Japan Association of Chronic Kidney Disease Initiatives (J-CKDI)

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Chronic Kidney Disease (CKD) is defined by Kidney Disease: Improving Global Outcome (KDIGO), as kidney damage that has continued for more than 3 months, as defined by structural or functional abnormalities of the kidney, with or without decreased glomerular filtration rate (GFR), that can lead to decreased GFR, or GFR$<$60 mL/min/1.73 m^2 for $\geq$3 months, with or without kidney damage.[1]

CKD has emerged as a non-communicable life-threatening disease. CKD increases not only the number of chronic dialysis patients but also mortality from cardiovascular diseases in both developing and developed countries. Symptoms of kidney diseases are generally mild and patients often only become aware of CKD at the end stage of the kidney disease or when they suffer myocardial infarction or stroke. The Japan Association of Chronic Kidney Disease Initiatives (J-CKDI) was established to promote the prevention, early detection, and treatment of CKD in Japan. J-CKDI was founded by the Japanese Society of Nephrology in association with Japanese Society of Dialysis Therapy and Japanese Society of Pediatric Nephrology in 2006. The Japan Medical Association (JMA) became an official member of J-CKDI in 2008.

The purpose of the J-CKDI is to improve the care and outcomes for kidney disease patients in Japan through the early detection of CKD and adequate treatment standardized by the formulation of guidelines. We also undertake activities to raise awareness of the harmfulness of CKD on World Kidney Day, the 2nd Tuesday in March each year, in coordination with other CKD initiatives worldwide.

Development of the Japanese Equation for Estimating GFR and Estimation of the CKD Population

Measured GFR or estimated GFR (eGFR) is essential for the diagnosis of CKD. Measurement of GFR using inulin clearance is cumbersome and expensive in clinical practice and screening in annual health check programs. We evaluated the Modification of Diet in Renal Disease (MDRD) equations of estimated GFR for Japanese in 2007.[2] However, the value of eGFR was overestimated in the MDRD equation, which had coefficients for Black and White but not for Asian. Therefore, we decided to create a Japanese equation for estimating GFR. We measured inulin renal clearance in 413 CKD patients from 80 medical institutions and generated a Japanese equation for estimating GFR. The equation was validated using measurements of inulin clearance in 350 CKD patients.[3] The Japanese equation is shown in **Table 1**. We also calculated the coefficient for MDRD equations and recently also provided a coefficient for the CKD Epidemiology Collaboration (CKD-EPI) equation,[4] which was created from measurements of GFR in more than 5,000 participants. The coefficients for Japanese are constantly lower than 1.0, suggesting that the muscle mass was less in Japanese compared with Black or White patients.

We estimated that the CDK population in Japan using data from the annual health check program in 8 districts and the 2005 national census. The prevalence of CKD in Japan was 13.3 million and of CKD stages 1, 2, 3 and 4+5 were 0.6, 1.7, 10.7, and 0.2 million, respectively.[5]

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Table 1 Japanese equations for estimating GFR and coefficients for MDRD and CKD-EPI equations

Japanese Equation (3 variables): $194 \times (SCr)^{-1.094} \times (Age)^{-0.287} \times 0.739$ (if female)

Japanese Equation (5 variables): $142 \times (SCr)^{-0.923} \times (Age)^{-0.185} \times Alb^{0.414} \times BUN^{-0.233} \times 0.772$ (if female)

IDMS-MDRD: $175 \times (SCr)^{-1.154} \times (Age)^{-0.203} \times 0.742$ (if female)   Japanese Coefficient 0.808

CKD-EPI: Female: $SCr \leq 0.7\,mg/dL$ $eGFR = 144\,(SCr/0.7)^{-0.329} \times 0.993^{(Age)}$
            $SCr > 0.7\,mg/dL$ $eGFR = 144\,(SCr/0.7)^{-1.209} \times 0.993^{(Age)}$
       Male: $SCr \leq 0.9\,mg/dL$ $eGFR = 141\,(SCr/0.9)^{-0.411} \times 0.993^{(Age)}$
            $SCr > 0.9\,mg/dL$ $eGFR = 141\,(SCr/0.9)^{-1.209} \times 0.993^{(Age)}$

Japanese Coefficient 0.813

Cockcroft-Gault: $(140 - Age) \times (Body\ Weight)/72 \times SCr$ Japanese Coefficient 0.789

The risk of progressive declining of GFR was increased at $GFR < 50\,mL/min/1.73\,m^2$.[6] Thus, we estimated the number of CKD patients in Japan with a risk of progressively declining GFR to be about 6 million.

World Kidney Day

Coordinated action to spread awareness of CKD in the form of a World Kidney Day has been taking place on the 2nd Thursday of March each year since 2006.[7] We have repeatedly emphasized the importance of CKD awareness over the past 5 years under the themes "Are your kidneys OK?" in 2006; "CKD is common, harmful and treatable" in 2007; "Amazing kidneys" in 2008, "Protect your kidneys; keep pressure down" in 2009; "Protect your kidneys: control diabetes." in 2010; and "Protect your kidneys and save your heart." in 2011. In Tokyo as well as in local cities we have held symposiums on CKD and provided dipstick tests for self-urinalysis to detect CKD early.[8] In 2011, events for raising CKD awareness were performed in 17 prefectures: Aichi, Ehime, Fukushima, Fukuoka, Hiroshima, Hokkaido, Hyogo, Ishikawa, Kochi, Nara, Niigata, Okayama, Shiga, Wakayama, Yamagata, Yamaguchi, and Yamanashi. In meetings local participants in CKD initiatives appealed to people to be aware of CKD and handed out dipsticks for urinalysis. These campaigns received TV, radio, and newspapers coverage.

Change in the Incidence of Dialysis in Japan

The number of dialysis patients in Japan is over 300 thousand and has been increasing continually over the last 30 years. The prevalence of chronic dialysis is one in 450 of population. However, the incidence of dialysis in 2008, 2009 and 2010 was 38,180, 37,565, and 37,532, respectively,[9] a decrease that suggests that the incidence of dialysis peaked in 2008. Of particular note is the fact that the incidence of new dialysis patients due to diabetes, which is the leading cause of kidney disease requiring dialysis (43.5%), also decreased by 1% for the first time in 2010. The incidence of dialysis due to glomerulonephritis has continuously decreased over the past 3 decades.

The Japanese Society of Nephrology (JSN) published guidelines for CKD treatment in 2007 and 2009 in order to standardize treatment of CKD.[10,11] A number of meetings and lectures were held for general physicians to educate them regarding the definition, classification, early detection and treatment of CKD using these guidelines.

The Ministry of Health, Labour and Welfare (MHLW) provided grants for research on CKD in 2007. A randomized control study entitled "Frontier of Renal Outcome Modifications in Japan (FROM-J)" was undertaken to evaluate the intensive support provided for CKD patients by family physicians, nurses and dieticians compared with the standard of care prescribed by the CKD guidelines. The results will be made public in 2013. In addition to the FROM-J, the MHLW has supported 7 studies on CKD during the past 3 years. The coordinated actions taken by J-CKDI, JSN, MHLW and JMA have so far improved awareness of CKD and may reduce the incidence of dialysis.

Comorbidity of Cardiovascular Diseases (CVD)

The reduction of CVD in patients with CKD is another important task for J-CKDI. The risk of CVD is increased in patients with CKD in association with the progression of CKD.[12] There is a strong association between albuminuria and cardiovascular disease, particularly coronary heart disease and stroke. The risk of CVD is independently associated with declining GFR.[13] However, the risk of CVD seems to be lower in Japanese compared with Black or White patients.[14,15] The incidence of stroke is significantly higher in the Japanese CKD population.[16]

The risk of CVD is much higher amongst patients with diabetes than those with glomerulonephritis.[14,15] Arteriosclerosis appears to progress in diabetic patients with CKD and emerging microalbuminuria indicates the presence of advanced arteriosclerosis in systemic arteries.[17] In contrast, massive proteinuria of nephrotic syndrome may not be associated with systemic arteriosclerosis.

Perspectives

J-CKDI has operated successfully for the past 5 years. The method for estimating GFR using the Japanese equation is established and well disseminated. Most hospitals provide values for eGFR. Information about renal function can be shared by physicians, nurses, pharmacists, dieticians, and patients to prevent the progression of CKD. We will release a new equation for estimating GFR using a combination of Cr and cystatin C to improve the accuracy of the GFR estimation in a normal range.

Japanese collaboration with other Asian countries has steadily progressed and will soon bear fruit in an Asian GFR equation for the early detection of CKD and Asian guidelines for the treatment of CKD.[18] Inulin renal clearance originally developed in Japan is being measured in Taiwan, China, Korea, India, Singapore, Malaysia, and Thailand.

Prospective observational studies and randomized control trials with CKD patients are ongoing and will provide evidence-based treatment for CKD in Japan. We are optimistic for the development of structure, support, and strategy for the management of CKD in Japan.

References

1. Levey AS, Eckardt KU, Tsukamoto Y, et al. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int. 2005 Jun;67(6):2089–2100.
2. Imai E, Horio M, Nitta K, et al. Estimation of glomerular filtration rate by the MDRD study equation modified for Japanese patients with chronic kidney disease. Clin Exp Nephrol. 2007 Mar;11(1): 41–50.
3. Mastuo S, Imai E, Horio M, et al. Revised equations for estimating glomerular filtration rate (GFR) from serum creatinine in Japan. Am J Kidney Dis. 2009;53:982-992.
4. Horio M, Imai E, Yasuda Y, Watanabe T, Matsuo S. Modification of the CKD-EPI equation for Japanese: Accuracy and use for population estimates. Am J Kidney Dis. 2010 Jul;56(1):32–38.
5. Imai E, Horio M, Watanabe T, et al. Prevalence of chronic kidney disease in the Japanese general population. Clin Exp Nephrol. 2009 Dec;13(6):621–630.
6. Imai E, Horio M, Yamagata K, et al. Slower decline of glomerular filtration rate in the Japanese general population: a longitudinal 10-year follow-up study. Hyperetens Res. 2008;31:433–441.
7. http://www.worldkidneyday.org/
8. http://j-ckdi.jp/jckdi/
9. http://www.jsdt.or.jp/
10. Japanese Society of Nephrology. Clinical Practice Guidebook for Diagnosis and Treatment of CKD. Nippon Jinzou Gakkai Shi. 2007;49(7):757–761. (in Japanese)
11. Japanese Society of Nephrology. Evidence-based practice guideline for the treatment of CKD. Clin Exp Nephrol. 2009 Dec; 13(6):537–566.
12. Go AS, Chertow GM, Fan D, McCulloch CE, and Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004 Sep 23;351(13): 1296–1305.
13. Hillege HL, Fidler V, Diercks GF, et al.; Prevention of Renal and Vascular End Stage Disease (PREVEND) Study Group. Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. Circulation. 2002 Oct 1; 106(14):1777–1782.
14. Nakayama M, Sato T, Sato H, et al. Different clinical outcomes for cardiovascular events and mortality in chronic kidney disease according to underlying renal disease: the Gonryo study. Clin Exp Nephrol. 2010 Aug;14(4):333–339.
15. Imai E, Matsuo S, Makino H, et al. Chronic Kidney Disease Japan Cohort Study: Baseline characteristics and factors associated with causative diseases and renal function. Clin Exp Nephrol. 2010 Dec;14(6):558–570.
16. Nakayama M, Nakayama K, Zhu WJ, et al. Polymorphonuclear leukocyte injury by methylglyoxal and hydrogen peroxide: a possible pathological role for enhanced oxidative stress in chronic kidney disease. Nephrol Dial Transplant. 2008 Oct; 23(10):3096–3102.
17. Ito S, Nagasawa T, Abe M, Mori T.. Strain vessel hypothesis: a viewpoint for linkage of albuminuria and cerebro-cardiovascular risk. Hypertens Res. 2009 Feb;32(2):115–121.
18. Li PTK, Chow KM, Matsuo S, et al. Asian Chronic Kidney Disease (CKD) Best Practice Recommendations—Positional Statements for Early Detection of CKD from Asian Forum for CKD Initiatives (AFCKDI). Nephrology. In press