Chronic Kidney Disease in Japan

Kunitoshi Iseki

Abstract

Chronic kidney disease (CKD) is defined as either kidney damage with urine, imaging, and histologic abnormalities, or a low estimated glomerular filtration rate (GFR) for more than 3 months. The GFR is calculated using either the Modification of Diet in Renal Disease (MDRD) Study equation or the Cockcroft-Gault formula. CKD is a risk factor for end-stage renal disease (ESRD) and cardiovascular disease. In Japan, the prevalence of ESRD is increasing and is currently more than 2,000 per million population. More than 40% of incident ESRD is due to diabetes mellitus (DM). The prevalence of a low GFR (<60 ml/min/1.73 m²) is estimated to be 20% of the adult population. Studies based on several community-based screening programs suggest that Japan has a higher prevalence of CKD than any other country. Early detection and treatment of CKD are necessary to decrease the incidence of ESRD and cardiovascular disease.

Key words: chronic kidney disease (CKD), end-stage renal disease (ESRD), screening, proteinuria, glomerular filtration rate (GFR)

(Inter Med 47: 681-689, 2008)
(DOI: 10.2169/internalmedicine.47.0906)

Introduction

Chronic kidney disease (CKD) is a new medical term developed to educate patients, family members of patients, non-nephrology physicians, and even nephrologists. The concept of CKD was developed to prevent end-stage renal disease (ESRD) and other related medical complications. Proteinuria is a known risk factor for cardiovascular disease (CVD) and mortality. CKD is now also widely accepted as a risk factor for CVD and mortality (1-3). Recent reports, including some from Japan, support this notion (4-6). In addition to the conventional risk factors for CVD, CKD is often associated with non-conventional risk factors such as anemia and serum calcium and phosphate disturbances, which are proportional to CKD stage (7-10). According to the Japanese Society for Dialysis Therapy (JSDT), since 2005 the incidence of patients with ESRD starting chronic dialysis therapy has been greater than 2,000 per million population. The survival rate of ESRD patients is poor and the main cause of death is CVD. The prevalence of ESRD is increasing despite several strategies, including universal screening and new drugs pharmaceutical intervention (Fig. 1).

The definition of CKD is simple and easy to understand, and therefore helpful for practitioners treating undiagnosed CKD patients. Multidisciplinary collaboration between physicians, health care workers, and the government is necessary to halt the progression of CKD. Consistent with this notion, the Japanese Society of Nephrology (JSN) published a CKD Practice Guide in September 2007. The prevalence of CKD is higher in Japan than in other Asian countries and the US. The present paper summarizes recent observations, both published and unpublished, up to the end of 2007.

What is CKD?

CKD is defined as a syndrome of low glomerular filtration rate (GFR<60 ml/min/1.73 m²) and/or kidney damage determined by abnormal findings in urine, imaging, and histology lasting for more than 3 months. There are five CKD stages, based on the estimated GFR (eGFR): stage 1 (GFR>90), stage 2 (GFR: 60-89), stage 3 (GFR 30-59), stage 4 (GFR 15-29), and stage 5 (GFR<15). Kidney damage is evident in CKD stages 1 and 2. For patients with CKD that are on dialysis or have had a kidney transplant, the stage is expressed in association with a D or T, respectively. The CKD staging system was developed by the Kidney Disease Improving Global Outcomes program, which was established...
in 2003 by the International Board of Directors with the stated mission to improve the care and outcome of kidney disease patients (11, 12).

Although inulin clearance testing is the gold standard for measuring GFR, it is cumbersome and not suitable for general health practitioners or screening programs. Therefore, GFR estimation without urine collection has been proposed for screening. Recent evaluations of the Modification of Diet in Renal Disease (MDRD) Study equation showed conflicting results for Asian populations (13-15). The GFR estimation equations usually include age, sex, and race to account for differences in muscle mass among subgroups; however, the magnitude of the association of muscle mass with such variables may vary among populations, compromising the generalizability of serum creatinine-based GFR estimation equations. Creatinine production depends on muscle mass. Diet and clinical conditions such as malnutrition and inflammation also affect muscle mass. Differences in diet or muscle mass may prevent the MDRD Study equation from being applicable in Asians. The Cockcroft-Gault equation tends to overestimate the true GFR. Ideally, each ethnic group should have a separate GFR formula. The JSN recently created a Japanese GFR formula that was validated by measuring GFR with inulin clearance tests. All GFR estimation equations, however, have limitations.

**ESRD Risk Factors**

Lysaght estimated that there will be more than 2 million dialysis patients in the world by 2010, and approximately 0.3 million in Japan alone (16). The economic impact is significant even in developed countries. In developing countries, ESRD patients will die due to the small number of dialysis facilities available. Community-based screening programs have provided data for several papers on this topic. Among them, the Okinawa General Health Maintenance Association, a nonprofit organization founded in 1972, conducts an annual large community-based health examination screening program (17). Dipstick testing using an Ames dipstick (Tokyo, Japan) is performed in spontaneously voided fresh urine. Computer-based registry data for standard analysis are available for the 1983 (n=106,171), 1993 (n=143,948), and 2003 (n=154,019) screenings (Table 1). Participant demographics have changed significantly from the 1983 to the 2003 screenings. While both systolic and diastolic blood pressure levels decreased, the mean levels of serum cholesterol, triglycerides, and fasting plasma glucose,
Figure 2. Effect of proteinuria and estimated creatinine clearance on the cumulative incidence of ESRD (Ref 19). Ccr: creatinine clearance

and the prevalence of overweight and obesity have increased. Approximately 14% of the total adult population of Okinawa participated in each screening.

The ESRD patient registry in Okinawa was used to investigate the outcome of the screenees. The details of every ESRD patient treated in Okinawa since 1971 are maintained in an independent community-based registry, the Okinawa Dialysis Study registry (18-20). All chronic dialysis patients residing in the prefecture who survived for at least 1 month on scheduled dialysis were included in the registry. All patients (n=5,246) were followed up until the occurrence of a major medical event or until January 2001, whichever occurred first, and all outcomes were verified.

Using the two registries, we identified screening participants who later entered a dialysis program (17). Furthermore, patient data were verified by medical records. Important predictors of developing ESRD are dipstick-positive proteinuria and hypertension. Low GFR per se, which is often observed in the elderly population, is not a strong predictor of developing ESRD unless associated with proteinuria (Fig. 2).

In Japan, DM has been the leading cause of ESRD since 1998. In both Japan and the US, the main cause of ESRD is DM, but the second most common cause is glomerulonephritis in Japan and hypertension in the US. There are wide regional variances in the prevalence and incidence of ESRD in Japan and the US, which might be related to socio-economic differences, including drug usage. The medical cost of ESRD is approximately 4.1% of the total health care budget in Japan, more than 1,000 billion yen (>10 billion US dollars). Other significant risk factors are obesity and metabolic syndrome. Both the prevalence and incidence of CKD increase with an increase in the number of components of metabolic syndrome. The higher the body mass index (BMI), the higher the risk of developing proteinuria and ESRD. Mean BMI levels are increasing in men, but not in women. Such observations may support the increasing trend of obesity among incident dialysis patients in the US (21). The relationship between baseline BMI and the cumulative incidence of ESRD is linear, particularly in men (22, 23), but a similar trend in both men and women has been reported (23).

### Predictors of CKD Stages 1 to 4

The natural course of CKD progression is largely unknown. CKD is often asymptomatic and late referral to nephrologists, defined as referral just before dialysis is required, is common. CKD, however, often develops in those with conventional risk factors for atherosclerosis, such as hypertension, DM, hyperlipidemia, and a history of CVD. Lifestyle-related factors that are often associated with obesity and metabolic syndrome may have a role in the development and progression of CKD. The obesity-related risk of developing proteinuria is independent of hypertension and DM (24). Among the lifestyle-related factors, smoking is a known risk factor of CKD (25). Smoking may accelerate kidney damage in patients with metabolic syndrome (25, 26). Moderate alcohol intake, less than 20 g/day, decreases the risk of CKD (25). Hyperuricemia is often associated with CKD, and is also a risk factor for developing CKD (27, 28). Hyperuricemia per se induces an increase in blood pressure. A high fructose intake may raise the serum uric acid concentration (29).

Obesity and metabolic syndrome are associated with the increased prevalence and incidence of CKD. Morbid obesity per se may cause idiopathic, rapidly progressive focal segmental glomerulosclerosis in individuals without primary renal disease (30). The higher the BMI, the higher the incidence of proteinuria. In the community-based screened population, obese individuals have multiple risk factors for atherosclerosis (31-33). The prevalence of CKD increases linearly with the number of components of metabolic syndrome (34, 35). Metabolic syndrome is a significant predictor of developing CKD (Fig. 3) (36, 37). The findings of Ejerblad et al (38) support the notion of a positive relation between BMI and renal failure.

There are multiple mechanisms of CKD among metabolic
syndrome components that are not yet well delineated (39). Renal damage can be caused by each component of metabolic syndrome, such as dyslipidemia, low HDL cholesterol (40), high triglyceride levels (41, 42), and inflammatory cytokines. Obese individuals may also have an increased intake of protein and salt, which causes a metabolic overload in the glomeruli. Renal oppression by fat tissue increases the interstitial pressure in the kidney and may lead to increased salt retention. Sympathetic overactivity often causes hemodynamic changes leading to glomerular damage. Insulin resistance as well as hyper-insulinemia may cause salt retention, sympathetic overactivity, and renal hemodynamic change (43).

Sleep apnea syndrome is often associated with obesity (44, 45). The disorder is widely associated with a high rate of morbidity and mortality, mostly due to CVD and traffic accidents (46, 47). Sleep apnea is also common in patients with ESRD (48, 49). Few studies, however, have examined the prevalence of apnea in patients with CKD who are not on dialysis (50).

**CKD as a Risk Factor for CVD**

The risk of death, hospitalization, and CVD increases with a decrease in eGFR, particularly in those with an eGFR of less than 15 ml/min/1.73 m². Recent reports, including some from Japan, support these findings (Fig. 4) (51). The prevalence of a low GFR (<60 ml/min/1.73 m²) is estimated to be 20% of the adult population. Prevalence of CKD stage 3, however vary with the eGFR equation. CKD is found among those suffering from stroke, CVD, DM, and other medical conditions. One-third of patients with acute myocardial infarction have CKD. Other than a high prevalence of CKD, longer survival among patients with CVD may partly explain the steadily increasing incidence of ESRD in Japan (52). Several studies demonstrate the high prevalence of CVD among incident dialysis patients (53, 54).

CKD is more likely to develop in those with conventional risk factors for atherosclerosis, such as hypertension, DM, and hyperlipidemia. CKD and CVD share common risk factors: prevalence of DM, hypertension, metabolic syndrome, and anemia increase with a decrease in GFR. In addition to the conventional risk factors for CVD, CKD patients often have non-conventional risk factors, such as anemia and serum calcium and phosphate disturbances. People with a low GFR and the elderly often develop CVD. A low GFR is associated with CVD risk in the general population, but not with the eGFR. The cut-off levels of eGFR are not known. Because the Japanese have a lower incidence of myocardial infarction compared to those in Western countries, further studies are needed to define the relationship between CKD and CVD (55).

**CKD Screening**

Early detection and treatment might decrease the incidence of ESRD. In this regard, Japan has a long history of universal screening (56). 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 years and over, and in 1992 measurement of serum creatinine was mandated in the community-based health examination program.

It is important to determine the prevalence of CKD among the general population. The screening strategy, however, may differ depending on age. Hallan et al reported that more than 95% of CKD occurs in patients with DM and hypertension, and in patients older than 55 years of age (57). Strategies for the early detection of CKD are summarized in Table 2. Family members of ESRD patients might have similar risk factors for CKD, such as hypertension, DM, and other lifestyle-related factors. The American Heart Association recently recommended that GFR should be estimated using the MDRD Study formula in patients with CVD (58). Kidney disease was mentioned along with other major
chronic diseases by the new director general of the World Health Organization. If possible, universal screening is preferable, but most countries are urged to at least screen the target population.

The progression rate of CKD varies among individuals. Normal results at the screening do not indicate that there is no risk of developing CKD or ESRD. Nonetheless, we estimate that the risk for developing ESRD among those without any risk factors is very low; one per million per year. The optimal time to offer therapy to asymptomatic subjects with risk factors is not clear. The cost-benefit of screening frequency and test extent has been analyzed. Boulware et al. reported that the early detection of proteinuria, aimed at slowing the progression of CKD and decreasing mortality, was not cost-effective unless selectively directed toward high-risk groups (59).

Kidney function deteriorates with aging. The average GFR decline, however, is less than 0.5 ml/min/1.73 m$^2$ in the general Japanese population. Unless associated with hypertension, DM, and obesity, people do not progress into CKD stage 3. One-third of normal individuals showed no change in creatinine clearance in a 20-year longitudinal study (60).

### Table 2. Strategies for early detection of CKD (Ref. 12)

<table>
<thead>
<tr>
<th>Early detection of CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albinominuria</td>
</tr>
<tr>
<td>Blood Pressure</td>
</tr>
<tr>
<td>Cholesterol</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Estimated GFR</td>
</tr>
</tbody>
</table>

### Treatment of CKD

Lifestyle modifications among those with metabolic syndrome are required. Weight reduction is effective for reducing proteinuria in obese patients (61, 62). There is a protective effect of weight loss on CKD progression prior to progression to ESRD, but weight reduction may no longer be indicated once a patient progresses to ESRD, as renal replacement therapy has a paradoxical effect on survival (63). A higher BMI has a beneficial effect on survival in ESRD patients. These observations support the significance of the effect of malnutrition on survival in ESRD patients. Bariatric surgery is often performed in cases of extreme obesity (BMI>40 kg/m$^2$). Navarro-Diaz et al reported a remarkable improvement in glomerular hyperfiltration following recovery from renal alterations (64).

Renin-angiotensin system inhibitors prevent the progression of CKD and the development of microalbuminuria in DM patients. The new antihypertensive drugs such as angiotensin converting enzyme inhibitors, which have been available since 1983, might retard the progression of renal failure. Angiotensin receptor blockade (ARB) has been available since 1998 in Japan (Fig. 1). Angiotensin-converting enzyme inhibitors, ARBs, or their combination are effective for reducing proteinuria and CKD progression. Calcium-channel blockers are also effective for reducing proteinuria. Effective treatment of dyslipidemia decreases proteinuria and retards the progression of CKD, as indicated by meta-analysis (65). In the case of sleep apnea, continuous positive airway pressure is effective for preventing CVD and maybe CKD (66, 67). Appropriate hypoxia, however, such as that induced by high altitude, is good for humans.
Table 3. Timing of Referral to Nephrologists (CKD Practice Guide, www.jsn.or.jp)

<table>
<thead>
<tr>
<th>Subjects should be referred to a nephrologist</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Proteinuria: 0.5 g/g creatinine or dipstick ≥ 2+</td>
</tr>
<tr>
<td>2. eGFR &lt; 50 mL/min/1.73 m²</td>
</tr>
<tr>
<td>3. Both proteinuria &amp; hematuria (1+ and over)</td>
</tr>
</tbody>
</table>

and can also naturally treat obesity (68). Benefits of anemia correction and the treatment target for anemia are not yet known.

Perspectives

Glomerulonephritis remains the leading cause of ESRD in Japan. The mean age at the start of dialysis, however, is increasing in both men and women, and the absolute number of incident patients is decreasing. Because asymptomatic proteinuria and hematuria are clues to the diagnosis of IgA nephropathy, universal screening might have had a role in these observations. In contrast, the diagnosis of DM is often late, since two-thirds of DM-ESRD patients are diagnosed with hypertension, proteinuria, or CVD at the time of DM diagnosis (69).

Automatic reporting of eGFR may alert other clinical disciplines to the possible presence of CKD in their patients, which might otherwise go unrecognized. Such a system might alert physicians in non-nephrology services and increase the rate of referrals to nephrologists. Implementation of an eGFR reporting system should be associated with comprehensive education of practitioners. A practice guide for CKD will be necessary for non-nephrology services (www.jsn.or.jp, Table 3). Further studies are necessary to determine the benefits of this system on daily practice and the future incidence of ESRD. Late referral to nephrologists, however, defined as referral just before the dialysis is required, is common (70, 71).

Conclusion

The Japanese population is at high-risk for CKD and ESRD. Because the elderly population is growing, more attention should be paid to the early detection of CKD, particularly in those near retirement age, 60 to 65 years, and those with obesity, metabolic syndrome, hypertension, and DM. Compared to the prevalence of CKD in the US (72), the prevalence is higher in the Japanese (51). Proteinuria, hypertension, anemia, DM, and metabolic syndrome may indicate the presence of CKD. The incidence of a decrease in the GFR due to aging is not as high as expected and is not associated with hypertension and DM (73). The prevalence of CKD seems to be increasing along with the increase in BMI, DM, and hypertension. Based on the eGFR, baseline GFR and the extent of an age-related GFR decline differ among ethnic groups (Fig. 5). CKD is common in Japan and is expected to increase, particularly in the aging population. According to the Hisayama study, CKD prevalence is increasing in both men and women (Fig. 6) (74). The reasons for this trend may be related to both genetic and environmental factors (Table 4). Subjects with low birth weight, which is associated with a lower nephron number (75), might develop insulin resistance and therefore have an increased risk of CKD (76, 77).

The concept of CKD is a new tool to facilitate communication between nephrologists and other medical professionals. CKD should be investigated in patients being treated for hypertension, DM, heart disease, and stroke. Such patients should have both urine and serum creatinine examined at least once a year to determine the presence of CKD. To prevent ESRD and CVD, proper management of CKD through mutual collaboration with multiple disciplines is necessary.
Proper use of nephrotoxic agents such as antibiotics, radiocontrast media, and non-steroidal anti-inflammatory drugs may prevent acute renal injuries. More public relations programs to educate the public on CKD are necessary, especially among those with hypertension and DM, and the elderly population.

Acknowledgement
The author is grateful for the collaboration of the staff of the Okinawa General Health Maintenance Association and the Okinawa Dialysis Study (OKIDS) group.

References


58. Brosius FCI, Hostetter TH, Kelepouris E, et al. AHA Science Advisory:Detection of chronic kidney disease with or at increased risk of cardiovascular disease: A science advisory from the American Heart Association kidney and cardiovascular disease council; the Councils on high blood pressure research, cardiovascular disease in the young, and epidemiology and prevention;and the Quality of care and outcomes research interdisciplinary working group: Developed in collaboration with the National Kidney Foundation. Circulation 114: 1083-1087, 2006.


© 2008 The Japanese Society of Internal Medicine
http://www.naika.or.jp/imindex.html