Clin Exp Nephrol (2008) 12:1–8
DOI 10.1007/s10157-007-0010-9

REVIEW ARTICLE

Chronic kidney disease perspectives in Japan and the importance of urinalysis screening

Kunihiro Yamagata · Kunitoshi Iseki · Kousaku Nitta · Hirokazu Imai · Yasuhiko Iino · Seiichi Matsuo · Hirofumi Makino · Akira Hishida

Received: 24 August 2007 / Accepted: 20 September 2007 / Published online: 5 January 2008

Abstract There are racial differences in primary renal diseases for end-stage renal disease (ESRD) and the incidence and prevalence of cardiovascular disease (CVD). To reduce the number of patients with both ESRD and CVD, an effective screening method for CKD should be established. In Japan, screening with the urine dip-stick test for proteinuria has been used since 1972 targeting every child and worker and since 1983 for every resident over 40 years old. There are several reasons for continuing this screening program. First, the positive rate of proteinuria is high in the Japanese general population, especially subjects with neither hypertension nor diabetes. Most of these subjects have no symptoms, and the only sign of renal disease is asymptomatic urinary abnormalities. Second, the prevalence and incidence of glomerulonephritis, especially IgA nephropathy, are high in the Japanese and Asian races, and urinalysis is the only method for early detection of chronic glomerulonephritis. Third, 10-year survival of the ESRD patients due to glomerulonephritis was approximately twice that of ESRD patients due to diabetes and nephrosclerosis. Consequently, reducing the incidence of ESRD due to glomerulonephritis is one of the best ways to reduce the prevalence of ESRD. Furthermore, higher incidence of ESRD in Asian races than in Caucasians was reported. Proteinuria is known to be the best predictor for reducing renal function, and the urine dip-stick test for proteinuria is less expensive and is cost-effective. For an effective screening strategy to reduce the ESRD population in Japanese and Asians, universal screening with the urine dip-stick test for proteinuria could be one solution.

Keywords CKD · CVD · Screening · Proteinuria · Racial difference

Introduction

The estimated global maintenance dialysis population is just over 1.5 million patients [1]. The size of this population has

K. Yamagata (✉)
Department of Nephrology, Institute of Clinical Medicine, Graduate School of Comprehensive Human Science, University of Tsukuba, Tsukuba, Japan
e-mail: k-yamaga@md.tsukuba.ac.jp

K. Iseki
Dialysis Unit, University Hospital of the Ryukyus, Okinawa, Japan

K. Nitta
Department of Medicine, Kidney Center, Tokyo Women's Medical University, Tokyo, Japan

H. Imai
Department of Internal Medicine, Division of Nephrology and Rheumatology, Aichi Medical University School of Medicine, Aichi, Japan

Y. Iino
Department of Nephrology, Nippon Medical School, Tokyo, Japan

S. Matsuo
Department of Nephrology, Nagoya University Graduate School of Medicine, Nagoya, Japan

H. Makino
Department of Medicine and Clinical Science, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan

A. Hishida
First Department of Medicine, Hamamatsu University School of Medicine, Sizuoka, Japan

been expanding at a rate of 7% per year. If current trends in end-stage renal disease (ESRD) prevalence continue, the ESRD population will exceed 2 million patients by the year 2010 [2]. At the end of 2005, patients with ESRD who required renal replacement therapy (RRT) were 257,765 in Japan. The prevalence of patients with ESRD was 1,797 per million population, and the incidence of patients with ESRD was 267 per million population in 2003 in Japan. Figure 1 shows yearly changes in the dialysis population from 1968 to the present in Japan (Fig. 1) [3]. Japan has the largest prevalence of ESRD patients in the world. Furthermore, Japan was the fourth in terms of ESRD incidence patients worldwide [4]. A health-related quality of life among dialysis patients was also poor [5], and life expectancy of the ESRD population is about half that of the general population in Japan [3]. The growing dialysis population is emerging not only to be a major global socio-economic problem, but also a public health problem.

In 2002, the Kidney Disease Outcomes Quality Initiative (K/DOQI) of the National Kidney Foundation gave a definition and classification system for chronic kidney disease (CKD) [6]. The definition and classification of CKD were accepted by the international board of directors of Kidney Disease: Improving Global Outcomes [7]. CKD was defined in five stages based on the appearance of proteinuria and GFR levels. It was estimated that there are 19.2 million US adults with CKD; patients with early stage CKD had no symptoms, and the majority of individuals in early stage CKD were undiagnosed, even in developed countries [8, 9]. Furthermore, patients with CKD have an increased risk of not only ESRD, but poor cardiovascular outcomes and death [10–13]. A vast number of those with moderate CKD die before they develop more advanced CKD [14]. To reduce the number of patients with both ESRD and cardiovascular disease (CVD), effective screening and treatment methods for CKD should be established [7, 15, 16]. However, primary renal diseases for ESRD differ by race and area [17–20]. Also, the incidence and prevalence of CVD and its mortality differ by race and area [21, 22]. Consequently, the screening procedure for CKD requires different approaches depending on the patient's race, habitual, and socio-economical status. We should pay more attention to these differences to clarify a strategy for an effective screening procedure.

In Japan, an annual urinalysis screening program was introduced for every school child in 1973, for every working adult in 1972, and for every resident older than 40 years of age in 1982 under the auspices of local governments and the Ministry of Health, Labor and Welfare of Japan. Also, an annual measurement of serum creatinine was started in 1992 for every resident over 40 years of age [23, 24], although most countries do not perform universal urinalysis screening [25].

In this review, we will focus on our experiences with the Japanese urinalysis screening program and its achievement, problems, and reasons why it has continued until today. Furthermore, we will discuss our strategies for screening systems for CKD in Japan and in Asian populations, and future perspectives.

Racial and geographical differences in primary renal disease in Japan and other countries in terms of ESRD

At the end of 2005, patients with ESRD who required RRT were 257,765 in Japan. The incidence of patients with

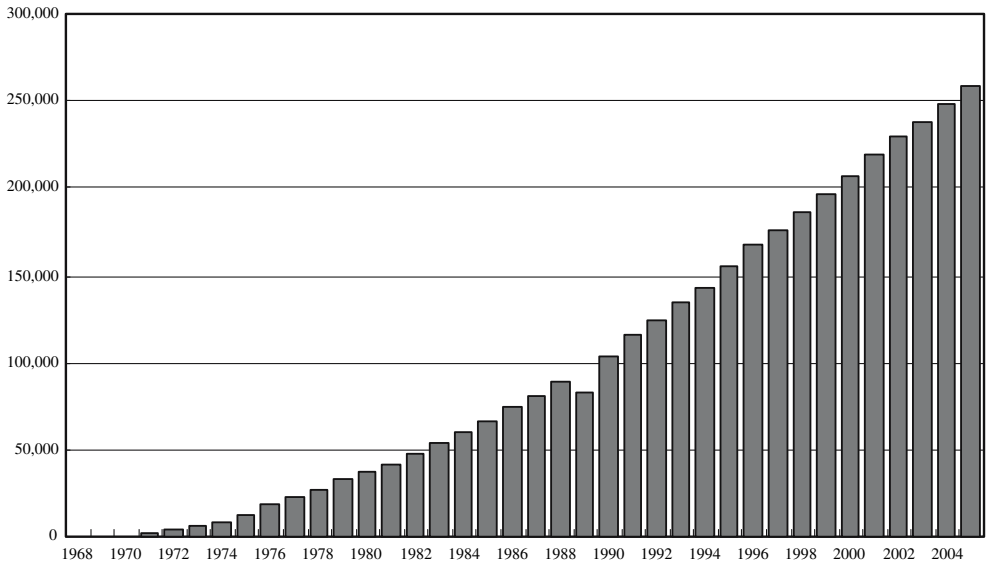

Fig. 1 Yearly changes of maintenance dialysis patients in Japan. A linear increase of maintenance dialysis patients was observed. (Data source: Japanese Society of Dialysis Therapy, registration data)

ESRD was 36,063 in Japan [3]. Figure 2 shows international comparisons of primary renal disease for those who started RRT for ESRD treatment [3, 4, 26–28]. Not only primary renal disease, but also the availability of ESRD treatment, along with age and population growth, race and the number of people with diabetes also vary between countries and areas [29, 30]. As shown in Fig. 2, while the proportion of diabetes was almost the same as in all countries, the proportion of nephrosclerosis and glomerulonephritis among countries was quite different. In Japan, glomerulonephritis was the most frequent primary renal disease for ESRD, actually accounting for more than 50% of patients entering the ESRD program in Japan from 1969 to 1996. In Taiwan, which has the highest incidence of ESRD patients in the world [4, 31], primary renal disease in patients with ESRD showed almost the same pattern as Japan.

Screening method for early detection of CKD

Most primary chronic glomerulonephritis is first manifested as asymptomatic proteinuria and/or hematuria [32, 33]. Figure 3 shows clinical manifestation of IgA nephropathy among 487 patients in Japan [34]. Approximately 68.2% of the patients with IgA nephropathy were discovered by asymptomatic proteinuria and/or hematuria [34]. For early detection of glomerulonephritis, urinalysis has been considered one of the best methods [35, 36]. The level of proteinuria is one of the strongest predictors for renal function deterioration [24, 37–41]. Consequently, to prevent an increase in the number of ESRD patients in Japan, a dipstick urine examination has been continued under the auspices of local governments and the Ministry of Health, Labor and Welfare of Japan since 1972 [23, 24]. However, in 1989 the US preventive service task force reported that routine dipstick urinalysis was not recommended for asymptomatic persons [25]. Although urinalysis screening may detect early glomerular diseases, the efficacy of early treatment of glomerulonephritis had not been studied in a randomized controlled trial at that time [25]. Furthermore, as shown in Fig. 2, about half of ESRD cases in the USA were due to hypertension or diabetes, which caused proteinuria after several years of exposure to hypertension and diabetes, and few cases of significant diseases had been detected with dipstick screening for hematuria and proteinuria after reviewing several population-based studies in both adults and children [25]. Also, most other countries did not recommend annual urinalysis screening for the same reasons [42].

Figure 4 shows yearly changes for the number of patients starting RRT in three major primary renal diseases

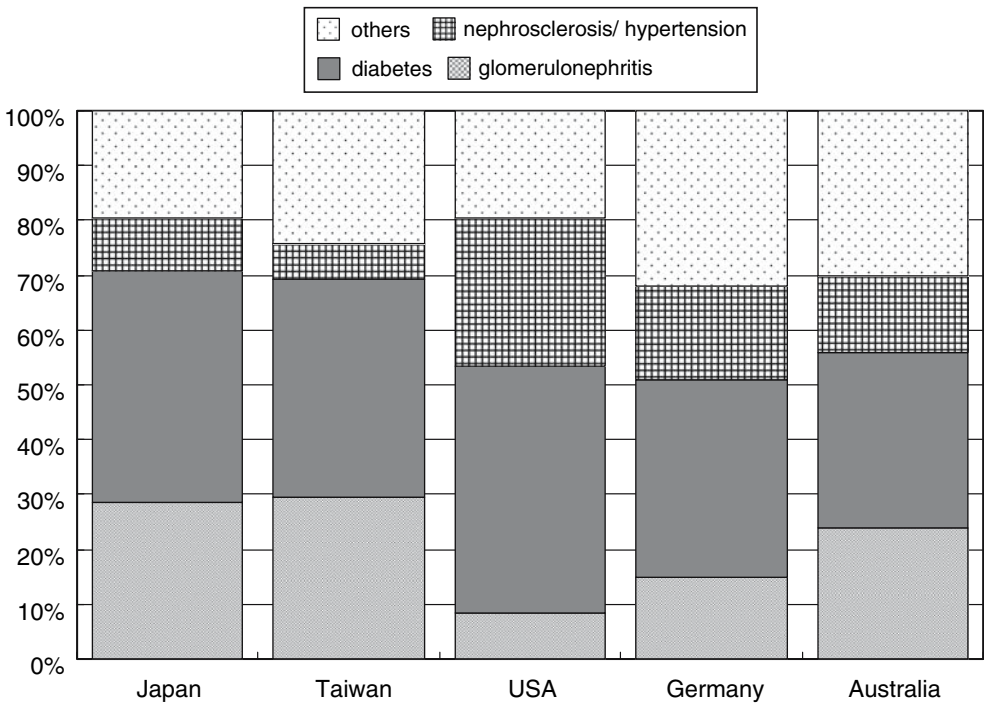

Fig. 2 Primary renal disease of new ESRD patients in several countries. Most countries showed diabetes as the most frequent cause of new ESRD. The proportion of nephrosclerosis and glomerulonephritis among those countries was quite different. In Asian countries, the proportion of glomerulonephritis was three to five times more than the proportion of nephrosclerosis as primary renal disease for ESRD. However, this tendency was not observed in the USA and European countries

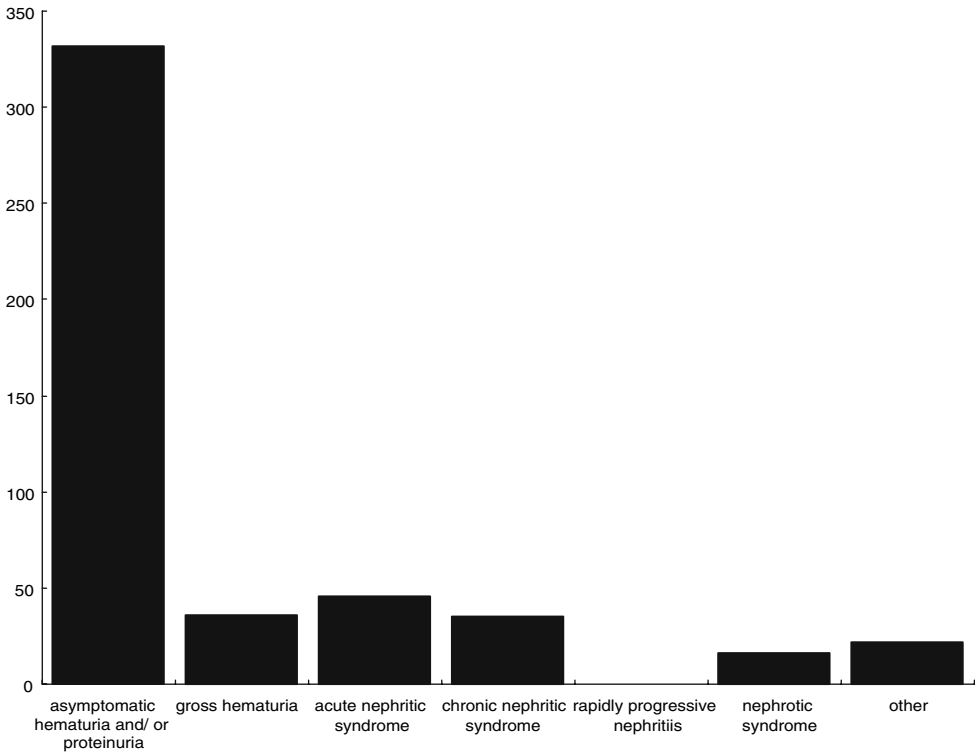

Fig. 3 Clinical manifestation of IgA nephropathy among 487 patients. Approximately 68.2% of the patients with IgA nephropathy were discovered by asymptomatic proteinuria and/or hematuria by a urinalysis screening program held in Japan

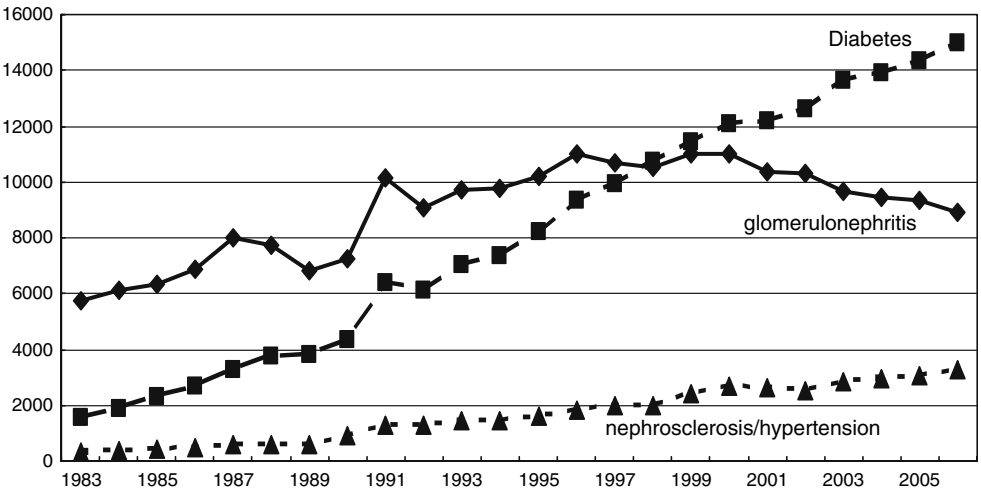

Fig. 4 Yearly changes for the number of patients starting RRT due to diabetes, glomerulonephritis and nephrosclerosis/hypertension. A significant linear relationship was observed between the year and incidence of RRT patients due to diabetes and nephrosclerosis/hypertension [20], while the number of ESRD cases due to glomerulonephritis has decreased recently

in Japan. Recently the number of ESRD cases due to glomerulonephritis has decreased in Japan [20, 43]. There are several reasons for this decrease. One is an improvement in the prognosis of patients with IgA nephropathy. IgA nephropathy is the most common glomerulonephritis worldwide [44, 45], and 68.2% of patients with IgA nephropathy were detected by the Japanese urinalysis screening program as mentioned above [23, 34]. Early referral to a nephrologist and starting early treatment were established by this program [20, 43]. Although treatment methods for protenuric subjects were an angiotensin converting enzyme (ACE) inhibitor [46] or angiotensin receptor blocker (ARB) [47], treatment methods for IgA nephropathy were diverse, including steroids [48, 49], immunosuppressants [49] and tonsillectomy [50, 51], which showed superior results than treatment to ACEI or ARB alone. In countries or races where glomerulonephritis was the frequent primary renal disease for ESRD, such as Japan and Asian countries, universal dip-stick proteinuria screening is recommended.

Racial difference of proteinuria prevalence

Boulware et al. [52] reported that annual screening for proteinuria in US adults was not cost-effective because the prevalence and incidence of proteinuria were very low. However, selective annual testing focusing on high-risk groups is highly cost-effective. They reported that annual screening starting at age 60 years or older is cost-effective for persons with neither hypertension nor diabetes, and annual screening from ages 30 to 70 years is highly cost-effective for persons with hypertension. Table 1 shows the prevalence of proteinuria from NHANES III [53] and annual urinalysis data held in Ibaraki prefecture in Japan [54]. As shown in Table 1, the prevalence of proteinuria in US adults aged 60 years or older with neither hypertension nor diabetes was 0.8%, while the prevalence of proteinuria in Japanese adults with neither hypertension nor diabetes of same age group was 1.8%. Furthermore, the prevalence of proteinuria in US adults with hypertension was 2.2%, but the prevalence of proteinuria in Japanese adults with hypertension was 3.3%. Iseki et al. [55] reported that the positive rate of proteinuria in screened subjects was as high as 5.3% among 106,177 subjects in Okinawa, Japan. This high prevalence of proteinuria in the overall Japanese population supported the idea that annual urinalysis screening for the whole population in Japan might be cost-effective. A striking difference between the Japanese population and US population is the high prevalence of proteinuria in Japanese adults with neither hypertension nor diabetes. Most of these subjects have no symptoms, and the only sign of renal disease is asymptomatic urinary abnormalities [56]. The Malay race, a Southeast Asian population, also showed a high prevalence of proteinuria [57].

Table 1 Prevalence of proteinuria in US and Japan

	Age range (years)					Total
	40–49	50–59	60–69	70–79	80	
Whole population						
Japan						
Number	18,639	35,212	49,249	30,561	2,941	136,602
Proteinuria (%)	1.0	1.4	2.2	3.3	5.1	2.1
USA						
Number	2,330	1,680	2,078	1,524	1,011	8,623
Proteinuria (%)	0.8	1.1	1.7	2.3	4.7	1.8
Diabetic population						
Japan						
Number	334	1,509	3,401	2,317	214	7,775
Proteinuria (%)	5.1	6.2	6.1	8.2	9.8	6.8
USA						
Number	149	194	325	257	129	1,054
Proteinuria (%)	7.4	5.3	5.4	6.8	12.5	6.8
Non-diabetic hypertensive population						
Japan						
Number	2,602	9,899	21,765	17,423	1,873	53,562
Proteinuria (%)	3.2	2.5	3.0	3.7	5.9	3.3
USA						
Number	661	645	1,033	841	641	3,821
Proteinuria (%)	1.7	1.5	1.7	1.8	4.8	2.2
Non-diabetic non-hypertensive population						
Japan						
Number	15,703	23,804	24,083	10,821	854	75,265
Proteinuria (%)	0.5	0.7	0.9	1.7	2.1	0.9
USA						
Number	1,503	829	710	417	233	3,692
Proteinuria (%)	0.1	0.2	0.7	1.2	0.5	0.4

Data source: USA: NHANES III, macroalbuminuria, Japan: annual urinalysis screening data held in Ibaraki prefecture, Japan in 2001

Proteinuria is a better risk marker for developing ESRD than impaired renal function

Both proteinuria and impaired renal function predict a worse prognosis with respect to cardiovascular morbidity and mortality [10–13]. Subjects with proteinuria showed three times faster GFR loss than both control and impaired renal function subjects [58]. Therefore, proteinuria is a better risk marker than impaired renal function in population screening of individuals to identify who is at risk for developing ESRD [58]. Hallan et al. [59] reported that during an 8-year follow-up, only 38 of 3,069 people (1.2%) with impaired renal function (CKD stage 3 or later) progressed to ESRD, while Iseki et al. [37] reported that during a 17-year follow-up, 186 of 5,436 people (3.4%) with proteinuria progressed to ESRD.

There are several reasons for the large dialysis population in Japan, including a low transplantation rate, full coverage of medical expenses for dialysis patients and an excellent survival rate after initiation of RRT. From the Japan ESRD registry, 10-year survival of the ESRD population is 52.7% for glomerulonephritis, 28.0% for diabetes, and 27.0% for nephrosclerosis (hypertensive nephropathy) [3]. Consequently, to reduce the prevalence of ESRD patients effectively in Japan, both increasing kidney transplantation and decreasing the incidence of ESRD due to glomerulonephritis are effective methods.

Furthermore, there are several reports about a higher incidence of ESRD in Asian races than in Caucasians [60–62]. Reasons for these differences are unclear, but genetic [60, 63] and environmental differences [64] are related. Further studies are needed to clarify about these points.

Future strategy for CKD screening in Japan

Chronic kidney disease was first proposed by K/DOQI, and it was accepted by KDIGO; however, most written standards and effective CKD perspectives are suitable for Caucasians or people living in Western countries [65, 66]. One example is CVD morbidity and mortality differences between Japanese and Caucasians. Hollan et al. [67] reported that the prevalence of CKD in the USA and Norway was the same, and the occurrence of CVD in CKD patients in Norway was almost the same as in the US population, while the proportion of heart disease and stroke among CVD patients was identical between Norway and the USA [21]. During an 8-year observation period, 2,604 of 5,640 deaths were from CVD, and 691 of 2,604 deaths (26.5%) had CKD stage III or higher in Norway [59]. However, during a 10-year observation period, 1,932 of 6,906 deaths were from CVD, while only 307 subjects (15.9%) had CKD in Japan [68], and the Japanese general population had an incidence of CVD among CKD subjects that was much lower than the US population [69].

Another example is the indication for microalbuminuria. Previous studies in general Western populations have suggested that microalbuminuria was a significant predictor for both coronary heart disease and stroke [70, 71]. Some people proposed that universal testing for microalbuminuria should be considered [72–74]. However, the prevalence of microalbuminuria in mass screening was 11.8–17.8% of the study population in Asians [75, 76], which was a several times higher positive rate compared to the USA [53]. It is possible to improve microalbuminuria by using ARB, ACEI and statins [74, 77–81] and to avoid the development of both ESRD and CVD. However, medical fees for follow-up and prescriptions of these drugs are very expensive, especially in countries and for races with a high prevalence of microalbuminuria. Furthermore, urinary albumin and creatinine ratio testing is more expensive than the urine dip-stick test for proteinuria. Consequently, universal screening with the urine dip-stick test for proteinuria is suitable for most countries or races that have a high prevalence of proteinuria such as Asians and Japanese. However, there are lifestyle modifications; along with a higher prevalence of diabetes in the general population and a higher incidence of stroke and stroke mortality in Japan, we might have to change urinalysis screening policy from the urine dip-stick test for proteinuria to microalbuminuria in the near future.

In summary, universal screening with the urine dip-stick test for proteinuria has been used in Japan. There are several reasons for continuing this screening program. First, the positive rate of proteinuria is high in the Japanese general population. Second, the prevalence and incidence of glomerulonephritis, especially IgA nephropathy, are high in Japan. Third, urinalysis is the only method for early detection of most chronic glomerulonephritis. Fourth, reducing the incidence of ESRD due to glomerulonephritis is one of the best ways to reduce the prevalence of ESRD. Furthermore, the death rate due to CVD was the same between Japan and the USA. Although CKD is one of the important risk factors for CVD in the Japanese general population, the Japanese incidence of CVD and mortality due to CVD among CKD subjects were lower than those of Caucasians. Japanese and Asians should focus on reducing ESRD and subjects with reduced renal function. To do this, universal screening with the urine dip-stick test for proteinuria could be one solution.

References

1. Xue JL, Ma JZ, Louis TA, Collins AJ. Forecast of the number of patients with end-stage renal disease in the United States to the year 2010. J Am Soc Nephrol. 2001;12:2753–8.
2. Lysaght MJ. Maintenance dialysis population dynamics: current trends and long-term implications. J Am Soc Nephrol. 2002;13(Suppl 1):S37–40.
3. Nakai S, Masagane I, Akiba T, Iseki K, Watanabe Y, Itami Y, et al. An overview of dialysis treatment in Japan (as of Dec. 31, 2005). J Jpn Soc Dial Ther. 2007;40:1–30.
4. Systems USRD: USRDS 2006 Annual Data Report. Bethesda: National Institute of Health; 2007.
5. Fukuhara S, Lopes AA, Bragg-Gresham JL, Kurokawa K, Mapes DL, Akizawa T, et al. Health-related quality of life among dialysis patients on three continents: the Dialysis Outcomes and Practice Patterns Study. Kidney Int. 2003;64:1903–10.
6. K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: evaluation, classification, and stratification. Part 5. Evaluation of laboratory measurements for clinical assessment of kidney disease. Am J Kidney Dis. 2002;39:76–110.
7. Levey AS, Eckardt KU, Tsukamoto Y, Levin A, Coresh J, Rossert J, et al. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int. 2005;67:2089–100.
8. Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. Am J Kidney Dis. 2003;41:1–12.
9. Schieppati A, Remuzzi G. Chronic renal diseases as a public health problem: epidemiology, social, and economic implications. Kidney Int. 2005;67(Suppl 98):S7–10.
10. Levey AS, Beto JA, Coronado BE, Eknoyan G, Foley RN, Kasiske BL, et al. Controlling the epidemic of cardiovascular disease in chronic renal disease: what do we know? What do we need to learn? Where do we go from here? National Kidney Foundation Task Force on Cardiovascular Disease. Am J Kidney Dis. 1998;32:853–906.
11. Anavekar NS, McMurray JJ, Velazquez EJ, Solomon SD, Kober L, Rouleau JL, et al. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. N Engl J Med. 2004;351:1285–95.
12. Weiner DE, Tighiouart H, Amin MG, Stark PC, MacLeod B, Griffith JL, et al. Chronic kidney disease as a risk factor for cardiovascular disease and all-cause mortality: a pooled analysis of community-based studies. J Am Soc Nephrol. 2004;15:1307–15.

13. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351:1296–305.
14. Foley RN, Murray AM, Li S, Herzog CA, McBean AM, Eggers PW, et al. Chronic kidney disease and the risk for cardiovascular disease, renal replacement, and death in the United States Medicare population, 1998 to 1999. J Am Soc Nephrol. 2005;16:489–95.
15. Eknoyan G, Lameire N, Barsoum R, Eckardt KU, Levin A, Levin N, et al. The burden of kidney disease: improving global outcomes. Kidney Int. 2004;66:1310–4.
16. Uhlig K, Macleod A, Craig J, Lau J, Levey AS, Levin A, et al. Grading evidence and recommendations for clinical practice guidelines in nephrology. A position statement from kidney disease: improving global outcomes (KDIGO). Kidney Int. 2006;70:2058–65.
17. Maisonneuve P, Agodoa L, Gellert R, Stewart JH, Buccianti G, Lowenfels AB, et al. Distribution of primary renal diseases leading to end-stage renal failure in the United States, Europe, and Australia/New Zealand: results from an international comparative study. Am J Kidney Dis. 2000;35:157–65.
18. Racial differences in trends of end-stage renal disease, by primary diagnosis-United States, 1994–2004. MMWR Morb Mortal Wkly Rep. 2007;56:253–6.
19. Hemmelgarn BR, Chou S, Wiebe N, Culleton BF, Manns BJ, Klarenbach S, et al. Differences in use of peritoneal dialysis and survival among East Asian, Indo Asian, and white ESRD patients in Canada. Am J Kidney Dis. 2006;48:964–71.
20. Yamagata K, Takahashi H, Suzuki S, Mase K, Hagiwara M, Shimizu Y, et al. Age distribution and yearly changes in the incidence of end-stage renal disease in Japan. Am J Kidney Dis. 2004;43:433–43.
21. World Health Organization: World Health Statistics 2006, 2007.
22. Wu Z, Yao C, Zhao D, Wu G, Wang W, Liu J, et al. Sino-MONICA project: a collaborative study on trends and determinants in cardiovascular diseases in China, Part I: morbidity and mortality monitoring. Circulation. 2001;103:462–8.
23. Yamagata K, Takahashi H, Tomida C, Yamagata Y, Koyama A. Prognosis of asymptomatic hematuria and/or proteinuria in men. Nephron. 2002;91:34–42.
24. Ishida K, Ishida H, Narita M, Sairenchi T, Saito Y, Fukutomi H, et al. Factors affecting renal function in 119 985 adults over three years. QJM. 2001;94:541–50.
25. Woolhandler S, Pels RJ, Bor DH, Himmelstein DU, Lawrence RS. Dipstick urinalysis screening of asymptomatic adults for urinary tract disorders. I. Hematuria and proteinuria. JAMA. 1989;262:1214–9.
26. Nephrology TSo: Anual data report of ESRD in Taiwan. http://www.tsn.org.tw/ (2006).
27. Caskey FJ, Schober-Halstenberg HJ, Roderick PJ, Edenharter G, Ansell D, Frei U, et al. Exploring the differences in epidemiology of treated ESRD between Germany and England and Wales. Am J Kidney Dis. 2006;47:445–54.
28. Registry AaNZDaT: The 29th Annual Report 2006 Report—Data to 2005. http://www.anzdata.org.au/ (2007).
29. Stewart JH, McCredie M, Disney AP, Mathew TH. Trends in incidence of end-stage renal failure in Australia, 1972–1991. Nephrol Dial Transplant. 1994;9:1377–82.
30. Wimmer F, Oberaigner W, Kramar R, Mayer G. Regional variability in the incidence of end-stage renal disease: an epidemiological approach. Nephrol Dial Transplant. 2003;18:1562–7.
31. Kuo HW, Tsai SS, Tiao MM, Yang CY. Epidemiological features of CKD in Taiwan. Am J Kidney Dis. 2007;49:46–55.
32. Tiebosch ATMG, Wolters J, Frederik PFM, van der Wiel TWM, Zeppenfeldt E, van Breda Vriesman PJC. Epidemiology of idiopathic glomerular disease: a prospective study. Kidney Int. 1987;32:112–6.
33. Simon P, Ramee MP, Autuly V, Laruelle E, Charasse C, Cam G, et al. Epidemiology of primary glomerular diseases in a Frecnch region. Variations according to period of age. Kidney Int. 1994;46:1192–8.
34. Koyama A, Igarashi M, Kobayashi M. Naturals history and risk factors for immunoglobulin A nephropathy. Am J Kid Dis. 1997;29:526–32.
35. Cameron JS. Proteinuria and progression in human glomerular diseases. Am J Nephrol. 1990;1:81–7.
36. Cameron JS. The long-term outcome of glomerular diseases. 6th ed. Boston/Tronto/London: Little Brown and Company;1997.
37. Iseki K, Ikemiya Y, Iseki C, Takishita S. Proteinuria and the risk of developing end-stage renal disease. Kidney Int. 2003;63:1468–74.
38. Usui J, Yamagata K, Kai H, Outeki T, Yamamoto S, Muro K, et al. Heterogeneity of prognosis in adult IgA nephropathy, especially with mild proteinuria or mild histological features. Intern Med. 2001;40:697–702.
39. Keane WF. Proteinuria: its clinical importance and role in progressive renal disease. Am J Kidney Dis. 2000;35:S97–105.
40. Remuzzi G, Benigni A, Remuzzi A. Mechanisms of progression and regression of renal lesions of chronic nephropathies and diabetes. J Clin Invest. 2006;116:288–96.
41. Bartosik LP, Lajoie G, Sugar L, Cattran DC. Predicting progression in IgA nephropathy. Am J Kidney Dis. 2001;38:728–35.
42. Nagai R, Wang EEL, Feldman W. Dipstick proteinuria screening of asymptomatic adults to prevent progressive renal disease. In: Canadian Task Force on the Periodic Health Examination. Otawa: Health Canada; 1994.
43. Murakami M, Hayakawa M, Yanagihara T, Hukunaga Y. Proteinuria screening for children. Kidney Int Suppl. 2005; 67:S23–7.
44. D'Amico G. The commonest glomerulonephritis in the world: IgA nephropathy. Quart J Med. 1987;64:709–27.
45. Nair R, Walker PD. Is IgA nephropathy the commonest primary glomerulopathy among young adults in the USA? Kidney Int. 2006;69:1455–8.
46. Jafar TH, Stark PC, Schmid CH, Landa M, Maschio G, de Jong PE, et al. Progression of chronic kidney disease: the role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: a patient-level meta-analysis. Ann Intern Med. 2003;139:244–52.
47. Laverman GD, Navis G, Henning RH, de Jong PE, de Zeeuw D. Dual renin-angiotensin system blockade at optimal doses for proteinuria. Kidney Int. 2002;62:1020–5.
48. Pozzi C, Bolasco PG, Fogazzi GB, Andrulli S, Altieri P, Ponticelli C, et al. Corticosteroids in IgA nephropathy: a randomised controlled trial. Lancet. 1999;353:883–7.
49. Shoji T, Nakanishi I, Suzuki A, Hayashi T, Togawa M, Okada N, et al. Early treatment with corticosteroids ameliorates proteinuria, proliferative lesions, and mesangial phenotypic modulation in adult diffuse proliferative IgA nephropathy. Am J Kidney Dis. 2000;35:194–201.
50. 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.
51. Xie Y, Nishi S, Ueno M, Imai N, Sakatsume M, Narita I, et al. The efficacy of tonsillectomy on long-term renal survival in patients with IgA nephropathy. Kidney Int. 2003;63:1861–7.
52. 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.

53. Garg AX, Kiberd BA, Clark WF, Haynes RB, Clase CM. Albuminuria and renal insufficiency prevalence guides population screening: results from the NHANES III. Kidney Int. 2002;61:2165–75.
54. 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.
55. 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.
56. Yamagata K, Yamagata Y, Kobayashi M, Koyama A. A long-term follow-up study of asymptomatic hematuria and/or proteinuria in adults. Clin Nephrol. 1996;45:281–8.
57. Ramirez SP, McClellan W, Port FK, Hsu SI. Risk factors for proteinuria in a large, multiracial, southeast Asian population. J Am Soc Nephrol. 2002;13:1907–17.
58. Halbesma N, Kuiken DS, Brantsma AH, Bakker SJ, Wetzels JF, De Zeeuw D, et al. Macroalbuminuria is a better risk marker than low estimated GFR to identify individuals at risk for accelerated GFR loss in population screening. J Am Soc Nephrol. 2006;17:2582–90.
59. Hallan SI, Dahl K, Oien CM, Grootendorst DC, Aasberg A, Holmen J, et al. Screening strategies for chronic kidney disease in the general population: follow-up of cross sectional health survey. BMJ. 2006;333:1047.
60. Chandie Shaw PK, Baboe F, van Es LA, van der Vijver JC, van de Ree MA, de Jonge N, et al. South-Asian type 2 diabetic patients have higher incidence and faster progression of renal disease compared with Dutch–European diabetic patients. Diabetes Care. 2006;29:1383–5.
61. Burden AC, McNally PG, Feehally J, Walls J. Increased incidence of end-stage renal failure secondary to diabetes mellitus in Asian ethnic groups in the United Kingdom. Diabet Med. 1992;9:641–5.
62. Lightstone L, Rees AJ, Tomson C, Walls J, Winearls CG, Feehally J. High incidence of end-stage renal disease in Indo-Asians in the UK. QJM. 1995;88:191–5.
63. Iyengar SK, Abboud HE, Goddard KA, Saad MF, Adler SG, Arar NH, et al. Genome-wide scans for diabetic nephropathy and albuminuria in multiethnic populations: the family investigation of nephropathy and diabetes (FIND). Diabetes. 2007;56:1577–85.
64. Trehan A, Winterbottom J, Lane B, Foley R, Venning M, Coward R, et al. End-stage renal disease in Indo-Asians in the North-West of England. QJM. 2003;96:499–504.
65. Brown WW, Peters RM, Ohmit SE, Keane WF, Collins A, Chen SC, et al. Early detection of kidney disease in community settings: the Kidney Early Evaluation Program (KEEP). Am J Kidney Dis. 2003;42:22–35.
66. McGill JB, Brown WW, Chen SC, Collins AJ, Gannon MR. Kidney Early Evaluation Program (KEEP). Findings from a community screening program. Diabetes Educ. 2004;30:196–8 (200–192, 206).
67. Hallan SI, Coresh J, Astor BC, Asberg A, Powe NR, Romundstad S, et al. International comparison of the relationship of chronic kidney disease prevalence and ESRD risk. J Am Soc Nephrol. 2006;17:2275–84.
68. Irie F, Iso H, Sairenchi T, Fukasawa N, Yamagishi K, Ikehara S, et al. The relationships of proteinuria, serum creatinine, glomerular filtration rate with cardiovascular disease mortality in Japanese general population. Kidney Int. 2006;69:1264–71.
69. Ninomiya T, Kiyohara Y, Kubo M, Tanizaki Y, Doi Y, Okubo K, et al. Chronic kidney disease and cardiovascular disease in a general Japanese population: the Hisayama Study. Kidney Int. 2005;68:228–36.
70. Hillege HL, Fidler V, Diercks GF, van Gilst WH, de Zeeuw D, van Veldhuisen DJ, et al. Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. Circulation. 2002;106:1777–82.
71. Yuyun MF, Khaw KT, Luben R, Welch A, Bingham S, Day NE, et al. Microalbuminuria independently predicts all-cause and cardiovascular mortality in a British population: The European Prospective Investigation into Cancer in Norfolk (EPIC-Norfolk) population study. Int J Epidemiol. 2004;33:189–98.
72. Dell'Omo G, Penno G, Giorgi D, Di Bello V, Mariani M, Pedrinelli R. Association between high-normal albuminuria and risk factors for cardiovascular and renal disease in essential hypertensive men. Am J Kidney Dis. 2002;40:1–8.
73. Remuzzi G, Weening JJ. Albuminuria as early test for vascular disease. Lancet. 2005;365:556–7.
74. de Jong PE, Brenner BM. From secondary to primary prevention of progressive renal disease: the case for screening for albuminuria. Kidney Int. 2004;66:2109–18.
75. Konta T, Hao Z, Abiko H, Ishikawa M, Takahashi T, Ikeda A, et al. Prevalence and risk factor analysis of microalbuminuria in Japanese general population: the Takahata study. Kidney Int. 2006;70:751–6.
76. Jafar TH, Chaturvedi N, Hatcher J, Levey AS. Use of albumin creatinine ratio and urine albumin concentration as a screening test for albuminuria in an Indo-Asian population. Nephrol Dial Transplant. 2007.
77. de Zeeuw D, Remuzzi G, Parving HH, Keane WF, Zhang Z, Shahinfar S, et al. Albuminuria, a therapeutic target for cardiovascular protection in type 2 diabetic patients with nephropathy. Circulation. 2004;110:921–7.
78. de Zeeuw D, Remuzzi G, Parving HH, Keane WF, Zhang Z, Shahinfar S, et al. Proteinuria, a target for renoprotection in patients with type 2 diabetic nephropathy: lessons from RENAAL. Kidney Int. 2004;65:2309–20.
79. Eijkelkamp WB, Zhang Z, Remuzzi G, Parving HH, Cooper ME, Keane WF, et al. Albuminuria is a target for renoprotective therapy independent from blood pressure in patients with type 2 diabetic nephropathy: post hoc analysis from the reduction of endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) Trial. J Am Soc Nephrol. 2007;18:1540–6.
80. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med. 2001;345:861–9.
81. Jafar TH, Stark PC, Schmid CH, Landa M, Maschio G, Marcantoni C, et al. Proteinuria as a modifiable risk factor for the progression of non-diabetic renal disease. Kidney Int. 2001;60:1131–40.