First International Summit on Kidney Disease Prevention, 25–27 July 2002: Consensus Document

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This Summit on the Prevention of Kidney and Related Diseases was held at the NKF Singapore to identify approaches to preventing the global epidemic of end-stage renal disease. During the meeting, a list of discussion points was generated and areas for focused future research were identified. Through a series of presentations and discussions during the summit, specific recommendations for the prevention of chronic kidney disease were generated and categorized as: (1) Interventions or Clinical Action Plans that merit immediate implementation; (2) Randomized Clinical Trials that should be prioritized; and (3) Observational Studies that deserve consideration.

I. Priority Areas That Require Further Discussion

A. Population-based surveys, prospective observational studies, and clinical trials related to chronic kidney disease should use common terminology and methods to characterize their populations.
1. The global burden of chronic kidney disease is unclear and likely underestimated in part because of inconsistent research methods.
2. To better define the prevalence of chronic kidney disease, the following are needed:
   a. A standard nosology for defining chronic kidney disease.
   b. The linking of population-based survey information to end-stage renal disease registries.

B. Clinical studies are needed to further demonstrate that proteinuria or albuminuria are both risk factors for chronic kidney disease and therapeutic targets for prevention.
1. The distribution of proteinuria in different populations needs to be determined.
2. Albuminuria should be validated as a marker of clinical outcome, as well as a measure of therapeutic benefit in different populations.
3. In this regard, secondary analysis of existing randomized trials, which primarily targeted BP reduction rather than proteinuria reduction, should be considered.

C. There continues to be a need to evaluate various clinical and demographic characteristics as well as risk factors or risk markers for the occurrence and progression of chronic kidney disease. Some markers for consideration include:
1. Urinary C5b-9 membrane attack complex (index of complement activation).
2. TGF-β1, interleukins, and other markers of inflammation.
3. Markers of oxidative stress (e.g., reactive oxygen species) and nitric oxide status (e.g., nitric oxide concentration, nitric oxide synthase activity).
4. Homocysteine, lipoprotein (a), apoprotein (a), and other markers of dyslipidemia.
5. Obesity or body mass index.
7. Family history of renal disease.
8. Cystatin C.

D. To identify individuals with chronic kidney disease at the earliest possible stage, there is a need to develop prediction equations for the occurrence and progression of chronic kidney disease.
1. There is a need to develop estimating equations for GFR that have been validated across populations.
2. Methodology for the measurement of serum creatinine and GFR should be universally standardized.

E. Both population-based primary prevention strategies and high-risk individualized intervention initiatives need to be implemented to reduce the burden of chronic kidney disease on a population-wide scale.
1. Prevention strategies need to incorporate not only renal disease prevention but general chronic disease prevention (obesity, cardiovascular disease, diabetes, and hypertension), as these conditions and diseases are themselves risk factors for chronic kidney disease.
2. In designing strategies to implement population-wide changes in systems of health care, discussions on public health policy, legislation, and health care reimbursement should be included.
3. Novel primary care models for the delivery of primary and secondary prevention programs should be studied and considered for implementation.
4. Primary care physicians should be targeted to increase their awareness of the problem, and to aid in development and implementation of prevention strategies:
   a. Education of the patient population is a potentially effective vehicle to positively influence physician behavior.
   b. Improvement is needed in the dissemination to and implementation by primary care physicians of clinical practice guidelines for the prevention of chronic kidney disease. General approaches to accomplish this task should be identified and implemented.
   c. Global guidelines for chronic kidney disease prevention may need to be developed.
5. Simultaneously, priority should be given to educating the general population and to implementing prevention programs. Such prevention and education programs need to take into account sociocultural factors in their design.
6. Differences in resource availability in various target populations should be taken into account in the design of education and prevention programs. Indeed, there needs to be a specific emphasis on the creation of programs for economically disadvantaged populations and less-developed countries.

F. Consideration should be given to potential ethnic differences, which may occur in response to prevention and intervention strategies.
1. In general, the results of clinical trials may be extrapolated across ethnic groups.
2. Whereas ethnic-specific responses to interventions should be evaluated, standards of care should be implemented regardless of ethnic group.
3. Although policies and clinical standards may be universal, methods for translating these policies into clinical practice need to be population- and culture-specific.
4. In the process of evaluating the generalizability of intervention strategies across populations, variations in the relative risk associated with various risk factors for chronic kidney disease should be measured and taken into consideration in developing prevention programs. In particular, age-, gender-, and ethnic-specific absolute risks for chronic kidney disease should be evaluated.

G. Molecular genetics and epidemiology will serve as the basis upon which prevention interventions will be designed in the future. The following issues related to molecular genetics as applied to prevention should be considered:
1. Genetic markers for risk prediction.
   a. As more information becomes available, genetic markers shown to be associated with increased susceptibility to the development of renal disease, diabetes, or hypertension, should be evaluated in research studies designed to define population-based risk prediction, as well as individual risk prediction.
   b. Although specific screening strategies have not been identified, it is possible that there is a role for genetic screening of populations at high-risk for chronic kidney disease.
   c. In the study and implementation of genetic screening and risk prediction, ethnic differences in susceptibility genes must be taken into consideration. Thus, broader representation of specific ethnic groups should be ensured in large genetic studies.
2. In performing genetic studies, the following should be considered:
   a. In addition to well-established analytic methods such as sib-pair analysis, linkage analysis, linkage disequilibrium mapping, and quantitative trait loci analysis, novel methodologies should be developed and applied.
   b. Environmental effects should be taken into consideration in genetic studies. Novel techniques to evaluate the effect of gene–environment interactions should be utilized.
   c. The existence and degree of population strata (“admixture”) should be taken into account and adjusted for in genetic case-control association studies, using established molecular epidemiologic methodologies that have been specifically developed for this purpose.
3. Numerous clinical studies demonstrate the increased likelihood of renal disease in family members of patients with end-stage renal disease. Before the identification of specific genetic susceptibility genes, the presence of family history of end-stage renal disease should already be incorporated in risk prediction equations, as well as in the development of screening guidelines.
4. Other issues to be considered include:
   a. The need to establish protocols and policies to provide accessibility of population-based materials/tissue to investigators in order to facilitate genetic studies.
   b. The recognition of the need to implement appropriate legal and ethical safeguards to preserve patients’ rights.

H. Economic issues should be considered in the design of prevention and education programs.
1. In addition to determining the incidence and prevalence of chronic disease, its economic burden should be an additional consideration in estimating population disease burden.
2. Studies on the cost-effectiveness of various prevention approaches, including population-based screening as opposed to high-risk intervention strategies, should be performed.
3. The creation of economically favorable reimbursement models for health care systems may be an effective approach to the modification and improvement of chronic kidney disease care delivered by the medical community.

II. Clinical Action Plan
The following are interventions considered to have undergone sufficient evaluation to demonstrate their efficacy in prevention of chronic kidney disease and related diseases, such as diabetes mellitus and hypertension. As such, the following should be implemented urgently:
A. Population-based intervention strategies:
1. Develop effective obesity prevention initiatives that provide specific emphasis on physical activity.
2. Develop population-wide educational programs to promote a healthy lifestyle for the entire population.
3. Initiate a review of health resource allocation and a greater allocation of funds to education and prevention.

B. High risk intervention strategies:
1. Develop a chronic kidney disease surveillance model for national end-stage renal disease registries, including routine collection, screening, analysis, and reporting of patterns and outcomes of care for chronic kidney disease.
2. Implement disease management models for the approach to diabetes, hypertension, and chronic kidney disease.
3. Implement proven primary care models to optimize standards of care for chronic kidney disease and other associated chronic diseases.
4. Promote the screening for chronic kidney disease in family members of patients with end-stage renal disease.
5. Implement physician-focused intervention strategies.
   a. Develop practical tools to assist physicians in meeting guidelines for chronic kidney disease care.
   b. Engage industry to provide resources (marketing, education, and others) to promote the implementation of chronic kidney disease prevention guidelines.
   c. Initiate the systematic reporting of GFR using estimating equations that rely on serum creatinine. Simultaneously, a standardized creatinine measurement with validation in a range of populations should be developed and promoted.

III. Suggestions for Clinical Trials

The discussants identified several clinically relevant research questions that could be addressed in the setting of randomized clinical trials. Prioritization would be useful because it is likely that only a few trials could be conducted.

1. Does aggressive BP reduction to a lower BP goal (<120/75 mmHg), compared with the usual goal, retard kidney disease progression in diabetic patients with or without microalbuminuria?
2. What is the appropriate BP goal in other populations of chronic kidney disease patients with chronic kidney disease unrelated to diabetes or polycystic kidney disease?
3. Is comprehensive team-based care to reduce chronic kidney disease risk factors superior to standard care in retarding the progression of chronic kidney disease?
4. Do the effects of aggressive therapies that reduce proteinuria retard progression of kidney disease independent of their blood-pressure lowering effects?
5. What is the appropriate target for anti-proteinuric therapy using angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB)?
6. In the setting of ACEI, is there added benefit from ARB in delaying chronic kidney disease progression?
7. Are HMG-CoA inhibitors effective in the reduction of proteinuria?
8. Do appetite suppressive drugs have a role in the management of diabetes mellitus?
9. Do ACEI and/or ARB therapy prevent incident diabetes mellitus among individuals with impaired glucose tolerance?

In addition to trials that address the above research questions, there was a consensus that additional research that focuses on developing and evaluating strategies to implement lifestyle changes for obesity, diabetes, or hypertension, particularly in the clinic setting should be conducted.

IV. Suggestions for Observational and Laboratory-Based Studies

1. Validation of the MDRD equation for estimation of creatinine clearance in other ethnic populations.
2. Appropriately designed genetic association study of angiotensin converting enzyme (ACE) gene and angiotensin II (AGII) receptor gene haplotypes with response to ACEI/ARB therapy, to determine if at-risk haplotypes can identify patients who are most likely to benefit from ACEI/ARB therapy.
3. Longitudinal cohort study of diabetic patients with microalbuminuria from different ethnic groups to estimate the true frequency of progression to overt diabetic nephropathy and end-stage renal disease in specific ethnic groups.
4. Screening:
   a. Longitudinal cohort study evaluating the efficacy of screening in the detection and intervention of the development or progression of chronic kidney disease in the general population.
5. Laboratory-based studies:
   a. Study the regulation of glomerular matrix synthesis and degradation.
   b. Study the regulation of growth factors/cytokines in the kidney.
   c. Identify urinary protein expression patterns using proteomic approaches to predict or detect chronic kidney disease progression or regression.
6. Comorbidities in the setting of chronic kidney disease:
   a. Study the progression of cardiovascular risk factors as a function of change in GFR
   b. Study the prevalence and incidence of noncardiovascular conditions, including anemia, metabolic bone disease, depression, and others, as a function of change in GFR.

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