this study is the decreasing additional expenditures in dipstick test only scenario. This suggests that current policy which mandates dipstick test only would contain medical care expenditure.

Keywords CKD · Budget impact · Dipstick test · Mass screening · Proteinuria · Serum creatinine assay

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-year old since 1992 [8]. However, glomerulonephritis was replaced by diabetic nephropathy as the leading cause of ESRD in 1998, and the focus of mass screening policy for adults was shifted to the 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 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]. 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 was 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, which had been published elsewhere [12]. It concludes that the current policy which mandates dipstick test only is cost-effective, while a policy that mandates serum Cr assay is also cost-effective.

However, it is said that there are five hurdles to overcome in the nationwide application of health intervention: quality, safety, efficacy, cost-effectiveness and affordability (Fig. 1) [13, 14]. Among these hurdles, 'cost-effective' in the economic evaluation framework means that it is acceptable for the society to sacrifice the total value of cumulative costs with discount over the time horizon to gain additional health outcomes brought by the suggested public health programme, whereas it does not directly mean affordability that the government or the third party payer such as social insurers are able to expend required cash to implement the policy. Prevention including mass screening always accompanies costs in advance and effectiveness in the future, which instantly raises a question about its impact on health care financing over time. This paper aims to examine the fifth hurdle, that is, affordability of CKD mass screening test under Japan's health system by estimating its impact on public health care expenditure [15]. The results would have implications for CKD screening programmes not only in Japan but also for other populations with high prevalence of CKD such as Asian countries [16, 17].

Methods

We conducted a budget impact analysis of CKD screening test in SHC based on our previous economic model reporting cost-effectiveness [12]. As shown in Fig. 1, the budget impact analysis is to demonstrate budget changes in terms of cash flows, in which payer's perspective is always taken; health outcomes are excluded; and financial costs are included.

As the summary of the economic model constructed in our previous cost-effectiveness analysis is shown in Table 1, it evaluated two reform policy options based on

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the economic model comparing do-nothing scenario with dipstick test only, serum Cr assay only, and both. The two policies were: mandate the use of serum Cr assay in addition to the current dipstick test (Policy 1); or mandate the use of serum Cr assay only and abandon dipstick test (Policy 2). Policy 1 meant that the current SHC practice, which was a mandatory 100 % use of dipstick test with 60 % use of serum Cr assay at discretion, would become a mandatory 100 % use of both dipstick test and serum Cr assay; while Policy 2 meant that the current practice would switch to the mandatory 100 % use of serum Cr assay and no use (0 %) of dipstick test. The latter assumption was made by the change in diagnosis criterion of diabetes [18], in which a blood test to check the level of haemoglobin A1c instead of a dipstick test to check urinary sugar level had become pivotal. And the model estimator comparing

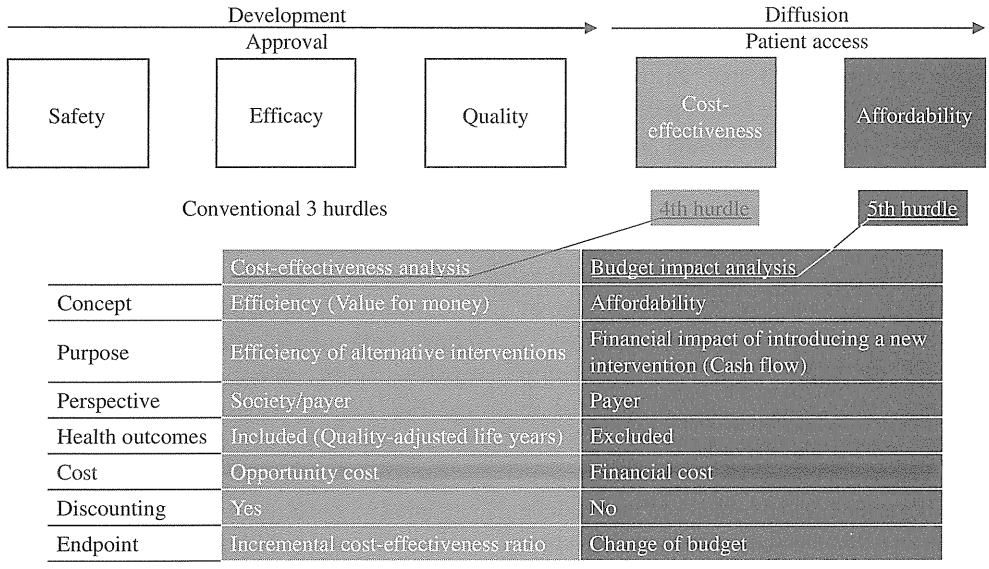


Fig. 1 In addition to conventional three hurdles for approval through development phase, two modern hurdles for patient access through diffusion phase are widely recognised these years: 4th hurdle for cost-effectiveness and 5th hurdle for affordability. These hurdles are appraised by cost-effectiveness analysis and budget impact analysis, respectively. Cost-effectiveness analysis concerns efficiency of resources use based on the valuations of cost and effectiveness at the same time comparing technical alternatives, while budget impact analysis concerns affordability of the government or the third party payer by demonstrating changes of cash flows as a result of making an intervention accessible for the population

Table 1 Summary of cost-effectiveness of chronic kidney disease (CKD) screening test in Japan

Objective The study aims to assess the cost-effectiveness of population strategy, i.e. mass screening, for CKD control 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 Number of screened patients and incremental cost-effectiveness ratios (ICERs) of mass screening compared with do-nothing were calculated as 832 patients out of 100,000 participants and ¥1,139,399/QALY (US $12,660/QALY) for dipstick test only; 3,448 patients and ¥8,122,492/QALY (US $90,250/QALY) for serum Cr assay only; and 3,898 patients and ¥8,235,431/QALY (US $91,505/QALY) for both. Number of additionally screened patients and ICERs associated with the reform were calculated as 1,061 (3,898 from 2,837) patients out of 100,000 participants and ¥9,325,663/QALY (US $103,618/QALY) for mandating serum Cr assay in addition to the currently used mandatory dipstick test (Policy 1), and 611 (3,448 from 2,837) patients ¥9,001,414/QALY (US $100,016/QALY) for mandating serum Cr assay and applying dipstick test at discretion (Policy 2). The decrease of new haemodialysis patients compared with do-nothing in the fifth year and tenth year were estimated as 0.293 %/1.128 % for dipstick test only, 5.092 %/4.380 % for serum Cr assay only, and 5.094 %/4.380 % for both. The decrease of new haemodialysis patients associated with the reform was 1.249 %/1.346 % for Policy 1 and 1.251 %/1.346 % for Policy 2

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. 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 population with high prevalence of the disease

Source Kondo et al. [12]

do-nothing scenario with dipstick test only scenario reflected the choice of continuing the current policy. Our budget impact analysis evaluated these policy options.

Health care budget impact is defined as a forecast of rates of use (or changes in rates of use) with their consequent short- and medium-term effects on budgets and other resources to help health service managers plan such changes [19]. We took the following three steps in our analysis: (1) the estimation of annual incremental budget per person, (2) the estimation of annual number of adults who would uptake SHC and (3) the estimation of budget impact by combining the results from (1) and (2).

The first step (1) was implemented on our economic model assuming that the annual economic model would be good for 15 years (Table 2). It included costs borne by adults and social insurers from the societal perspective, while costs of sectors other than health and productivity losses were uncounted. Costs expended by social insurers without discounting were counted as budgets. Costs for screening were fully borne by social insurers, and costs for further detailed examination and treatment at health facilities were 70 % reimbursed except in case of dialysis. Fixed co-payment for dialysis patients, ¥10,000 (US$100, US$1 =¥100) per month, was subtracted from the total cost. Assumed annual budgets per person are shown in Table 2.

In the second step (2), we used a population projection for Japan [20], and sex and age structure was applied to our annual economic model. We assumed that the uptake of SHC was fixed at 41.3 % for 15 years [21]. In the third step (3), estimated annual incremental budgets per person were multiplied by estimated annual number of adults who would uptake SHC.

Table 2 Assumptions for budget impact analysis

1. The annual economic model is good for 15 years	
2. Annual budgets per person (costs in the economic model [12])	
Screening	
Dipstick test only	¥ 267 (¥267)
Serum Cr assay only	¥138 (¥138)
Dipstick test and serum Cr assay	¥342 (¥342)
Detailed examination at clinic or hospital	¥17,500 (¥25,000)
CKD treatment	
Stage 1	¥84,000 (¥120,000)
Stage 2	¥102,900 (¥147,000)
Stage 3	¥235,900 (¥337,000)
Stage 4	¥555,100 (¥793,000)
Stage 5	¥691,600 (¥988,000)
ESRD treatment	¥5,880,000 (¥6,000,000)
Heart attack treatment	
1st year	¥1,946,000 (¥2,780,000)
2nd year and after	¥125,300 (¥179,000)
Stroke treatment	
1st year	¥700,000 (¥1,000,000)
2nd year and after	¥125,300 (¥179,000)
3. A population projection for Japan [17] is used and sex and age structure is applied for the annual economic model	
4. The uptake of SHC is fixed at 41.3 % for 15 years [18]	

Results

Table 3 shows the model estimators of budget impact. Compared with do-nothing scenario, total additional expenditure of dipstick test only decrease from ¥79 million (US$0.79 million) in the first year (2012) to ¥−1,067 million (US$−10.67 million) in the fifteenth year (2026); those of serum Cr assay only increase from ¥2,505 million (US$25.05 million) to ¥9,235 million (US$92.35 million); those of both dipstick test and serum Cr assay increase from ¥2,517 million (US$25.17 million) to ¥9,251 million (US$92.51 million); and those of status quo increase from ¥1,542 million (US$15.42 million) to ¥5,122 million (US$51.22 million). These estimators are also shown in Fig. 2. The breakdown of additional expenditures for screening and curative care is also reported in Table 3. Additional expenditures for screening are almost constant: ¥16 million (US$0.16 million) for dipstick test only, ¥8 million (US$0.08 million) for serum Cr assay only, ¥20 million (US$0.2 million) for dipstick test and serum Cr assay, and ¥18 million (US$0.18 million) for status quo. Decreases or increases during the 15 years are attributable to the changes in additional expenditure for curative care.

Table 4 shows the results of budget impact analysis in the same way focusing on the two policy options. Compared with status quo, the budget impacts as total additional expenditure of Policy 1 which requires serum Cr assay increase from ¥975 million (US$9.75 million) in the first year (2012) to ¥4,129 million (US$41.29 million) in the fifteenth year (2026); and those of Policy 2 which requires serum Cr assay and abandons dipstick test increase from ¥963 million (US$9.63 million) to ¥4,113 million (US$41.13 million). These are drawn in Fig. 3 as well. Breakdowns of screening and curative care are also reported in Table 4. Additional expenditures for screening are almost constant: ¥2 million (US$0.02 million) for Policy 1, and ¥−10 million (US$−0.1 million) for Policy 2. Increases during the 15 years are attributable to the changes in additional expenditure for curative care.

Discussion

We estimate the budget impacts of CKD screening test in SHC, of which use has been found cost-effective elsewhere [12]. With regard to two reform policy options: mandate

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

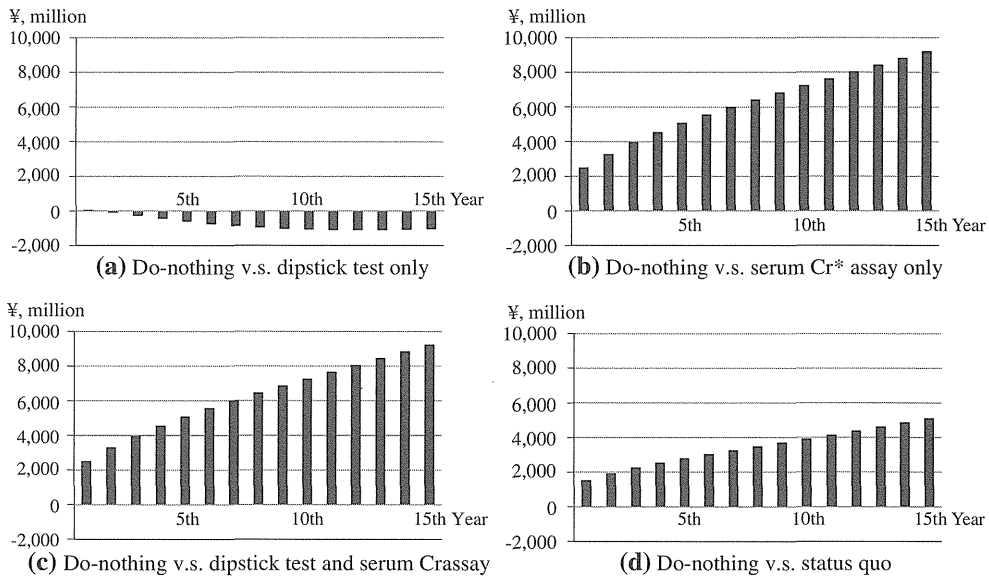


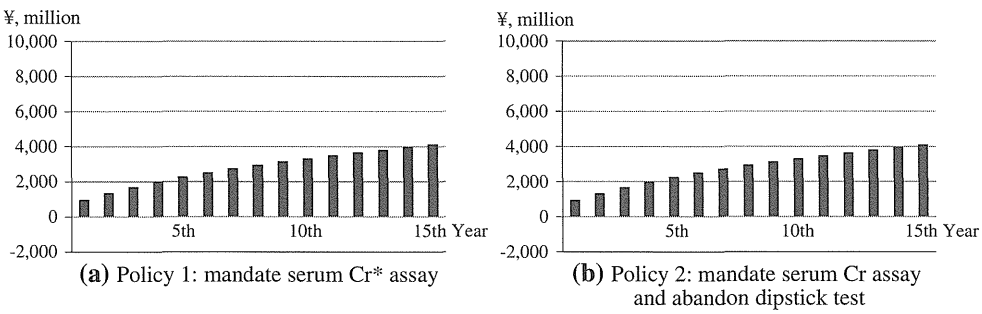
Fig. 2 *Black bars* depict annual budget impacts of mass screening compared with do-nothing scenario. Negative budget impacts on (**a**) imply that the continuation of current policy which mandates dipstick test only would contain medical care expenditure. **a** Do-nothing versus dipstick test only.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

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

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ORIGINAL ARTICLE

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

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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 anti-hypertensive 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/

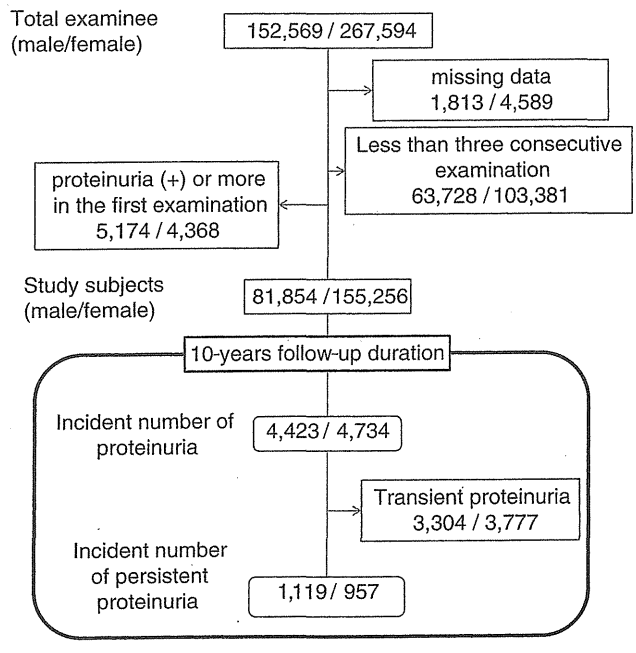

Fig. 1 Number of examinee and study subjects and their male:female ratio are shown

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 (%)*

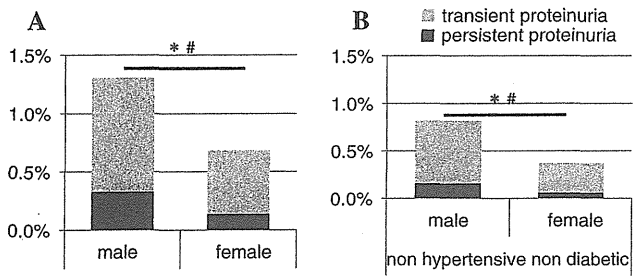

Fig. 2 The annual incidence of proteinuria and persistent proteinuria. *Black and gray bar* indicates the annual incidence of persistent proteinuria and transient proteinuria, respectively. A total of *stacked bars* mean annual incidence of proteinuria. The incidence of proteinuria and persistent proteinuria 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

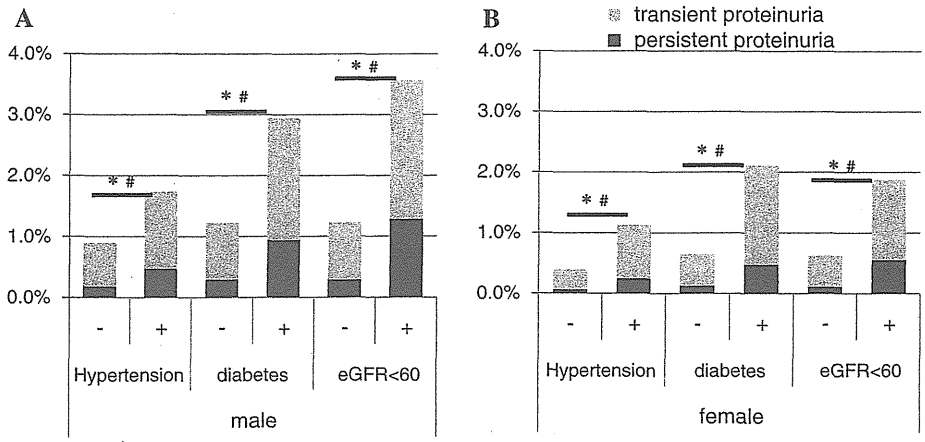

Fig. 3 The different annual incidence between the presence and absence of co-morbid conditions. *Black and gray bar* indicates the annual incidence of persistent proteinuria and transient proteinuria. A total of *stacked bars* mean annual incidence of proteinuria. Every co-morbid condition was significantly 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.

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Conflict of interest None declared.

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ORIGINAL ARTICLE

Health-related quality of life and prognosis in patients with chronic kidney disease: a 3-year follow-up study

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Abstract

Background Chronic kidney disease (CKD) is a major global problem and is also associated with a decreased health-related quality of life (HRQOL). The aim of this study was to evaluate measured HRQOL based on the new CKD classification including proteinuria stage, and the effect of measured HRQOL on CKD progression and clinical outcomes over a 3-year period.

Methods EuroQol (EQ-5D), a generic preference-based questionnaire, was administered to 537 CKD outpatients at the University of Tsukuba Hospital between November and December 2008. We evaluated disease progression in CKD patients including the incidence of end-stage kidney disease (ESKD), cardiovascular disease (CVD) and all-cause mortality over a 3-year follow-up period.

Results The proportions progressing to the higher stages were 32.6, 20.0, 36.6, 39.5, and 45.8 % from glomerular filtration rate (GFR) stages (G) 1–4, respectively. The proportion progressing to ESKD (G5D) was 0.7 % from G2, 3.9 % from G3b, 20.8 % from G4 and 63.4 % from G5. The incidence of CVD and/or death was 1.2, 4.6, 4.9, 5.3, 8.3 and 21.1 % from G1–G5, respectively. The quality-adjustment weights at G4–5 were significantly lower than at G1–2 and the weights at proteinuria stage (A) 3 were significantly lower than at A1–2. The quality-adjustment weights of patients with events such as 50 % estimated GFR decline, dialysis, CVD, and/or death were significantly lower than those without events.

Conclusion We showed CKD progression and clinical outcomes over a 3-year period. Quality-adjustment weights in CKD patients were associated with not only disease progression such as initiation of dialysis treatment and incidence of CVD events and all-cause death, but also the level of proteinuria at baseline.

Keywords Chronic kidney disease (CKD) · Health-related quality of life (HRQOL) · Quality-adjustment weight · EuroQol (EQ-5D) · Prognosis · Proteinuria

Introduction

Chronic kidney disease (CKD) is a major independent risk factor for cardiovascular disease (CVD), including progression to end-stage kidney disease (ESKD), stroke and premature death [1, 2]. CKD is thus a worldwide public health problem and socioeconomic concern. In fact, there are >300,000 ESKD patients in Japan. The annual medical cost of dialysis treatment was >130 billion yen in 2011 [3]. Moreover, the total number of cases estimated for CKD stages G1, G2, G3, G4 + 5 in the Japanese adult population were 0.61, 1.71, 10.74, and 0.23 million, respectively [4]. Therefore, early detection and initiation of treatment for CKD are important in order to prevent progression to kidney failure as well as cardiovascular complications and death, and also to decrease medical cost. However, patient characteristics and clinical course in predialysis stages under the care of nephrologists are not well described. Therefore, the first objective of this study was to evaluate disease progression in patients with CKD including

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incidence of ESKD, CVD and all-cause death over a study period of 3 years.

The high morbidity of CKD and high cost of dialysis have promoted interest in developing cost-effective interventions for CKD and in understanding the health-related quality of life (HRQOL) of patients with CKD. It is now widely accepted that HRQOL is significantly compromised in patients with ESKD and is associated with increased mortality and morbidity [5, 6]. It is also well known that CKD including dialysis patients is associated with a decreased HRQOL [7–9]. We first measured the HRQOL in terms of quality-adjustment weight using EuroQol (EQ-5D), a generic preference-based questionnaire [10, 11], in patients with CKD to conduct a cost-effective analysis. HRQOL decreases with progression of CKD stages and measured weights were 0.940 for stage 1, 0.918 for stage 2, 0.883 for stage 3, 0.839 for stage 4, 0.798 for stage 5, and 0.885 for all stages. We also showed decreases of HRQOL with presence of anemia, undernutrition, hypertension, diabetes, or history of CVD [12]. In this study, we aimed to evaluate the effect of the measured HRQOL on CKD progression and clinical outcomes including development to ESKD, CVD events and all-cause death over a 3-year study period, because few studies have investigated longitudinal effects of HRQOL on disease progression in CKD patients.

Recently, the Kidney Disease: Improving Global Outcomes (KDIGO) group recommended that patients with CKD should be assigned to stages and composite relative risk groups according to criteria of glomerular filtration rate (GFR) (G) and proteinuria (A) [13]. In Japan, the CKD Clinical Practice Guide was revised by the Japanese Society of Nephrology, and the stages and composite relative risk groups were described according to GFR (G) and proteinuria (A) criteria. Proteinuria, an independent risk factor for death, myocardial infarction and progression to kidney failure at a given level of eGFR [14], are also related to HRQOL in patients with advanced type 2 diabetic nephropathy [15]. However, whether proteinuria is also related to HRQOL in patients with CKD has not been examined. Therefore, we evaluated the relationship between HRQOL and proteinuria according to the new CKD classification. Thus, the association of HRQOL in CKD patients, disease progression such as initiation of dialysis treatment and incidence of CVD events and all-cause death, and the level of proteinuria of baseline can all be studied.

Materials and methods

Instrument for measuring quality-adjustment weights

We used EQ-5D, a generic preference-based measure of quality-adjustment weights, which is standardized and validated for use in Japan [10, 11]. It is administered to patients who are asked to grade five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) of their health state as one of three levels ('no problem', 'some problems', and 'extreme problem'). The quality-adjustment weight ranges from 1 for perfect health (no problem in any dimension) to 0 for death and −0.111 for severe problems in all dimensions. A positive weight means that the health status is better than death and a negative weight is worse than death in EQ-5D.

Study design and patients

A 3-year follow-up study was conducted with outpatients previously diagnosed with CKD at the Department of Nephrology, University of Tsukuba Hospital. A total of 537 patients were recruited between November 2008 and December 2008 and followed prospectively until January 2012. At baseline, EQ-5D was given after written informed consent was obtained. This study complied with the Helsinki Declaration and was approved by the Ethics Committee of the Graduate School of Comprehensive Human Science, University of Tsukuba (approval number H20-295).

Study variables

From patient records, sex and age were included in our analysis as demographic baseline characteristics. Assays were performed for creatinine, hemoglobin, serum albumin, urinary protein, and urinary creatinine on the day of the questionnaire survey. GFR was estimated (eGFR) from serum creatinine, age, and sex using the new Japanese equation as follows: eGFR (ml/min/1.73 m^2) = 194 × serum creatinine$^{-1.094}$ × age$^{-0.287}$ × 0.739 (if female) [16]. CKD stage was determined at baseline according to the modified classification for the Japanese people based on the KDIGO Consensus Conference [13]; GFR stages G1–5 were defined as G1, GFR ≥90 ml/min/1.73 m^2; G2, 60–89; G3a, 45–59; G3b, 30–44; G4, 15–29; and G5, <15. Proteinuria stages A1–3 were defined as A1, <0.15 g/g creatinine; A2, 0.15–0.49; and A3, ≥0.50. Annual eGFR decline was calculated as last available eGFR minus baseline eGFR divided by 3 years. Annual eGFR decline of patients who started dialysis treatment at the University of Tsukuba Hospital during the 3-year study period was corrected by the duration from baseline to initiating dialysis. A 50 % eGFR decline was defined when the eGFR declined to 50 % from baseline. The primary disease was defined by clinical course, diagnostic imaging or biopsy findings. According to progression of CKD stages, patients were stratified into 'non-progressive group' if their stages were stable or improved, 'progressive group' if their stages progressed, 'dialysis group' if they

started dialysis therapy among progress group, and 'death group' if they died during the follow-up period. The presence of complications and clinical outcomes was also assessed using the records. Hypertension and diabetes were classified based on clinical records. A history of CVD was regarded as present if stroke, congestive heart disease, or ischemic heart disease was recorded. Primary outcomes included CVD such as angina pectoris, acute myocardial infarction, congestive heart failure, stroke and all-cause death were surveyed using hospital medical records and interviews with attending physicians.

Statistical analysis

All statistical analyses were performed using SAS. Quality-adjustment weights were calculated as the mean weight values of a group of patients according to the Japanese value set for EQ-5D, and 95 % confidence intervals were computed. The weight differences among CKD stages were tested by ANOVA. The level of significance was set at $P < 0.05$.

Results

The patients included 282 males (52.5 %) and 255 females (47.5 %) with an overall mean age of 55.2 years. Mean creatinine was 1.7 mg/dl; mean eGFR was 56.1 ml/min/1.73 m^2; mean hemoglobin 12.7 g/dl; and mean serum albumin was 4.1 g/dl. Regarding complications, 388 (72.3 %) patients had hypertension; 146 (27.2 %) patients had diabetes, with a mean HbA1c (NGSP) of 6.4 %; and 38 (7.1 %) patients had a history of CVD [12]. Proportions of patients in new CKD stages were 16.0, 27.9, 15.3, 14.2, 13.4 and 13.2 % for GFR stages G1–5 and 40.5, 19.7 and 39.9 % for proteinuria stages A1–3, respectively. During the 3-years observation period, 460 patients (85.7 %) completed follow-up visits, 64 (11.9 %) progressed to ESKD, 21 CVD events (3.9 %) occurred, and 19 patients (3.5 %) died (Fig. 1).

Figure 2 shows the CKD stage progression and incidence of CVD and/or death during 1 year of observation. The proportions progressing to higher stages were 18.6, 6.0, 14.6, 17.1 and 25.0 % from stages G1–4, respectively. The proportion progressing to ESKD (stage G5D) was 1.3 % from stage G3b, 1.4 % from stage G4 and 42.3 % from stage G5. The incidence of CVD and/or death was 1.2, 1.3, 1.2, 2.6, 4.2, and 9.9 % for stages G1–5, respectively. The proportion of unchanged CKD stage was 66.3, 77.3, 64.6, 63.2, 63.9, and 49.3 % for stages G1–5, respectively (data not shown). Figure 3 shows the progression of CKD stages and incidence of CVD and/or death during 3-year observation period. The proportions

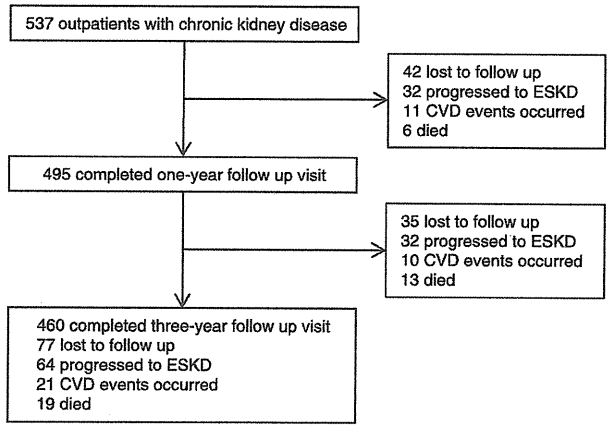

Fig. 1 Patient flow during the 3-year study period—460 patients (85.7 %) completed follow-up visits, 77 (14.3 %) moved away or were lost-to-follow-up, 64 (11.9 %) progressed to ESKD, 21 CVD events (3.9 %) occurred, and 19 patients (3.5 %) died

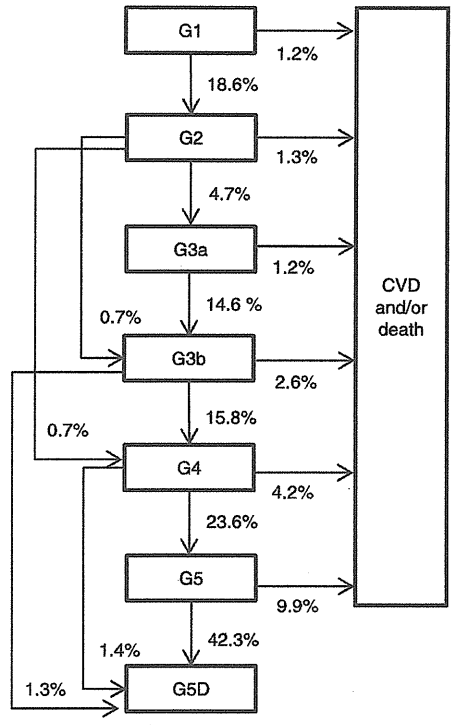

Fig. 2 CKD stage progression and incidence of CVD and/or death (after 1 year). The proportion progressing to the higher stages was 18.6, 6.0, 14.6, 17.1, and 25.0 % from stages G1–4, respectively. The proportion progressing to ESKD (stage G5D) was 1.3 % from stage G3b, 1.4 % from stage G4 and 42.3 % from stage G5. The incidence of CVD and/or death was 1.2, 1.3, 1.2, 2.6, 4.2, and 9.9 % for stages G1–5, respectively

progressing to higher stages were 32.6, 20.0, 36.6, 39.5, and 45.8 % from stages G1–4, respectively. The proportion progressing to ESKD (stage G5D) was 0.7 % from stage G2, 3.9 % from stage G3b, 20.8 % from stage G4 and

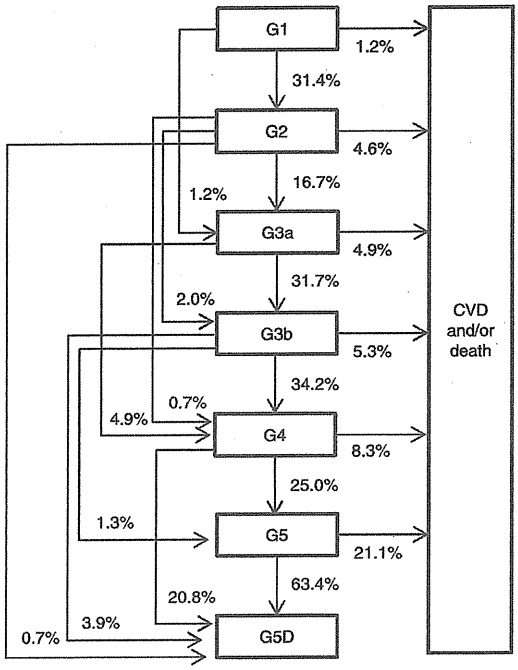

Fig. 3 CKD stage progression and incidence of CVD and/or death (after 3 years). The proportion progressing to the higher stages was 32.6, 20.0, 36.6, 39.5, and 45.8 % from stages G1–4, respectively. The proportion progressing to ESKD (stage G5D) was 0.7 % from stage G2, 3.9 % from stage G3b, 20.8 % from stage G4 and 63.4 % from stage G5. The incidence of CVD and/or death was 1.2, 4.6, 4.9, 5.3, 8.3 and 21.1 % from stages G1–5, respectively

63.4 % from stage G5. The incidence of CVD and/or death was 1.2, 4.6, 4.9, 5.3, 8.3 and 21.1 % from stages G1–5, respectively. The proportions of CKD stages that remained unchanged were 45.3, 58.7, 46.3, 32.9, 34.7, and 19.7 % for stages G1–5, respectively (data not shown).

As shown in Table 1, the annual eGFR decline was -3.17 ± 5.02 ml/min/1.73 m^2/year in all patients. The annual eGFR decline tended to be larger in the higher disease stages except stages G1 and G2 (−4.70, −2.44, −1.76, −2.90, −2.90 and −5.55 ml/min/1.73 m^2/year for stages G1–5) and higher with increases of proteinuria (−2.15, −2.47 and −4.60 ml/min/1.73 m^2/year for stages A1–3). During the 3-year follow-up period, 8.4 % of patients experienced a 50 % eGFR decline (0, 0.7, 2.4, 7.9, 26.4 and 23.9 % for stages G1–5).

Table 2 shows measured quality-adjustment weights by CKD stage—0.939 (95 % CI, 0.915–0.963), 0.915 (0.892–0.938), 0.894 (0.861–0.927), 0.882 (0.843–0.921), 0.834 (0.789–0.879) and 0.798 (0.757–0.839) for stages G1–5 and 0.912 (0.893–0.931), 0.901 (0.873–0.929) and 0.849 (0.824–0.874) for proteinuria stages A1–3, respectively. Quality-adjustment weights of all respondents decreased with decline of eGFR and increase of proteinuria. The weights at stages G4–5 were significantly lower than at stages G1–2 and the weights at stage A3 were significantly lower than at stages A1–2. The weights according to disease progression are shown in Table 3, and the weights of presence and absence of diabetes in each group are shown in Table 3. The weights were 0.907 (95 % CI 0.889–0.925) for the non-progressive group, 0.894 (0.874–0.914) for the progressive group, 0.842 (0.800–0.884) for the dialysis group and 0.617 (0.531–0.703) for the death group. The weights in the dialysis and death groups were significantly lower than in the non-progressive group. The presence of diabetes affected the quality adjustment weights in each group. The quality-adjustment weights of patients with events such as 50 % eGFR decline, dialysis, CVD, and/or death were also significantly lower than those without events in Table 4.

Table 1 Annual eGFR decline by CKD stage (total $n = 421$)

CKD stage		Proteinuria stage			
		A1	A2	A3	A1–3
GFR stage	*n*	173	82	166	421
G1	66	−4.16 ± 6.33	−6.31 ± 5.88	−6.20 ± 4.84	−4.70 ± 6.14
G2	118	−1.76 ± 3.23	−2.32 ± 2.68	−3.78 ± 4.49	−2.44 ± 3.52
G3a	72	−1.38 ± 2.32	−1.01 ± 2.46	−2.70 ± 4.70	−1.76 ± 3.34
G3b	61	−1.12 ± 2.09	−1.23 ± 3.23	−5.24 ± 7.69	−2.90 ± 5.70
G4	54	−0.01 ± 2.12	−2.18 ± 1.45	−4.03 ± 3.11	−2.90 ± 3.19
G5	50	0.45 ± 0	−0.57 ± 1.10	−6.00 ± 7.61	−5.55 ± 7.46
G1–5	421	−2.15 ± 4.25	−2.47 ± 3.63	−4.60 ± 5.94	−3.17 ± 5.02

A total of 421 patients had both eGFR and proteinuria measurement

The annual eGFR decline was -3.17 ± 5.02 ml/min/1.73 m^2/year in all patients (-3.33 ± 4.97 for males and -2.98 ± 5.08 for females)

The annual eGFR decline tended to be higher with increase of proteinuria

eGFR estimated glomerular filtration rate, *CKD* chronic kidney disease

Table 2 Quality-adjustment weights by CKD stage

CKD stage	*n*	Mean	95 % CI	*P* value
GFR stage				
G1	86	0.939	0.915–0.963	<0.001[a]
G2	150	0.915	0.892–0.938	
G3a	82	0.894	0.861–0.927	
G3b	76	0.882	0.843–0.921	
G4	72	0.834	0.789–0.879	
G5	71	0.798	0.757–0.839	
Proteinuria stage				
A1	214	0.912	0.893–0.931	<0.001[b]
A2	104	0.901	0.873–0.929	
A3	211	0.849	0.824–0.874	
All stages	537	0.885	0.871–0.899	

CKD chronic kidney disease, *CI* confidence interval, *GFR* glomerular filtration rate

[a] The weights at stages G4–5 were significantly lower than at stages G1–2 ($P < 0.001$)

[b] The weights at stage A3 were significantly lower than at stages A1–2 ($P < 0.001$)

Discussion

This study aimed to evaluate CKD progression and clinical outcomes among a hospital-based cohort of patients with CKD. The patients were under treatment by nephrologists, and received intensive care. During 12 months of follow-up, 32 cases (6.0 %) started renal replacement therapy, 11 CVD events (2.0 %) occurred, and 6 patients (1.1 %) died. These clinical outcomes were similar to the 12 months of observing 2,692 CKD outpatients by Nakayama et al. [17] where 113 patients (4.2 %) were introduced to renal replacement therapy, a total of 69 CVD events (2.6 %) occurred, and 24 patients (0.9 %) died. They also confirmed significant differences in the incidence of CVD events according to underlying renal disease. They concluded that patients with hypertensive nephropathy or diabetic nephropathy had a higher risk of a CVD event, while patients with primary renal disease had a lower risk.

In the present study, the annual eGFR decline was −3.17 ml/min/1.73 m^2/year (−3.33 for males and −2.98 for females) for the 3-year observation period. The rate of decline in kidney function was higher than the expected rate of −1.0 ml/min/1.73 m^2/year, which is widely considered to be the normal decline in kidney function with age [18]. This decline is also higher than the results from a hospital-based cohort of Japanese CKD patients (−1.01 ml/min/1.73 m^2/year, −1.18 for males, and −0.78 for females per year) [19]. Hanratty et al. [20] reported that in CKD patients who did not have diabetes or vascular disease, eGFR decline at −1.5 ml/min/1.73 m^2/year and diabetes at baseline was associated with an additional decline of

Table 3 Quality-adjustment weights according to the disease progression

Group		*n*	Mean	95 % CI	*P* value[a]
Quality-adjustment weights by each group					
Non-progressive group		245	0.907	0.889–0.925	
Progressive group		196	0.894	0.874–0.914	0.635
Dialysis group		64	0.842	0.800–0.884	0.009[b]
Death group		19	0.617	0.531–0.703	<0.001[c]
Group	**Diabetes**	***n***	**Mean**	**95 % CI**	***P* value[d]**
Quality-adjustment weights by each group and with/without diabetes					
Non-progressive group	Presence	48	0.891	0.848–0.934	0.381
	Absence	197	0.911	0.891–0.931	
Progressive group	Presence	70	0.857	0.821–0.893	<0.05
	Absence	126	0.915	0.892–0.938	
Dialysis group	Presence	31	0.797	0.739–0.855	<0.05
	Absence	33	0.885	0.827–0.943	
Death group	Presence	9	0.660	0.554–0.766	0.368
	Absence	10	0.578	0.444–0.712	

CI confidence interval

[a] *P* value, each group versus the non-progressive group

[b] The weights in the dialysis group were significantly lower than in the non-progressive group ($P = 0.009$)

[c] The weight in the death group were significantly lower than in the non-progressive group ($P < 0.001$)

[d] *P* value, presence versus absence of diabetes