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Original Article

Asian chronic kidney disease best practice recommendations: Positional statements for early detection of chronic kidney disease from Asian Forum for Chronic Kidney Disease Initiatives (AFCKDI)

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SUMMARY AT A GLANCE

These guidelines relate to screening for chronic kidney disease, specifically in an Asian setting. They draw on considerable experience across Asia from a specially convened workshop.

AFCKDI RECOMMENDATIONS FOR EARLY DETECTION OF CHRONIC KIDNEY DISEASE

1. Targets
Patients with diabetes, hypertension
Those with family history of chronic kidney disease (CKD)
Individuals receiving potentially nephrotoxic drugs, herbs or substances or taking indigenous medicine
Patients with past history of acute kidney injury
Individuals older than 65 years
2. Tools
Spot urine sample for protein with standard urine Dipstick test (need a repeat confirmatory test if positive)
Dipstick for red blood cells (need confirmation by urine microscopy)
An estimate of glomerular filtration rate based on serum creatinine concentration
3. Frequency of screening
Screening frequency for targeted individuals should be yearly if no abnormality is detected on initial evaluation.
4. Who should perform the screening
Doctors, nurses, paramedical staff and other trained healthcare professionals
5. Intervention after screening
Patients detected to have CKD should be referred to primary care physicians with experience in management of kidney disease for follow up. A management protocol should be provided to the primary care physicians. Further referral to nephrologists for management will be based on the protocol together with clinical judgment of the primary care physicians with their assessment of the severity of CKD and the likelihood of progression.
6. Screening for cardiovascular disease risk
It is recommended that cardiovascular disease risk factors should be screened in all patients with CKD.

Patients with chronic kidney disease (CKD) are at increased risk of progression to end stage kidney disease and cardiovascular disease if they are not identified and properly managed. This is true for all patients with CKD. Despite the increasing prevalence of CKD in Asia, there are few guidelines for early detection of CKD in Asian countries.

Although there is broad agreement about targeted screening directed at subgroups of the population who would derive the most benefit from CKD detection, there are differing views regarding the costs and benefits of a population wide surveillance programme. Table 1 summarizes the existing international guidelines on screening for CKD.[1–5] There are no randomized controlled trials examining outcomes of kidney disease screening programmes (including cardiovascular risk), and little information specifically dealing with the issues of cost-effectiveness and public health policies. Recommendations have been reported by the 2006 Kidney Disease Improving Global Outcomes (KDIGO) Controversies Conference regarding strategies for implementation of screening and surveillance for CKD in developing countries.[3] For the purpose of uniformity, we use the same definitions of screening and surveillance.[3] Screening is an activity whereby persons in a defined population who are not aware of CKD are tested to detect the disease and, if present, are subsequently treated to reduce the risk of progression of CKD and its complications. Surveillance, on the other hand, refers to an activity to provide key information on CKD, such as time, location, magnitude, and severity, in order to guide implementation of medical and public health measures to control progression of CKD and its complications.[3] Screening efforts, unless population-based, cannot provide information about true prevalence of disease in a community.

The objective of the current guidelines is to give advice where possible on the early detection of CKD in Asian countries. We therefore focus largely on screening, which alone does not represent surveillance in all its facets. These guidelines are intended to be reviewed by the work group participants under the Asian Forum of CKD Initiative (AFCKDI). Members of the work group were selected based on the criteria of knowledge/expertise in CKD with a geographical representation of the Asian Pacific countries/region, diversity of views and expertise in the healthcare system.

BACKGROUND

The need for early detection

The global epidemic of CKD has posed a major public health problem, not only in high-income countries but also in Asia. This problem is compounded by the diabetes epidemic and the enormous disease burden of hypertension in Asian populations. Given the population growth and rate of urbanization in Asia, it has been estimated that India and China will be the two countries with the highest numbers of people with diabetes by 2030.[6] Five other Asian countries are among the top 10 countries in the number of diabetic patients – Indonesia, Pakistan, Bangladesh, Japan, and the Philippines.

High blood pressure has also been estimated to account for more than a third of deaths and almost a fifth of disability-adjusted life years in central Asia. Nevertheless, the proportion of awareness, treatment and control of high blood pressure is exceedingly low, partly related to low level of literacy and education, but also attributable to a low level of access to medical care in some Asian countries. Previous data from national surveys,[7–11] for instance, suggested a disappointingly low level of disease awareness and adequate treatment (Fig. 1). In a survey involving 141 892 Chinese adults, only 24% of affected adults were aware of their hypertension.[7] In fact, the percentage of hypertension awareness has been less than 50% in most Asian countries (Fig. 1), quite low when compared to that in the United States population. 80.7% of United States patients with hypertension in the National Health and Nutrition Examination Survey (NHANES), answered affirmative to the question, 'Have you ever been told by a doctor or other healthcare professional that you had hypertension, also called high blood pressure?'[12] This discrepancy in hypertension awareness percentage (Fig. 1) indicates a substantial knowledge gap between Asians and the Western population.

The priority of disease detection

Given the aforementioned problems of undiagnosed diabetes mellitus and hypertension in many areas of Asia with extreme poverty and limited healthcare resources, CKD screening should therefore form a second or third layer of healthcare. Screening for CKD should be given the same priority and in fact integrated with screening for hypertension and diabetes, and, depending on the circumstances and environment, must be balanced against the need in the developing countries for screening and managing malnutrition, acute and chronic infections (such as gastroenteritis, human immunodeficiency virus, tuberculosis and malaria). Prevalence of glomerular disease, particularly immunoglobulin A (IgA) nephropathy, is high in Asian countries. Glomerulonephritis is the second leading cause of ESRD following diabetes. The early detection of glomerulonephritis is also important and meaningful because it is a treatable disease.

SCREENING AND EARLY DETECTION OF CHRONIC KIDNEY DISEASE

Whom to screen

Universal screening of the general population would be time-consuming, and expensive and has been shown to be not cost-effective. Unless selectively directed towards high-

Table 1 Summary of international guidelines on screening of chronic kidney diseases (CKD)

Recommendation on screening		Target populations suggested	Screening tools
National Kidney Foundation, NKF[1]	Published in 2007	• Patients with diabetes • Patients with hypertension and cardiovascular disease • A family history of CKD • Age greater than 60 years	Urine test for proteinuria and a blood test to estimate GFR
Caring for Australasians with Renal Impairment, CARI[2]	Published in 2007	• Patients with vascular disease or hypertension • Immediate relatives of patients with kidney disease • Aboriginal Australians and Torres Strait Islanders • Patients complaining of prostatic symptoms	Proteinuria and renal function (serum creatinine and eGFR)
Kidney Disease Improving Global Outcomes, KDIGO[3]	Published in 2007	• Patients with hypertension • Patients with diabetes • Patients with cardiovascular disease • Families of patients with CKD • Patients with hyperlipidaemia • Patients with obesity • Patients with metabolic syndrome • Smokers • Patients treated with potentially nephrotoxic drugs • Age greater than 60 years	Urine test for proteinuria and a blood test for creatinine to estimate GFR
UK Renal Association and National Institute for Health and Clinical Excellence, NICE[4]	Published in 2008	• Patients with hypertension • Patients with diabetes mellitus • Patients with cardiovascular disease (ischaemic heart disease, chronic heart failure, peripheral vascular disease, cerebrovascular disease) • Patients with structural renal tract disease, renal calculi, or prostatic hypertrophy • Patient with multisystem diseases with potential kidney involvement • Family history of stage 5 CKD or hereditary kidney disease • Opportunistic haematuria or proteinuria	Urine albumin: creatinine ratio, serum creatinine (isotope dilution mass spectrometry traceable simplified MDRD equation) to estimate GFR
Japanese Society of Nephrology Guideline for treatment of CKD[5]	Published in 2009	• Hypertension • Impaired glucose tolerance, diabetes mellitus • Obesity, dyslipidaemia, metabolic syndrome • Collagen disease, systemic infection • Urinary tract stone, urinary tract infection, prostate hypertrophy • Family history of CKD, low birth weight • Past history of screening (urine tests, kidney function, kidney size and shape) • Habitual drugs (NSAIDs), supplements • Past history of acute kidney failure • Smoking • Elderly • Single kidney, kidney atrophy (small kidney)	Urine test for proteinuria and a blood test to estimate GFR
U.S. Preventive Services Task Force, USPSTF	No recommendation	No recommendation	No recommendation
Kidney Disease Outcomes Quality Initiative KDOQI	No recommendation	No recommendation	No recommendation
European Best Practice Guidelines EBPG	No recommendation	No recommendation	No recommendation

GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease.

risk groups, according to a cost-effectiveness analysis using a Markov decision analytic model, population-based dipstick screening for proteinuria has an unfavourable cost-effectiveness ratio.[13] The scale of screening programmes, therefore, should be individualized for each region. Before high-risk group screening can be recommended, surveillance needs to be performed to allow correct identification of target groups (for screening). This approach has been endorsed by the International Society of Nephrology 2004 Consensus Workshop statements on prevention of kidney diseases.[14]

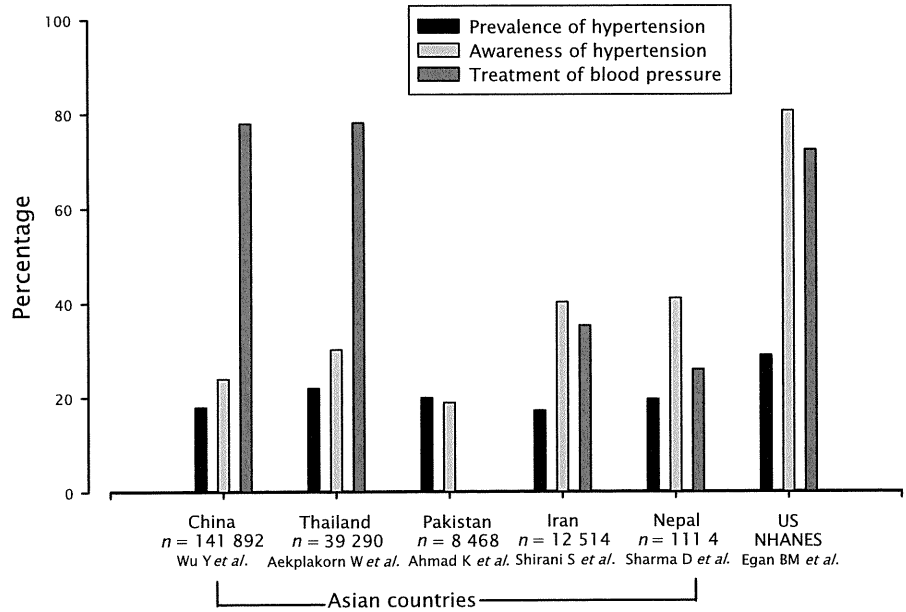

Fig. 1 Disease prevalence, awareness and treatment of hypertension from national survey studies within Asia: comparison with US National Health and Nutrition Examination Survey (NHANES) data. Disease prevalence refers to the percentage of overall population, awareness percentage is of disease prevalence and treatment percentage is of awareness population.

Data to guide identification of high risk-groups for screening are derived largely from analysis of several surveillance studies in Asia. Efforts have been made to characterize the scale of the problem and to identify candidates for screening CKD in Asian countries. Numerous large-scale surveillance studies have been performed in Asia (Table 2).[15–25] The prevalence of CKD has been estimated to be 13% in a large sample of 13 295 adults in China.[15] This is congruent with the findings from another cohort of 574 024 adults in Japan, where the same prevalence of CKD was reported.[18] New clinical studies suggest that a strikingly large percentage of patients who have AKI do not fully recover renal function or require permanent renal replacement therapy, and that this population has an important impact on the epidemiology of CKD and end-stage renal disease.[26,27]

Based on these studies and the opinion from our members, we recommend that **patients with diabetes, hypertension, a family history of CKD or a past history of acute kidney injury should have regular screening for detection of kidney disease** (Table 3). This recommendation is consistent with guidelines (Table 1) developed by the Kidney Disease Improving Global Outcomes (KDIGO),[3] UK Renal Association and National Institute for Health and Clinical Excellence (NICE),[4] the National Kidney Foundation (NKF),[1] Caring for Australasians with Renal Impairment (CARI)[2] and the Japanese Society of Nephrology.[5]

In addition, a recurring theme from the published data in Asia is the susceptibility of individuals to develop CKD if they are treated with potentially nephrotoxic medications including herbs. This should be highlighted with special reference to Asian countries. The need to look into the high-risk group with nephrotoxic medication use in Asian populations is well illustrated by a prospective study from Taiwan, where regular use of herbal medicines was associated with a quarter higher risk for developing CKD than among non-users.[19] These results showed a proportion of herbal medicine usage that rose with severity of disease; the relationship persisted even when those with advanced disease (stage 4 and 5) and those aware of their disease status were excluded. Another cross-sectional study in Taiwan confirmed that herbal therapy was associated independently with CKD and the stage of CKD in subjects not using analgesics.[28] A high risk (adjusted odds ratio 2.19) of developing CKD had also been shown among patients who receive nephrotoxic medication (non-steroidal anti-inflammatory drugs and herbs containing aristolochic acid) in a surveillance study in Beijing, China.[15] Similar findings have been replicated in India and Thailand, highlighting the popularity and risk of using traditional medicines.[21,22] It is our opinion that there is a definite need for screening **Asian individuals receiving potentially nephrotoxic drugs, herbs or substances or taking indigenous medicine.**

Whether or not screening targeted at elderly individuals has benefit is currently unknown. CKD has increasingly become a 'geriatric' disease, with a dramatic rise in incidence in the aging population. Elderly patients have developed into the fastest growing population commencing dialysis. In previous surveillance studies from China, Australia, Thailand, India and Singapore, old age has been associated with an increased risk of CKD,[15–17,21,22] but there is controversy regarding the current classification schema for applying

Table 2 Population-based epidemiological studies of chronic kidney disease (CKD) in Asia and Oceania

Region	Screened population	Screening tools	Prevalence	Identified risk factors
Beijing, China[15]	13 925 adults (response rate 90.6%)	Glomerular filtration rate using calibrated serum creatinine level and formula estimation	13%, defined as glomerular filtration rate <60 mL/min per 1.73 m^2 or markers of kidney damage	Independent predictors of CKD • Older age (odds ratio 1.83) • Nephrotoxic medication (odds ratio 2.19) • Rural area (odds ratio 0.47) • History of cardiovascular disease (odds ratio 2.04) • High-density lipoprotein cholesterol <1.03 mmol/L (odds ratio 3.00) • Hypertension status >10 years (odds ratio 1.85)
Australia[16]	11 247 adults (response rate 55.3%)	Spot urine protein to creatinine ratio Haematuria confirmed by urine microscopy Cockcroft-Gault estimated glomerular filtration rate	16% with one or more indicators of kidney damage	Independent predictors of proteinuria • Age ≥65 (odds ratio 2.5) • Diabetes mellitus (odds ratio 2.5) • Hypertension (odds ratio 3.1)
Singapore[17]	189 117 working adults	Dipstick analysis of urine protein and blood	1.1% with proteinuria ≥1 +	Independent predictors of proteinuria • Age ≥61 (odds ratio 2.7) • Malay race (odds ratio 1.3) • Diabetes mellitus (odds ratio 2.0) • Hypertension (odds ratio 1.8) • Renal disease (odds ratio 3.5) • Body mass index ≥30 kg/m^2 (odds ratio 2.5) • Haematuria (odds ratio 2.9) • Family history of kidney disease (odds ratio 2.0)
Japan[18]	574 024 adults	Japanese equation for estimated glomerular filtration rate Dipstick analysis of urine protein	13% with CKD (stage 1–5)	
Taiwan[19]	462 293 adults	MDRD equation for estimated glomerular filtration rate Dipstick analysis of urine protein	12% with CKD	Predictors of CKD • Regular use of Chinese herbal medicine (odds ratio 1.2)
Hong Kong[20]	1 201 adults	Dipstick analysis of urine protein and blood	3.2% with proteinuria ≥1 +	Predictors of urine abnormalities • Family history of diabetes or hypertension
Thailand[21]	3 459 adults	Serum creatinine standardized with isotope dilution mass spectrometry and MDRD equation for estimated glomerular filtration rate	17.5% with CKD (stage 1–5)	Independent predictors of CKD • Age ≥70 (odds ratio 7.34) • Diabetes mellitus (odds ratio 2.72) • History of kidney stone (odds ratio 2.72) • Hypertension (odds ratio 1.96) • Using traditional medicine (odds ratio 1.20) • Uric acid >0.33 mmol/L (odds ratio 2.87) • Female gender (odds ratio 1.70)
Delhi, North India[22]	5 252 adults (response rate 94.4%)	Serum creatinine, Cockcroft-Gault and MDRD equation for estimated glomerular filtration rate Dipstick analysis of urine protein	13.3%, defined as glomerular filtration rate <60 mL/min per 1.73 m^2 by Cockcroft-Gault equation 2.25% with proteinuria ≥1 +	Independent predictors of CKD • Age >60 (odds ratio 29.49) • Diabetes mellitus (odds ratio 1.51) • Hypertension (odds ratio 1.74) • NSAID intake (odds ratio 1.34) • Female gender (odds ratio 1.53) • Education less than primary (odds ratio 1.31) • Obese by waist circumference (odds ratio 1.34)
South Korea[23]	5 136 adults	MDRD equation for estimated glomerular filtration rate	6.8%, defined as glomerular filtration rate <60 mL/min per 1.73 m^2 by MDRD equation	Independent predictors of CKD • Female gender (odds ratio 3.53) • Metabolic syndrome (odds ratio 1.77) • Hypertension (odds ratio 1.33)
Indonesia[24]	9 412 adults	Dipstick analysis of urine protein Serum creatinine only measured in subjects with hypertension, proteinuria, glycosuria and/or a history of diabetes	2.8% with proteinuria ≥1 + persistently	
Nepal[25]	8 398 adult ≥20 years of age	Serum creatinine, fasting blood glucose, dipstick urinalysis with proteinuria confirmed by ACR, e-GFR using Modified MDRD equation	5.04% with proteinuria ≥1 +, CKD 14.4% defined as glomerular filtration rate <60 mL/min/1.73 m^2 by MDRD equation	
Mongolia[25]	997 adults	Dipstick analysis of spot urine protein Serum creatinine, e-GFR using Modified MDRD equation	13.9% with CKD (stage 1–5) defined as proteinuria+, glomerular filtration rate <60 mL/min/1.73 m^2 by MDRD equation	Independent predictors of proteinuria • Age ≥61 • Diabetes mellitus • Hypertension • Body mass index ≥25 • Family history of kidney disease

ACR, albumin/creatinine ratio; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; NSAID, non-steroidal anti-inflammatory drugs.

Table 3 Recommendations from Asian Forum for Chronic Kidney Disease Initiatives (AFCKDI) on screening

1. Targets:
   Patients with diabetes, hypertension
   Those with family history of chronic kidney disease (CKD)
   Individuals receiving potentially nephrotoxic drugs, herbs or substances or taking indigenous medicine.
   Patients with past history of acute kidney injury
   Individuals older than 65 years
2. Tools:
   Spot urine sample for protein with standard urine dipstick test (need a repeat confirmatory test if positive)
   Dipstick for red blood cells (need confirmation by urine microscopy)
   An estimate of glomerular filtration rate based on serum creatinine concentration
3. Frequency of screening
   Screening frequency for targeted individuals should be yearly if no abnormality is detected on initial evaluation.
4. Who should perform the screening:
   Doctors, nurses, paramedical staff and other trained healthcare professionals
5. Intervention after screening
   Patients detected to have CKD should be referred to primary care physicians with experience in management of kidney disease for follow up. A management protocol should be provided to the primary care physicians. The need for referral to nephrologists for management will be based on the protocol together with clinical judgment of the primary care physicians with their assessment of the severity of CKD and the likelihood of progression.
6. Screening for cardiovascular disease risk
   It is recommended that cardiovascular disease risk factors should be screened in all patients with CKD.

estimated glomerular filtration rate in the elderly.[29] Some concern has been expressed about the applicability of the same diagnostic glomerular filtration rate threshold for aged as for younger populations. A recent study looked into 8705 community-dwelling individuals aged ≥65 years and studied the relation of estimated glomerular filtration rate (eGFR) with 6-year mortality. It was found that moderately decreased eGFR <45 mL/min per 1.73 m^2 was related to poor outcomes and that the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) and the MDRD equations provided very similar prevalence and long-term risk estimates.[30] **We suggest that elderly individuals over 65 years should be screened.** Elderly patients have more co-morbid diseases and greater functional limitations that affect mortality and quality of life. Therefore, screening the elderly for CKD may be cost-effective in detecting a target population in need for CKD care. A cost-effectiveness analysis reported that early detection of urine protein with the aim of slowing progression of CKD and decreasing mortality is not cost-effective unless selectively directed toward high-risk groups (older persons and persons with hypertension) or conducted at an infrequent interval of 10 years.[13] It is important to note that cost-effectiveness is also dependent on the life expectancy of the population to which it is applied.

How to screen

To date no consensus exists as to the best screening tool(s) to use for early detection of CKD among the various options available.[31] Measurement of albuminuria by a spot urine sample, using either albumin-specific dipstick or albumin-to-creatinine ratio is now accepted. Other options include serum creatinine and equation estimated glomerular filtration rates.

Clearly, in resource-limited countries in Asia, in order to have a population impact, a practical or affordable means of screening CKD should be chosen. No cost-effectiveness studies of various screening tools have been performed in Asia. One simple tool would be anthropometric measurements (body mass index and blood pressure) and standard urine dipstick testing. Screening by spot morning urine albumin concentration and albumin-to-creatinine ratio, on the other hand, has been validated in an Indo-Asian population.[32] While this report from Pakistan confirmed that the conventionally recommended cut-off value of albumin-to-creatinine ratio of 30 mg/g was associated with over 95% specificity, its sensitivity remained suboptimal in women. Furthermore, the study reported a comparable diagnostic performance of urine albumin and urine albumin-to-creatinine ratio.[32] This observation seems to favour urine albumin concentration test alone, without the need to measure urine creatinine, which might incur substantial cost in a large-scale screening programme.

From an economic perspective, with or without the facilities for urine quantification of albumin-to-creatinine ratio, the simpler alternative tool of **standard urine dipstick testing** is currently considered acceptable, with urine quantification of albumin-to-creatinine ratio reserved for the population with diabetes mellitus. Regardless of the method used, a repeat test should be performed to confirm the presence of proteinuria.

Another strategy proposed by the National Kidney Foundation (NKF)[1] and Kidney Disease Improving Global Outcomes (KDIGO)[3] is that individuals be screened for CKD using a **spot urine sample for protein and an estimate of glomerular filtration rate based on serum creatinine concentration**. Although coefficients have been applied for different ethnic groups, the most accepted equations among

Asian countries are being debated. It is beyond the scope of our guidelines to discuss the standardized equations in Asia. This controversy per se should not be an obstacle to the use of serum creatinine for screening purposes. Over 66% of our group members are in favour of using serum creatinine or an estimation equation for screening and the consensus from the group is to use a locally agreed formula until one unified Asia formula can be validated.

In Asia, IgA nephropathy is the commonest primary glomerulonephritis. Microscopic hematuria is one common presentation of the disease.[33] It is recommended in Asia that **dipstick testing for red blood cells (RBC)** should be used as a screening tool. A positive result should be confirmed by microscopic examination of the urinary sediment. About 64% of the group agrees to this.

Frequency of screening

Since there is a continuing risk of acquiring CKD with increasing age and the development of hypertension, diabetes and obesity, there seems little reason to doubt that screening should be a continuing process rather than a 'once and for all' strategy. There are, nevertheless, few data on frequency of screening CKD. Accordingly, the proposed time interval of screening is largely based on expert opinion and cost-effectiveness analysis from simulated models.

To address the issue of optimal screening frequency, in principle, the considerations include both the clinical benefits patients may derive and the added cost. For example, lower frequency of screening, such as every 10 years, has been shown to yield better cost-effectiveness ratios for 50-year-old persons with neither hypertension nor diabetes.[13] It needs to be emphasized that improved cost-effectiveness thus calculated might be associated with decreased quality-adjusted life-years gained as a result of fewer persons benefiting from prevention of CKD progression and death by angiotensin system blockade therapy.

The marginal cost-effectiveness ratio for different screening frequencies is sensitive to factors such as underlying risk (diabetic versus non-diabetic population) and the effects of currently available treatments. According to guidelines from the United Kingdom,[4] kidney function should be screened at least annually in the targeted groups with a high risk of silent development of CKD, including hypertension, diabetes mellitus and atherosclerotic coronary, cerebral or peripheral vascular disease. The Kidney Disease Improving Global Outcomes (KDIGO) resolved that frequency of testing should be according to the target group to be tested.[3] In the absence of specific recommendations, it was stated that testing needs not be more frequent than once per year. Before optimal timing intervals for screening and surveillance are clearly identified by further studies, we concur with the KDIGO recommendations of annual screening. **Screening frequency for targeted individuals should be yearly if no abnormality is detected on initial evaluation.**

SPECIAL ISSUES IN SCREENING FOR CHRONIC KIDNEY DISEASE IN ASIA

Who should perform the screening

A key ingredient of any screening programme is the availability of personnel at a reasonable cost. Opportunistic screening in general practice, when the individuals are seeing their general practitioner at least once a year, has been proposed in countries like Australia.[34] We are not certain if this model can be applied to other impoverished rural areas in Asia, where the access to doctors, nurses and allied health professionals is markedly limited. For example, a regular screening programme has been implemented on a shoestring in South India,[35] where trained volunteers conduct domiciliary screening, instead of asking the local people to travel 10 to 15 kilometres to reach the primary health centre (and losing a day's wage each time they go). Similarly trained volunteers along with medical students, nurses and doctors screened people in Eastern Nepal through a door-to-door approach.[25] We recommend that the **screening as organized and directed by nephrologists can be performed by doctors, nurses, paramedical staff and other trained healthcare professionals.**

Intervention after screening

Success of a screening programme depends on the ability to recognize the disease in its early phase so that intervention can occur. In other words, a logical strategy is required to ensure appropriate implementation of subsequent intervention. Cost-effectiveness would be reduced if the screened people (including those from Asian regions with social disadvantage) are unlikely or unable to take prescribed medication. In many patients, medication use is restricted by financial issues; accordingly, the need to have lifestyle modification should be emphasized in all patients. It is our opinion that patient education (in particular, for areas with low levels of literacy) about low salt intake and smoking cessation (notably in China, India and countries with high consumption of cigarettes) should be an important component of the intervention.

On the other hand, analysis based on proprietary drug costs in the market previously[13] may underestimate the cost-effectiveness of screening because many angiotensin-converting enzyme inhibitors are now off patent and presumably can be obtained at a substantially cheaper price. **We recommend that patients detected to have CKD should be referred to primary care physicians with experience in management of kidney disease for follow up. A management protocol should be provided to the primary care physicians. The need for referral to nephrologists for further management will be based on the protocol together with clinical judgment of the primary care physicians with their assessment of the severity of CKD and the likelihood of progression.**

Validity of cost-effectiveness analysis derived from other ethnic groups

Furthermore, the cost-effectiveness analysis of screening CKD cannot be extrapolated from other racial groups when the prevalence and/or severity of the disease vary among the groups.

For example, in the United Kingdom Asian Diabetes Study,[36] researchers showed that among diabetes mellitus type 2 patients with normal, untreated blood pressure, the proportion who had microalbuminuria was three times higher among South Asian patients than among white Europeans. Most data from observational studies as well as clinical trials show that Asian patients with diabetes are more likely to develop end-stage renal disease than their white counterparts. Disparities or excess risk of end-stage renal disease among Asians, with non-diabetic kidney disease included, have also been suggested from registry-level data. For example, the United States Renal Data System (USRDS) showed that US Asians have a higher age-adjusted and gender-adjusted risk of end-stage renal disease than do US whites. To further adjust for the presence of baseline kidney disease, a study compared the incidence of end-stage renal disease in a prospective multiethnic cohort of 299 168 adults who underwent a screening health checkup in northern California between 1964 and 1985. The age-adjusted rate of end-stage renal disease for Asians was more than twofold higher than for whites.[37] If there is indeed a faster rate of glomerular filtration rate decline among Asians, the value of screening for CKD may differ from that of other ethnic groups. Presumably these factors would affect the cost-effectiveness of screening CKD in Asia.

Considerations for screening for CVD risk

Cardiovascular disease commonly occurs in CKD patients.[38–40] 81% of the group agree to consider CVD risk in CKD patients. Increased incidence of central obesity, metabolic syndrome and CVD risk has been shown in certain Asian ethnic groups, most notably South Asians. It is not cost effective to screen for CVD risk in the general population. **It is recommended that cardiovascular disease risk factors should be screened and followed in all patients with CKD.** These include documentation of smoking history, measurement of blood pressure, body weight, body mass index, abdominal obesity, fasting plasma glucose, fasting lipid profile, serum uric acid level, and 12-lead electrocardiogram (ECG).[14]

CONCLUSION

In conclusion, the current guidelines are based on the mounting evidence that a population-based screening programme is beneficial if implemented in certain high-risk groups. The success of this strategy would depend on the socioeconomic status of the region, and most important of all, the premise that therapeutic interventions can be provided or afforded after detection of the CKD at early stages. We also emphasize that the choice of screening programme for many Asian countries will depend on available health resources and competing health care priorities. Before final recommendations can be made, judgment of the effectiveness of early detection of CKD among adults, including from Asia, has to wait for randomized controlled trials. Each country should study the feasibility of applying the guidelines in their own setting, document the obstacles encountered and evaluate the cost effectiveness of applying these guidelines.

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APPENDIX

The following participants also hold an official capacity:
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Meet the Expert I

慢性腎臓病（CKD）の原疾患および進展因子としての生活習慣病の重要性

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慢性腎臓病は、尿所見異常と血清クレアチニンを基に計算した推算 GFR により診断され、腎機能障害の程度によりステージ分類される。明確な定義の元に誰にでも診断可能な分類である。このような慢性腎臓病の原因としては、日本人の生活習慣の変化、人口の高齢化とともに、糖尿病、高血圧、動脈硬化といったメタボリックシンドロームを含めたいわゆる生活習慣病の重要性が増している。我が国には 29 万人を超える末期慢性腎不全で維持透析施行中の患者が存在し、毎年約 4 万人の新規に維持透析を導入する患者が発生している。その新規透析導入患者の原疾患としては最も多いのが糖尿病性腎症、次いで慢性糸球体腎炎、第 3 位が腎硬化症、第 4 位が嚢胞腎、第 5 位が急速進行性腎炎で、この順位は過去数年間不変である。糖尿病性腎症ならびに腎硬化症による透析導入患者は年々着実に増加しており、慢性腎不全対策としても生活習慣病対策、メタボリックシンドローム対策の重要性の根拠となっている。このような CKD 患者の腎機能悪化のリスクファクターとしては、加齢、蛋白尿、血尿、高血圧、耐糖能障害、脂質代謝異常、喫煙など様々な要因が存在することが明らかとなった。中でもアルブミン尿ならびにタンパク尿の程度が、腎機能予後、心臓血管病発症リスクとして、最も重要である。従って生活習慣病にかかわる諸因子は CKD 発症のリスクファクターであるだけでなく、CKD 発症後の腎機能悪化にも深く関わることが知られており、適切な CKD 対策のためには、的確な生活習慣病対策の実践が重要であることが明らかである。

本講演では、CKD の様々なリスクファクターを重視した適切な CKD 対策について、生活習慣病関連の因子を中心に概説する。

6-S-5-5　慢性腎臓病診療の実際：医療連携システム構築を中心に

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慢性腎臓病（CKD）・末期腎不全患者数の増加、その原因疾患も生活習慣病関連疾患によるものが増加した。またRAS抑制薬、脂質異常症改善薬などが腎障害進行抑制に有効であることが証明された。さらに腎疾患の診療に生活食事指導等の非薬物療法が改めて重視されている。従って腎疾患重症化予防にはかかりつけ医、非腎臓専門医に通院中の糖尿病・高血圧、動脈硬化症患者の中から、進行性に腎機能の悪化を来す患者群を早期に発見、着実な治療へと持って行く診療体制の確立が必要である。さらに着実な生活／食事指導を行うためにコメディカルとの連携を含めた体制整備が必要で、CKD重症化予防のための戦略研究においても、かかりつけ医の場に管理栄養士の派遣を行うための栄養ケアステーションの体制整備が行われた。一方生活習慣病に効果的な行動変容を招来させる介入法には、更なる改善の余地が残されている。

第54回日本腎臓学会学術総会

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座長所属:	東京慈恵会医科大学腎臓・高血圧内科、福島県立医科大学腎臓高血圧・糖尿病内分泌代謝内科

腎疾患重症化予防のための戦略研究(FROM-J)

山縣 邦弘[1]

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腎疾患重症化予防のための戦略研究(FROM-J)は介入3年目を迎えた。戦略研究とは、頻度の高い慢性疾患・健康障害に対し、国民の健康を守る政策に関連するエビデンスを生み出すために、公的資金により実施される大型の臨床介入研究である。この中でFROM-Jの試験デザインは医師会単位でのクラスターランダム化による比較研究である。全国15都県の49医師会において、559名のかかりつけ医、527名の腎臓専門医、315名の管理栄養士が参加し、2417名の患者が登録された。登録患者の年齢は70－74歳、65－69歳、60－64歳の順に多く、男性72%、女性28%と男性が多く、CKDステージ3が46%と最も多く、次いでステージ2、ステージ1の順であった。クラスターごとに、CKD診療ガイドに則った診療を行う介入A群と、介入A群の診療に加えて患者への受診促進支援、生活・食事指導、かかりつけ医へ診療目標達成のフィードバックを行う介入B群の2群に割り付けが行われ、現在各群の介入が行われている。FROM-Jでは、かかりつけ医・非腎臓専門医、腎臓専門医、コメディカルをも含めた医療連携を実践してCKD診療ガイドの遵守率、CKD診療目標の達成度を上げることで、エビデンス－実践ギャップを解消し、末期腎不全への進行抑制、心臓血管病発症抑制をはかる医療の実現が求められている。 FROM-Jでは診療行動に影響を及ぼす可能性があるためこれまで中間解析は行われていないが、今年度は最終年度として研究結果の解析を行うとともに、このコホートの今後のフォローアップ体制についても検討する予定である。そしてFROM-Jの検討結果、効果の解析から、からCKD診療にとっての最適な方法を見いだし、現在の49地区医師会から、拡大、全国均てんか可能なCKDの診療体制を見いだすことが使命である。

学術講演会

慢性腎臓病（CKD）の重症化予防法について

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はじめに

慢性腎臓病（CKD：chronic kidney disease）の概念は、腎臓専門医のためというよりは、広くかかりつけ医/非腎臓専門医やコメディカル（看護師、栄養士、薬剤師、保健師など）が患者とともに腎疾患に対する理解を深めてもらい、確実な管理加療に結びつくようにという概念のもとに作成されたものである。軽度の腎障害の患者から透析や移植に至るまでの患者をすべてCKDという概念で包括的にとらえ、腎障害の進行に応じて切れ目なく、明確な目標をもって適切な治療や予防ができるように工夫されていることから、これまでに比較してより総合的なCKD対策のシステム構築、社会や市民、行政などへのアピールが可能になった。このような背景には、年々増加し続ける慢性腎不全患者、特に透析療法を要する末期慢性腎不全患者の世界的な増加があり、社会的にも、経済的にも大きな問題となりつつあるにもかかわらず、高血圧、糖尿病、生活習慣病といった一般に知られる疾患に比べ、腎臓疾患の注目度、認知度が極めて低いことが背景にある。

我が国の腎疾患の状況

日本透析学会による統計では、日本全国での透析患者数は2010年度にて29万人を超え、増加の一途を辿っている（図１）[1]。さらに2009年までに我が国では国内で23626人に腎移植が実施され[2]、１万人程度が生着腎を持っていると想定されている。2010年１年間の新規透析導入患者数は37532人で過去２年間、前年より減少を認めている（図２）。新規透析導入患者数を男女別にみると女性は2000年以降12000人代で横ばいを続け、2009年、2010年で減少した。男性は2008年以降、増加スピードを落としたものの増加基調に変化は無い。すなわち、2009年、2010年と透析導入患者の減少があったのは、女性透析導入患者の減少のためである。透析導入患者の年齢分布では、女性のピークは75歳～80歳にあり、男性では70歳～75歳にある。透析導入時年齢の平均は男性66.9歳に対し、女性69.5歳と2.6歳の差がある。女性透析導入患者数の減少は、透析導入時年齢80歳以上の患者の比率の上昇、すなわち透析導入時年齢の高齢化のためと考えられる。透析導入患者の原疾患では糖尿病性腎症が43.5%で、次いで慢性糸球体腎炎の21.2%、腎硬化症11.6%が続く。この上位３疾患は順位の変動はあるものの過去25年以上不変である（図２）。特に糖尿病性腎症による透析導入患者は一貫して増加を続けていたが、昨年より本年は1%減少した。我が国では糖尿病人口の増加は継続しており、糖尿病性腎症による透析導入が今後減少を続けるのか否か、注目すべき問題である。また慢性糸球体腎炎は減少を続けているものの、腎硬化症は本年も増加した。このような中で、透析導入原疾患を不明とする患者の比率は10.7%と高頻度になっている（図２）。

ただし、ここ数年透析導入患者の増加が止まったのは、先進国全体の共通と傾向の意見もある[3]。しかしながら、世界的には、人口の増加、高齢化、経済の発展により、特に発展途上国を中心に透析患者の増加は今後も持続すると考えられている[3]。早くもCKDキャンペーンの効果があがり、新規透析導入の減少に繋がっているのが理想的であるが、その判断を下すにはもう少し時間が必要であろう。

また、透析患者予備軍であるCKD患者は、我が国において約1300万人にも及ぶことが推定されている（表１）[4]。これは20歳以上の国民の７人に一人がCKDであることを意味する。CKDに至る原疾患については、日本透析医学会による透析導入患者の原疾患が唯一の全国調査である[5]。その調査によると、我が国のCKDに至る原疾患は欧米諸国とも共通であり、糖尿病の結果発症する糖尿病性腎症、一次性の腎糸球体障害である慢性糸球体腎炎、高血圧ならびに動脈硬化に起因とする腎硬化症が共通の３大原疾患である[6]。一方、1300万人におよぶCKD患者の原疾患については不明と言わざるを得ない。我々腎臓専門医療機関での原疾患の調査では、原疾患の75%以上が糸球体腎炎を占めていた（図３）[7]。しかし、健診で発見されるCKD患者の詳細をみると、その大半は加齢、高血圧、糖尿病、脂質異常症などの長期間の罹患に伴う動脈硬化、生活習慣病を背景に、腎機能の緩除な悪化を示す患者が主体と考えられえる[8]。これらの患者の大半は、自覚症状は皆無と考えられ、血清クレアチニンによる腎機能の評価により、初めてCKDの診断が可能である。このような尿所見に乏しい、腎機能低下症例の原疾患としては、表２に各疾患があげられる。

腎疾患の理想的な治療は原疾患の治癒であり、治癒した疾患ではそれ以上の腎機能低下等の危険性は格段に下がる。CKD患者の診療の第一歩はCKDに至った原疾患の診断である。原疾患の的確なコントロールを実施し、腎機能障害の進展に歯止めをかけることが最も重要である。次いで共通の悪化因子（common pathway）に対する治療である。

図１　我が国の維持透析患者数

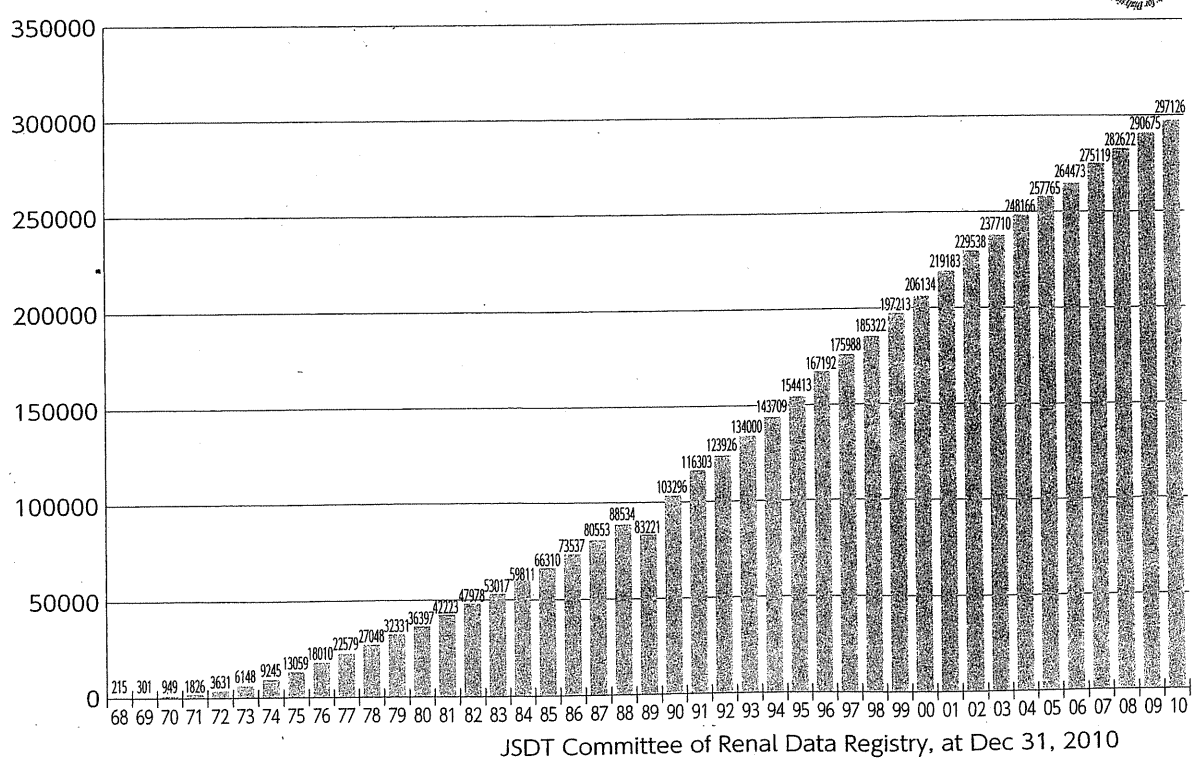
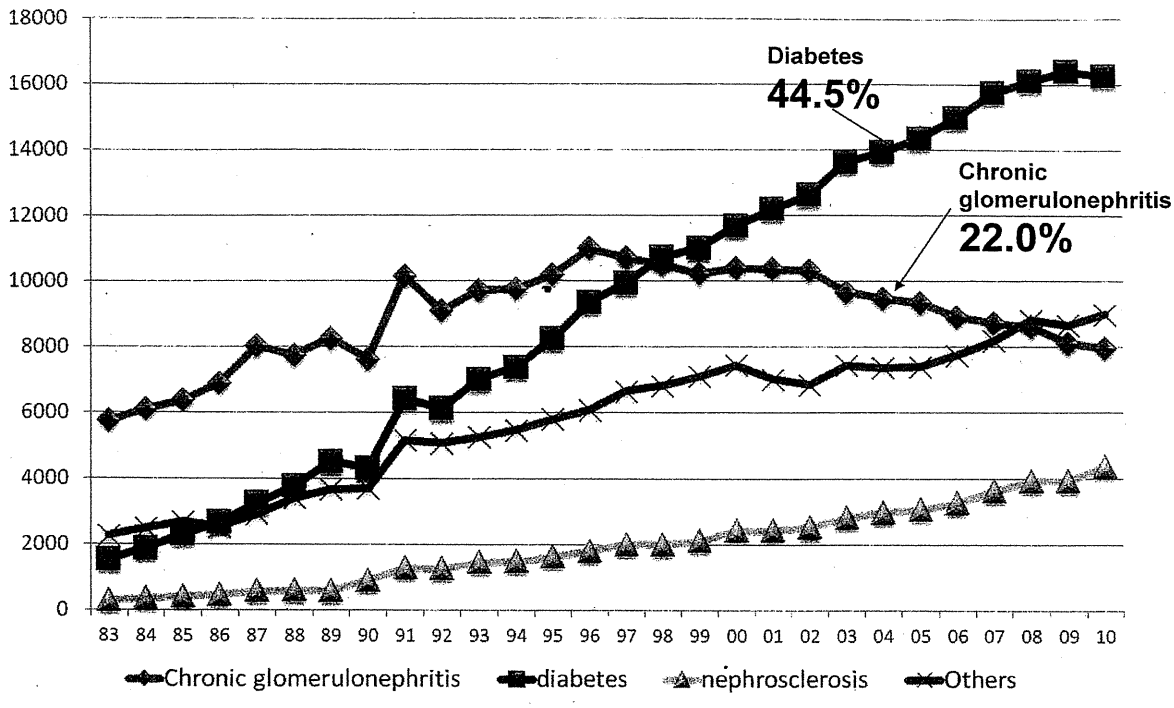


図2　新規透析導入患者原疾患の年次推移

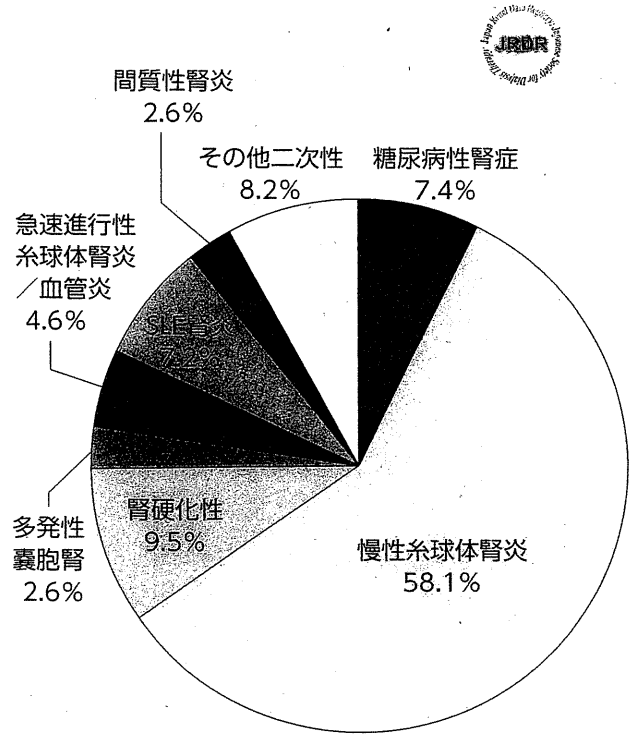


JSDT Committee of Renal Data Registry, at Dec 31, 2010

表1　我が国の推計CKD患者数

CKD stage	
1	60.5 万人
2	170.9 万人
3	1034.3 万人
4	19.1 万人
5	4.6 万人 (透析患者をのぞく)
Total	1289.4 万人

図3　筑波大学附属病院腎臓内科外来通院CKD患者の腎原疾患



筑波大学附属病院腎臓内科受診患者
Tajima R et al. Clin Exp Nephrol, 2010

表2　尿所見の乏しいCKDの原疾患

先天性・奇形	腎の発生異常
	先天性代謝障害
腎血流の異常（糸球体前の血行障害）	慢性心不全
	両側腎動脈狭窄
	腎梗塞後
	高血圧性腎症・腎硬化症
	加齢による腎障害（虚血性腎症）
間質性腎障害（糸球体以後の腎実質障害）	加齢による腎障害
	慢性間質性腎炎
	薬剤性腎障害の一部（鎮痛剤性腎症、シクロスポリン腎症）
	寛解後の慢性糸球体腎炎
	急性腎不全後
閉塞性尿路疾患	両側水腎症
	尿路結石
	尿道狭窄
	神経因性膀胱
	前立腺肥大

CKDのリスクファクターとしての糖尿病・生活習慣病

茨城県の健診受診者における10年間のCKD発症者（eGFR<60ml/min/1.73m²となる患者）の発症リスクを解析したところ、リスクファクターとして、年齢、血尿2＋以上、蛋白尿2＋以上、蛋白尿と血尿がともに1＋以上、高血圧、長期の糖尿病罹患、脂質代謝異常、喫煙など様々な要因が存在することが明らかとなった[9]。なかでも蛋白尿の存在は腎機能悪化因子として強い相関関係がみとめられ、蛋白尿を減少させるあるいは陰性化させることがCKD進展抑制を行っていくうえできわめて重要と考えられる。また、メタボリックシンドロームを含めたいわゆる生活習慣病にかかわる諸因子もCKDリスクファクターとしての重要性は明らかであり、したがってこれらのリスク因子を可能な限り是正し、CKDの発症を予防することが重要である。我が国の透析導入原疾患の一位を占める糖尿病性腎症は、多くの先進諸国においても透析導入原疾患の首位をしめている。これまでの検討からは、厳格な血圧コントロールとレニン・アンジオテンシン（RA）系阻害薬の使用、厳格な血糖コントロール、生活指導などを併せて行うことにより、糖尿病性腎症による透析導入をある程度減少させることが可能である。しかし、実際の診療においては平成14年の厚生労働省の糖尿病実態調査によると、治療を受けている糖尿病においてHbA1c<6.5%となっているのは約30%にすぎず、介入による効果が十分に期待出来るようになるまでは相当の時間を要することが予想される。また腎硬化症、高血圧患者については、茨城県の40歳以上の住民での検討において、高血圧を認めたのが、男性50.2%、女性38.3%であったが、そのうちの男性41.9%、女性49.2%のみが降圧治療をうけているに過ぎず[9]、さらに治療を受けている患者の50%程度は血圧コントロール不良[10]とされる。わが国の蛋白尿を伴うCKD患者の降圧薬処方

においてもRA系阻害薬の使用は以前に比べて増加したとはいえ、いまだ十分とは言えず[11]、これらの点も今後介入により多くの効果が期待できると考えられる。

健診機関との診療連携

健診などをきっかけとして、かかりつけ医/非腎臓専門医への受診を勧奨されたCKD患者あるいは、すでにかかりつけ医/非腎臓専門医を含めた医療機関において管理加療されているCKD患者の腎機能の悪化・進展予防・治療が確実に行うには、CKD診療ガイドに則り、診療にあたる事が求められる。具体的にはかかりつけ医/非腎臓専門医が検査すべき項目、検査結果から腎臓専門医に紹介すべき基準、腎臓専門医に紹介する基準に該当しないCKD患者に対する生活習慣改善や血圧・血糖・脂質などの管理について表３に示す[12]、各診療目標を目指すことである。このような中で、地域医師会、関連学会等、地域におけるCKD対策の推進に関係する機関が中心となり、かかりつけ医/非腎臓専門医・コメディカルや一般住民に対するCKD診療に関する研修会、講演会等の機会を提供することによる積極的な啓発活動を行い、CKD患者の着実な把握と確かな診療を確実に進めることが必要である。かかりつけ医/非腎臓専門医とコメディカルなどとの共同でCKDに対処することにより、更に効果的な生活指導を進めることが可能である。

表３　CKDステージごとの診療目標

ステージ	生活習慣改善	食事指導	血圧管理	血糖管理	脂質管理	貧血管理
ステージ１	禁　煙 BMI<25	高血圧があれば 減塩６g/日未満	130/80mmHg未満	HbA1c6.5%未満	LDL-cho 120mg/dl未満	腎性貧血以外の 原因検索
ステージ２	禁　煙 BMI<25	高血圧があれば 減塩６g/日未満	130/80mmHg未満	HbA1c6.5%未満	LDL-cho 120mg/dl未満	腎性貧血以外の 原因検索
ステージ３	禁　煙 BMI<25	減塩6g/日未満 たんぱく質制限 0.6～0.8g/kg体重/日	130/80mmHg未満	HbA1c6.5%未満	LDL-cho 120mg/dl未満	Hb10g/dl以上 12g/dl未満
ステージ４	禁　煙 BMI<25	減塩６g/日未満 たんぱく質制限 0.6～0.8g/kg体重/日 高K血症あればK制限	130/80mmHg未満	HbA1c6.5%未満	LDL-cho 120mg/dl未満	Hb10g/dl以上 12g/dl未満
ステージ５	禁　煙 BMI<25	減塩６g/日未満 たんぱく質制限 0.6～0.8g/kg体重/日 高K血症あればK制限	130/80mmHg未満	HbA1c6.5%未満	LDL-cho 120mg/dl未満	Hb10g/dl以上 12g/dl未満
備　考			蛋白尿１g/gCr以上 125/75mmHg未満			

（文献9）より引用改編）

CKD診療ガイドに示された診療目標は主として諸外国のエビデンスをもとに各項目の診療目標が立てられた。これらの診療目標の確実な実施がCKD各ステージの進行抑制を可能にするかどうか、われわれ日本人のエビデンスを得る必要がある。

かかりつけ医/非腎臓専門医と腎臓専門医の連携

さらにCKD診療ガイドにはかかりつけ医/非腎臓専門医から腎臓専門医への紹介タイミングが明記されている。

1）0.5g/gクレアチニン以上または2+以上の蛋白尿

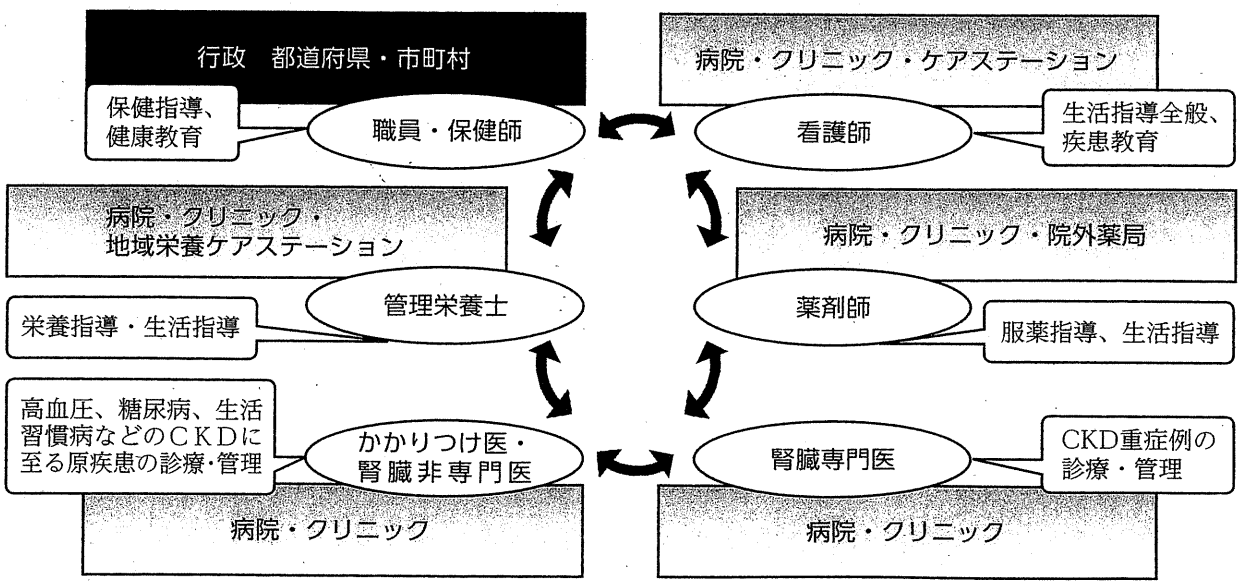
2）推算GFR50ml/min/1.73m^{2}未満

3）蛋白尿と血尿がともに陽性(1+以上)

この他にも急激な腎機能低下が出現した場合や血糖・血圧のコントロールが不良な場合など、かかりつけ医/非腎臓専門医が専門医への紹介が妥当であると判断した場合は当該患者を腎臓専門医へ紹介すべきであると考えられる。また、腎臓専門医は、腎生検を含めた精査にて今後の治療方針を決定し、かかりつけ医/非腎臓専門医と連携しながらCKDの診療を行うことも明記されている。すなわち、現場のかかりつけ医/非腎臓専門医、腎臓専門医が何を求めているかなどの個々のニーズに見合う形を各地域で具体的に検討し、お互いの信頼関係を構築していくことが最も重要であると考えられる。従来の診療ではかかりつけ医/非腎臓専門医は腎臓専門医への紹介は敷居が高く紹介を行いにくいであるとか、逆に腎臓専門医もかかりつけ医/非腎臓専門医から一度紹介された患者をかかりつけ医/非腎臓専門医に逆紹介することは行わないなどのいわゆる<一方通行>のような診療体系があったことも否めない。これらを是正し、紹介基準に該当する患者はなるべくかかりつけ医/非腎臓専門医と腎臓専門医で併診していくことがCKD診療における理想的な診療体制であると考えられる。

CKD地域連携クリティカルパス（図4）

図4　多職種の医療連携による生活習慣病を主とするCKDの重症化予防連携体制



CKD地域ネットワークの構築には、かかりつけ医/非腎臓専門医、腎臓専門医のいる病院・医療機関、地域のコメディカルとの協議の上で、地域連携クリティカルパス（地域の複数の医療機関における治療計画）を策定し、活用することがより効率よくCKD診療をすすめていくことが可能となりうるとされている。地域連携クリティカルパスは、疾患毎の連携・地域ネットワークの構築を基に、連携医療の標準化・適正化を図るための有用なツールである[13]。

クリティカルパスは、診療水準の向上や先進地域における優れた医療連携体制等の取り組みを反映して、随時改訂を図ることが望ましいとされている。患者の理解、病院スタッフの教育、かかりつけ医/非腎臓専門医との信頼関係の構築など、クリティカルパスを進めていくうえで行うべき課題は多くあり、まだまだ模索段階ではあるが、実現することによるメリットは計り知れないと考えられる。

おわりに

CKD対策を進めていく上でCKD患者の生活習慣を含めた病気に対する認識を深めることはもちろんであるが、かかりつけ医、腎臓専門医、コメディカル（管理栄養士、看護師、薬剤師、保健師）、行政が連携をより深めていくことが重要である。さらに、来年にはCKDの定義の若干の修正が予定されている。これまでの機械的な診断基準から、各国の疫学調査や臨床研究の結果を基にして、腎予後、生命予後、合併症発症を考慮し原疾患、腎機能ステージ、アルブミン尿（タンパク尿）ごとのステージに細分化される(14)。詳細は来年度に発刊予定のCKD診療ガイド2012にゆずる。いずれにしろ、今後の高齢者社会の進展に伴う医療費抑制、そして何より、高齢者となってもQOLの高い生活を送るために、CKD診療ガイドに則った治療を推進することにより新たな透析導入患者や心血管疾患の発症抑制がさらに進展することが期待される。

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