Kidney Disease Screening Program in Japan: History, Outcome, and Perspectives

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In the early 1970s, mandatory kidney disease screening was started with urinalysis in the Japanese health examination program for all workers and school-age children. In 1983, nationwide urinalysis screening in adults aged ≥40 yr was mandated in the community-based health examination program. Because glomerulonephritis was an endemic disease and the leading cause of end-stage renal disease in Japan until 1997, the urinalysis in the annual health examination program aimed for early detection of glomerulonephritis and early referral of patients to physicians. To the programs, measurement of serum creatinine was added for detection of chronic kidney disease in 1992 for adults aged ≥40 yr. Kidney disease screening and early intervention brought reduction of progressive glomerulonephritis or an increase in remission. Thus, in children and adults aged ≤45 yr, the number of patients with end-stage renal disease from glomerulonephritis has declined, and the mean age of patients with new end-stage renal disease has increased significantly. In 1998, the leading cause of end-stage renal disease was shifted from glomerulonephritis to diabetic nephropathy as a result of lifestyle changes in the Japanese population; however, the present comprehensive kidney disease screening in the health examination program for detection of glomerulonephritis must be continued, because even in 2005, 27.3% of newly developed end-stage renal disease was from glomerulonephritis. An additional kidney disease screening program should also be established to target patients with high risk for diabetes, hypertension, and metabolic syndrome, because 42% of newly introduced renal replacement cases were from diabetic nephropathy in 2005.


A n epidemic of chronic kidney disease (CKD) is a worldwide health problem (1,2). It not only progress to the ESRD but also is a major risk factor for cardiovascular disease (CVD) (3). Although every effort has been made to reduce CKD and the known leading causes of CKD—diabetes, hypertension, and metabolic syndrome—the past measures taken to treat these clinical conditions were insufficient. Eventually, the incidence of ESRD and CVD reached high in both developed and developing countries. In addition, many countries are burdened by their own endemic renal conditions (4); IgA nephropathy (IgAN) in Asia (5); hepatitis B–related nephropathy in Asia and Africa; and HIV-associated nephropathy in Africa, Asia, Europe, and the United States. Implementing and establishing a kidney disease screening program is important to prevent CKD and particularly to detect in the early stage of CKD.

History of Kidney Disease Screening of the Health Examination Program in Japan

Concern about health problems in the Japanese workforce, the Ministry of Labor implemented a mandatory, nationwide, company-based health examination program in 1973, including blood chemistry and urinalysis. In 1974, the Ministry of Education, Science and Culture initiated the mandatory school-based health examination program for school children aged 6 to 18 to meet the requirement of the School Health Law. In the program, urinalysis was performed to identify the early stage of glomerulonephritis in children. The screening, initially performed biannually, was reduced to annually in 1979. In 1983, the Ministry of Health and Welfare mandated the nationwide community-based health examination program for adults aged ≥40 yr by law, which included urinalysis. Since then, urinalysis in the annual health examination program has been accepted by the Japanese public. In 1992, measurement of serum creatinine level in adults aged ≥40 yr was added to both the company-based and community-based annual health examination program for detection of CKD. The combination of urinalysis and measurement of serum creatinine level has contributed to

Published online ahead of print. Publication date available at www.cjasn.org.

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ISSN: 1555-9041/206–1360
detection of early-stage CKD in Japanese adults aged ≥40 yr. The kidney disease screening implemented in Japan has been systemic and nationwide, covering both school-age children and adults.

Practice of the Japanese Kidney Disease Screening and Public Policy

Glomerulonephritis was an endemic disease in Japan and the primary cause of ESRD until 1997 (6). Because glomerulonephritis is easily diagnosed with proteinuria and hematuria, urinalysis in the annual health examination program was initially mandated to aim for identifying the early stage of glomerulonephritis and for the early referral to a physician. Although glomerulonephritis dropped to the second leading cause of ESRD in 1998, glomerulonephritis continued to be a major cause of ESRD. Even in 2005, still 27.3% of new ESRD cases involved glomerulonephritis (6).

The Minister of Health, Welfare and Labor has been making an extensive effort to reduce the number of patients with ESRD. The main strategy has been to establish an effective community-, company-, and school-based kidney disease screening system.

Screening Program for Children

In Japan, all school children receive a free urinalysis in the school-based health examination program. Urinalysis is generally carried out in three stages. Proteinuria is verified by two consecutive positive results of the tests. The first screening is carried out in all school children by dipstick urinalysis. Children are instructed to empty the bladder completely before sleep; the next morning, the first urine sample is brought to school for urinalysis. Dipstick urinalysis mainly detects protein and occult blood in urine. The second screening tests are performed within 1 to 3 mo from the first screening for the children who had proteinuria or hematuria in the first test. The child with two consecutive positive results receives a diagnosis of CKD, and the school physician suggests that that child see the family physician. The family physician generally checks serum creatinine, urea nitrogen, uric acid, total protein, albumin, IgA, complement 3, and anti-streptolysin O. From the results, the physician may recommend that the child see a nephrologist. The nephrologist may perform a renal biopsy if necessary.

From 1983 to 1999, 29 of 270,902 children who participated in the school urinalysis screening demonstrated suspected chronic nephritis on the basis of abnormal urinalysis and underwent renal biopsy (7). Of the 29 children, 14 children had IgAN confirmed. Pediatric IgAN occurred in 4.5 of 100,000 children who were younger than 15 yr per year. In 2004, the patient rate of proteinuria was 0.11% and that of hematuria was 0.83% according to the results of school urinalysis screening. The rate of children with both proteinuria and hematuria was 0.05% (124 of 246,368) in elementary school children (8). The prevalence of chronic glomerulonephritis is much lower in children than in adults.

Screening Program for Adults

For all workers in Japan, free urinalysis is given annually in company-based health examination programs. In 2004, 83% of workers aged 20 to 60 (11,933,703 individuals) received urinalysis tests. For the adults without full-time jobs, urinalysis and blood chemistry are available in the community-based health examination program, the same as the company-based screening programs. In general, approximately half of the people eligible participate in community-based health examination program. After the workers retire, they participate in the community-based screening program. With urinary protein +1 or more, the participants receive the second screening test for urinary protein. If both tests are positive, then they receive a diagnosis of proteinuria.

For adults aged ≥40 yr, the company- and community-based health examinations are carried out more extensively. The program includes a chest x-ray; urinalysis; and blood chemistry, including serum creatinine, aminotransferases, uric acid, blood glucose, total cholesterol, LDL cholesterol, triglycerides, and HDL cholesterol. According to the Ministry of Health, Welfare and Labor, 44% of Japanese adults who were aged ≥40 yr and did not have full-time jobs (12,983,593 individuals) participated the kidney disease screening in the health examination program in 2004.

A cross-sectional study reported that prevalence of proteinuria was 4.1% (12,238 of 298,537) when urinary protein in spontaneously voided fresh urine sample was measured by dipstick test, and the criteria for proteinuria was urinary protein +1 or more (approximately >30 mg/dl) (9). According to a study conducted in 1983 in Okinawa, proteinuria and hematuria both tested with dipstick methods occurred in 5.3 and 9.0% of the general population, respectively (10). In an average 6.3-yr follow-up study, new proteinuria developed in 0.4 to 0.9% of the Japanese working men, and among those with proteinuria, 20% had persistent proteinuria and 75% received a diagnosis of chronic glomerulonephritis by biopsy (11). Yamagata et al. (12) reported that newly developed proteinuria was found in 0.61% of men and in 0.34% of women annually on the basis of community-based health examination programs for adults aged ≥40 yr. In contrast, the prevalence of proteinuria was 0.01% in men and 0.19% in women of the screened population in the United States (13), which were 1/20 to 1/60 of the prevalence in Japan.

Evaluation of the Kidney Disease Screening Program

Kidney Disease Screening Program for Children

Has the school urinalysis screening contributed to the remission or regression of kidney disease in children? Glomerulonephritis was the leading cause of ESRD, 68.9%, in children between 1978 and 1980. By 1999, this percentage had fallen to 34.5% (14). The number of children with ESRD from glomerulonephritis had declined since 1974. In 1998, new ESRD occurred in 4 per 1 million children who were younger than 19 yr, whereas it occurred in 15 per 1 million in the United States (15,16). The early referral and adequate intervention for glomerulonephritis may have reduced the occurrence of ESRD in children. Overall, the school urinalysis screening system seems to be working effectively.
Kidney Disease Screening Program for Adults

Has the Japanese kidney disease screening program reduced the number of dialysis patients who progress from glomerulonephritis? Is the screening program reasonably cost effective? The effectiveness of the kidney disease screening system for adults was evaluated by two studies. Wakai et al. (17) reported that age-adjusted incidence of ESRD from chronic glomerulonephritis was decreased in both men and women since 1996 (Figure 1). The incidence of ESRD from glomerulonephritis in men was 96.3 per 1 million in 1995 to 1996 and decreased to 84.0 per 1 million in 1999 to 2000, whereas the incidence of ESRD from diabetes increased from 81.1 per 1 million in 1995 to 1996 to 96.7 per 1 million in 1999 to 2000 (17). In women, the phenomenon was similar. The incidence of ESRD from glomerulonephritis was 52.7 per 1 million in 1995 to 1996 and decreased to 46.1 per 1 million in 1999 to 2000, whereas that of diabetes increased from 38.2 per 1 million to 42.5 per 1 million, respectively (17). Yamagata et al. (18) reported that patients who have glomerulonephritis and reach ESRD is at higher age in Japan compared with in the United States. The mean age of developing new ESRD from glomerulonephritis shifted significantly to higher age, and the proportion of glomerulonephritis decreased in all causes of ESRD (Figure 2). In Japan particularly, new ESRD from glomerulonephritis decreased in number among those who were younger than 45 yr (18).

Various factors may explain the decline in the number of patients with ESRD from glomerulonephritis. One reason may be the reduced infection-related glomerulonephritis as a result of improved therapeutic intervention. Poststreptococcal acute glomerulonephritis and hepatitis B- and C-related glomerulonephritis were reduced probably by use of antibiotics and the appropriate prophylactic treatment after the diagnosis of hepatitis; however, both types of glomerulonephritis accounted for only a few percent in patients who underwent renal biopsy, suggesting that the decline in the infection-related glomerulonephritis may have little effect on the total number of cases of newly developed ESRD.

A significance of proteinuria in CKD progression and development of ESRD was reported by Iseki et al. (10). In the 17-yr follow-up study of 106,177 residents in Okinawa from 1983 to 2000, 420 people developed ESRD, and the adjusted odds ratio for development of ESRD from proteinuria was 2.71. The adjusted odds ratio even for urinary protein +1 was 1.93 in men and 2.42 in women. In addition, the study suggested that proteinuria is a strong, independent predictor of ESRD, and the screening result of proteinuria is a key predictor for ESRD. Moreover, Iseki et al. (19) studied the 7-yr cumulative incidence of ESRD in 143,948 individuals of the general population in Okinawa on the basis of baseline creatinine clearance (Ccr) quartile (Figure 3). The presence of proteinuria had a significant impact on the cumulative incidence of ESRD. Of individuals with Ccr <50 ml/min and proteinuria, 8.5% initiated to dialysis. In contrast, of individuals who had Ccr <50 ml/min without proteinuria, 0.1% reached ESRD. In individuals who had Ccr >80 ml/min without proteinuria, none developed ESRD, whereas in individuals with proteinuria, 1.0% developed ESRD. The results suggested that proteinuria is a strong indicator of CKD deterioration, and screening proteinuria is also clinically useful for identifying the high-risk population for ESRD.

Advancement in treatment of CKD also affects number of patients with ESRD. Angiotensin-converting enzyme inhibitors have been available in Japan since 1983 and angiotensin receptor blockers (ARB) since 1998. The effects of the treatments must be epidemiologically evaluated on CKD progression to ESRD.

Particularly in Japan, IgAN was the most common form of glomerulonephritis like other Asian countries. Among patients who had primary glomerulonephritis and underwent renal biopsy, 47.4% had IgAN (20). The higher incidence of IgAN in glomerulonephritis has been a characteristic in Japan. The Japanese kidney disease screening program has successfully detected milder forms of glomerulonephritis, in particular endemic IgAN, and has helped early intervention and perhaps has led to a delay in the need for renal replacement therapy. Specific treatments of IgAN, such as steroids (21), steroid pulse therapy (22), and tonsillectomy followed by steroid pulse therapy (23), have been widely used in patients with IgAN, as well as with angiotensin-converting enzyme inhibitor and ARB treatment in Japan. There are difficulties in interpreting the effectiveness of the kidney disease screening program from the declined number of cases of ESRD from glomerulonephritis for following reasons: (1) Significant improvement in therapy for glomerulonephritis occurred in the past 10 yr, and (2) not enough data on the effectiveness of the therapeutic intervention was accumulated in patients who were identified in the kidney disease screening.

The cost-effectiveness of kidney disease screening can be evaluated in following two aspects. CKD is a risk factor not only for ESRD but also for CVD. Go et al. (24) reported that the risk for cardiovascular events increased in proportion to decreased estimated GFR. Risk for CVD was evaluated in the Japanese CKD population. Irie et al. (25) reported that relative risk for all cardiovascular death in patients with both proteinuria and GFR <60 ml/min per 1.73 m² was 2.15-fold (95%
confidence interval [CI] 1.28 to 3.60) higher than in patients without proteinuria and with normal GFR in men and 4.00-fold (95% CI 2.62 to 6.10) higher in women. Ninomiya et al. (26) reported in a 12-yr study that the incidence of CVD was 1.62-fold (95% CI 1.10 to 2.39) higher in patients with CKD compared with patients without CKD. CKD is a risk factor for CVD in the Japanese general population, although the cardiovascular events occurred at 9.8 in 1000 person-years in Japan (26); the rate was 78% less than that in United States: 44.1 in 1000 person-years (24). Thus, preventing CKD by kidney disease screening plays a role in reduction of CVD, in turn reducing the expense of CVD treatment.

The most striking aspect of Japanese dialysis therapy is that the longevity of hemodialysis patients is much higher in those with glomerulonephritis than in those with diabetes. According to the Japanese Society of Dialysis Therapy (6), the rates for 5-, 10-, 15-, and 20-yr survival were 70.1, 52.7, 40.6, and 30.8%, respectively, in hemodialysis patients whose ESRD developed from glomerulonephritis. In contrast, the rates for 5-, 10-, 15-, and 20-yr survival were much less, 55.0, 28.0, 13.3, and 6.2%, respectively, in hemodialysis patients whose ESRD developed from diabetes, although the mean ages of entering dialysis were similar between patients with ESRD from glomerulonephritis and those with ESRD from diabetes, 65.8 and 65.1, respectively. The patients with glomerulonephritis composed 43.6% of the total hemodialysis patients, whereas those with diabetes accounted for only 31.4% in 2005, although diabetes has been a leading cause of ESRD (42.0% in 2005). These results depict a characteristic of Japanese hemodialysis therapy and strongly support the idea that reducing ESRD that is caused by glomerulonephritis is crucial to reducing the medical expense of dialysis therapy in Japan.

Perspectives of Kidney Disease Screening Program

Japan CKD initiatives

CKD screening in the Japanese general population is beneficial to both individuals and the government. In fact, CKD can be diagnosed by the combination of urinalysis and serum creatinine if accurate GFR could be estimated from serum creatinine; however, data from the kidney disease screening program have not been fully used for prevention of CKD in Japan. Family physicians do not always follow up with patients with proteinuria, and they do not routinely calculate estimated GFR by
underestimating the usefulness of serum creatinine value in early detection of CKD; therefore, the Japanese Society of Nephrology launched the Japanese CKD initiatives in 2004 and a comprehensive program to promote prevention of CKD and the education of physicians.

The first task was to conduct an epidemiologic study to survey the incidence of CKD in the Japanese general population; however, there are important problems to be solved in GFR estimation for Japanese. In general, GFR has been calculated by the Cockcroft-Gault equation or by the Modification of Diet in Renal Disease (MDRD) Study equation; however, both were developed in white and black individuals, so their performance is not adequate in the Japanese population. In fact, both Cockcroft-Gault and MDRD Study equations were found to overestimate GFR in Japanese, even when serum creatinine was assayed by the noncompensated Jaffe method (27). To correct the problems we modified the four-variable MDRD Study equation with a Japanese coefficient of 0.881 for accurate GFR estimation (27).

With the equation, we examined the prevalence of CKD in participants of the nationwide annual health examination program in seven prefectures of Japan using GFR estimated from the serum creatinine and with the Japanese coefficient-modified MDRD Study equation (27). From the study results of 527,594 individuals, prevalence of CKD was predicted at 19.1% in patients of stage 3 CKD and 200,000 in patients with stages 4 and 5 CKD among the general adult population using adult population of 103.2 million in 2004 (9).

Recently, we also improved the GFR estimation in Japanese using serum creatinine values determined by an enzymatic method and modified the isotope dilution mass spectrometry–traceable MDRD Study equation (28). To improve further the performance in GFR estimation, we have been creating an original equation for the Japanese using measured GFR of inulin clearance. The project just completed.

Change in Policy for the Kidney Disease Screening Program
As described, the kidney disease screening initially aimed to reduce glomerulonephritis in Japan; however, the leading cause of ESRD has changed to diabetes since 1998, and as the prevalence of diabetes increased, that of glomerulonephritis decreased. According to the Ministry of Health, Welfare and Labor, the prevalence of diabetes, with the definition of glycosylated hemoglobin >6.1%, was estimated to be 6.8% of the adult population (6.9 million) in 1997 and 7.3% (7.4 million) in 2002, and half of them were not treated. The third cause of ESRD has been hypertension since 1998 (17). In addition, metabolic syndrome has been recently recognized as a major risk factor for progressive CKD. Iseki et al. (29) reported that high body mass index was a risk for ESRD in Okinawa. In the study of the general population, Ninomiya et al. (30) and Tanaka et al. (31) reported that CKD incidence was significantly greater in individuals with metabolic syndrome, and the cumulative incidence of CKD increased in proportion to the increased number of metabolic syndrome risk factors, including hypertension, hypertriglyceridemia, low HDL cholesterol, and high blood glucose. It is interesting that triglyceride but not LDL cholesterol was a risk factor for proteinuria in Japan (32). Because the type of kidney disease has shifted from glomerulonephritis to diabetic nephropathy and hypertensive nephrosclerosis as a result of lifestyle change, a new screening system may be needed. Performing kidney disease screening that is limited to particular clinical conditions in a population may improve the cost-effectiveness; however, there remains a concern that limiting the screening to patients with hypertension, diabetes, and metabolic syndrome may not work effectively for Japanese, because the second leading cause of new ESRD, glomerulonephritis, is not associated with these conditions.

There have been reports that Asian patients with diabetes are predisposed to nephropathy compared with white patients (33). Parving et al. (34) reported that Asian patients had a higher prevalence of elevated urinary albumin/creatinine ratio (55%) than did white patients (40.6%; P < 0.0001). Wu et al. (35) also reported that the prevalence of microalbuminuria and macroalbuminuria were 39.8 and 18.8%, respectively, among patients with diabetes in Asian countries.

A subanalysis of data of Asian patients in the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study demonstrated that ARB tend to be more effective on Asian patients (36), particularly on Japanese (37), than on white patients in delaying the progression of diabetic nephropathy; therefore, early detection of diabetic nephropathy and intervention of progressive diabetic nephropathy are particularly meaningful in Japanese patients.

Lately, clinical relevance of microalbuminuria as a marker of diabetic nephropathy has drawn the attention of clinicians. According to a study (38) of the Japanese general population, there is a high prevalence of microalbuminuria, 13.7%, in adults aged ≥40 yr. As a clinical strategy to identify patients with microalbuminuria and to detect early-stage diabetes−, metabolic syndrome−, and hypertension-related renal disease, the initial screening may be ideal; however, the initial nationwide screening test is unrealistic because the cost is too expensive.
National health insurance has been allowing quarterly measurement of microalbuminuria for screening of diabetic nephropathy since 2000.

For early detection, a joint committee of the Japanese Diabetic Society and the Japanese Society of Nephrology published diagnostic criteria for diabetic nephropathy in 2004 (39). The committee recommended the following procedures for diagnosis: Microalbuminuria is to be verified by two positive results of the three urinary microalbumin tests. Microalbuminuria is defined by either 30 to 299 mg albumin/g creatinine in spot urine or 30 to 299 mg/d by 24-h urine collection. In addition, increased kidney size as observed by ultrasound and the appearance of urinary type IV collagen (8 μg/G Cr) in spot urine are the supportive data for the diagnosis (39); however, Japanese national health insurance does not allow measurement of urinary microalbumin for screening of renal injury as a result of hypertensive renal disease. Although clinical relevance of microalbuminuria in diabetes is well established, it is not widely recognized by physicians in Japan. Only half of the general physicians routinely perform the microalbumin test for patients with diabetes. Clinical usefulness of the microalbumin test in diagnosis of diabetic nephropathy and the treatment evaluation should be disseminated among physicians. We believe that mandatory measurement of microalbuminuria in kidney disease screening for the population with diabetes is a vital option for early detection of diabetic nephropathy in Japan. The relevance of microalbuminuria in hypertension and metabolic syndrome also must be evaluated in patients.

Recently in Japan, the Ministry of Health, Welfare and Labor decided to improve cost-effectiveness of the health screening program. The health administration has started a project to prevent metabolic syndrome and reduce the number of patients with metabolic syndrome, the prevalence of which is high, 25%, in Japanese men aged ≥40 yr (40); however, the administration is trying to reduce the expense in disease screening of the general population. In 2008, serum creatinine measurement will be deleted from the list of mandatory tests for adults aged ≥40 yr in the health examination program simply to reduce the cost of disease screening, although serum creatinine measurement will remain as an optional test. The Japanese Society of Nephrology has been expressing the concern that our once comprehensive kidney disease screening program will be inadequate without serum creatinine measurement and strongly recommending to keep both urinalysis and serum creatinine measurement as a part of the nationwide health examination program.

Japanese national health insurance has spent >$10 billion US annually for dialysis therapy. One percent of the expense for dialysis therapy would be sufficient for screening all individuals in Japan with serum creatinine measurement and dipstick urinalysis. We strongly believe that by keeping the present kidney disease screening program, the government could extensively save the future medical expense and improve the quality of life of patients with CKD by avoiding dialysis therapy.

Conclusion
We believe that Japan has been a leading country for having a kidney disease screening system in the world. The mandatory proteinuria screening has been practiced for >30 yr in school children and all workers, and serum creatinine measurement has been continued for the past 15 yr in adults aged ≥40 yr. The incidence of ESRD from glomerulonephritis declined and the rate of early referral to the physician increased yearly; however, as a result of lifestyle changes in Japanese in the past 10 yr, the types of kidney disease changed from glomerulonephritis to diabetic nephropathy and hypertensive nephrosclerosis. New kidney disease screening program for targeting patients with diabetes, hypertension, and metabolic syndrome may be required; however, keeping the present nationwide kidney disease screening system is crucial for management of major CKD and reducing medical costs in Japan.

Disclosures
None.

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