Chronic Kidney Disease Prevention in Singapore

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In consideration of the epidemiologic basis for screening and surveillance, a comprehensive program for chronic kidney disease prevention was initiated in Singapore by the National Kidney Foundation Singapore (NKF Singapore) in 1997. Reasons for developing this include the rising rate of end-stage renal disease in the country, and the projected escalation because of the increase in chronic diseases that lead to end-stage renal disease (ESRD) such as diabetes mellitus and hypertension. Presented are progress and preliminary findings of this program, as well as that of the parallel initiative of Singapore’s Ministry of Health. The NKF Singapore program incorporates primary, secondary and tertiary approaches to the prevention of chronic kidney disease. These include the population-based screening for early chronic kidney disease and chronic diseases that are associated with kidney disease and the implementation of disease management programs that aim to improve the multi-faceted care of patients with chronic diseases that lead to ESRD, including the development of community-based “Prevention Centers.” The screening program identified risk factors for proteinuria, including the Malay race, increasing age, family history of kidney disease, and higher levels of systolic and diastolic BP even within the normal ranges. Longitudinal follow-up of both prevention programs are critical to provide evidence for the efficacy of such screening and intervention programs in improving chronic kidney disease outcomes, while reducing the cost of care.


Rising rates for end-stage renal disease (ESRD) (1,2), the predicted continued increase in the country’s dialysis population because of the aging of its population, and the corresponding increase in the prevalence of chronic disease such as diabetes and hypertension (3,4) led to the development of the National Kidney Foundation of Singapore’s (NKF Singapore) Prevention Program in 1997. The NKF Singapore dialyzes nearly 70% of the country’s ESRD population (5), which puts it on the direct path for the increased need for dialysis care.

In parallel, the Ministry of Health, Singapore also developed its screening program, as well as an initiative that focuses on diabetes prevention and diabetes care (6). This manuscript describes the development and progress of these programs.

Epidemiologic Basis for Screening for Chronic Kidney Disease in Singapore

In the development of a screening program for chronic kidney disease, important disease and system-related factors should be considered (7). First is the need to establish the burden of kidney disease in the population as well as the determination of any benefit gained from early treatment on disease progression (8).

A second consideration in developing a screening system is to define the target population. The strength of a screening tool is not only dependent on its test characteristics, such as its sensitivity and specificity, but on the burden of chronic kidney disease in the screened population (9). Indeed, a screening test’s positive predictive value can be improved by focusing on the population at increased risk, which leads to race and ethnicity as risk factors for chronic kidney disease. The U.S. Renal Data System shows that certain race and ethnic groups have a higher risk of ESRD compared with whites after adjusting for age and gender (10). Potential explanatory factors include true biologic difference in risk and disease progression (11), a higher prevalence of low birth weight in certain racial ethnic groups, for which there is evidence that suggests increased risk for diabetes, hypertension, and chronic kidney disease (12), and socioeconomic factors that may lead to differential access to quality health care (13).

Indeed, racial differences in the prevalence and risk for chronic kidney disease are striking (14), and this has been extensively studied in the black population. Clear differences in various Asian ethnic groups have also been demonstrated in Hong Kong and Singapore (15,16). Based on the U.S. Renal Data System, in the only report which included Singapore, the latter was ranked as having the third highest ESRD incidence rate in the world (17).

Thus, it is evident that certain racial subgroups are at markedly greater risk for chronic kidney disease, which leads to one of the reasons for developing a screening program in a population with an ethnic mix that may predispose to a greater frequency of chronic kidney disease (18). Although such an approach is theoretically beneficial, no published studies demonstrate the clinical benefit gained from taking part in a screening program (8).

In Singapore, several factors influenced the development of a chronic kidney disease screening program (19,20). The rising annual incidence of ESRD in Singapore (1), its profound impact on morbidity and mortality, and the country’s ethnic composition, which may suggest an increased predisposition to kidney
disease such as IgA nephropathy (21), among others, led to the development of the Prevention Program of the NKF Singapore.

**NKF Singapore Prevention Program Overview**

The NKF Singapore Prevention Program presents a unique approach that incorporates a comprehensive multilevel strategy to address chronic kidney disease (19,20). What makes the NKF Singapore program different is that it incorporated a public health approach to preventing ESRD by using primary, secondary, and tertiary prevention initiatives that can intervene at several stages in the progression of kidney disease. These include 1) surveillance of the general population for urinary abnormalities, 2) screening of the general population for clinical conditions that increase the risk of chronic kidney disease, such as diabetes mellitus and hypertension, 3) the institution of a disease management program to facilitate the management of patients with diabetes and hypertension, which are among the leading causes of ESRD in the country, and to a limited extent, 4) tracking of the individuals who participate in the screening program. Thus, both population-based and high-risk prevention strategies were incorporated into the Singapore Prevention Program.

As opposed to other existing CKD screening programs, such as the Kidney Early Evaluation Program of the National Kidney Foundation (United States) that focuses on early detection of kidney disease in patients known to be at increased risk (22), the NKF Singapore Prevention Program, although a “kidney” disease initiative, also focuses on primary prevention by educating the public and by screening for chronic conditions, such as diabetes and hypertension, which are among the leading causes of ESRD in the country. Thus, this program design aimed to intervene before the onset of any evidence of kidney disease. Although the high risk approach to screening is the option supported by other existing programs because of its perceived cost-effectiveness, a population-based approach to prevention is thought to have a larger effect on diseases that are influenced by population behavior characteristics (19,23,24).

This is consistent with recommendations published by several workgroups that released consensus statements on kidney disease prevention (25,26). In the Singapore Summit on Kidney Disease Prevention, experts from various disease fields that relate to kidney disease, including endocrinologists, cardiologists, and molecular epidemiologists, in addition to nephrologists took part in reviewing existing evidence in addressing chronic kidney disease, from the viewpoint of both the primary and secondary prevention of the leading chronic diseases that cause ESRD, including diabetes and hypertension (25). The resulting consensus document on kidney disease prevention divided its recommendations into 3 categories: those interventions backed by sufficient evidence and therefore can be implemented, those areas in which clinical trials are proposed, and those clinical questions that may be addressed by observational studies. The overwhelming majority of recommendations in the document that were thought to be ready for implementation, and thus supported by published evidence, focused on screening of high-risk populations, development of kidney disease and prevention educational programs, and the primary, as well as secondary, prevention of diabetes and hypertension. Indeed, these components are each fully integrated into the NKF Singapore nationwide prevention program.

It is important to note that, in this Singapore consensus document, limitations of published studies in evaluating the role of kidney disease screening for the general population were clearly acknowledged. Indeed, the consensus document strongly recommended the design and implementation of efficacy and cost-effectiveness studies to evaluate the clinical benefits of screening programs in the detection and intervention of chronic kidney disease. This was one of the original goals of the NKF Prevention Program.

**Primary Prevention and Early Disease Detection Program**

Details of the primary prevention and screening programs are described elsewhere (16). Briefly, an important consideration in the design of the screening program was its accessibility to the general population, as well as an increased focus on identifying individuals at high risk for kidney disease and the chronic diseases that lead to it, particularly diabetes mellitus and hypertension. The key goals of the screening program include the education of the general public regarding kidney disease and related chronic diseases, the identification of individuals at increased risk for chronic kidney disease, diabetes, and hypertension; and the epidemiologic study of unique determinants of renal disease and disease progression in this Asian population.

Screening was targeted at four discrete populations: the working population where screening is performed at workplaces, the general adult population where screening is performed at housing estates and on mobile screening buses, the pediatric population through the school health screening program of the government, and the taxi driver population where screening is performed at the taxi offices. Screening involves the completion of a questionnaire that contains demographic questions and medical history, measurement of body mass index (BMI), blood pressure measurement, a dipstick urinalysis, and at some settings, random blood glucose and total cholesterol. Subjects were then given counseling based on the screening results and referred for follow-up to their own physicians.

To date, more than 1 million health screenings have been performed as part of the NKF Singapore health screening program since its initiation in 1997 (unpublished data). Between November 1997 and December 2001, a total of 621,183 Singaporeans had participated in the program (20). In an analysis of 213,873 adult workplace screening participants with a mean age of 36.3 yr and a median age of 34.0 yr, clinically significant proteinuria defined as a dipstick protein of ≥1 was detected in 1.1%, and isolated hematuria defined as dipstick hematuria of ≥1 was detected in 9.06% (16).

A key finding of the Singapore Prevention Program’s screening component is that ethnic differences exist in the frequency of proteinuria with the non-Chinese populations manifesting a significantly increased risk of proteinuria (16). In our analysis, the Malay race was associated with an odds ratio (OR) of
proteinuria of 1.3 ($P < 0.0001$) that persisted even after adjusting for the confounding effects of age, blood pressure, or pre-existing chronic diseases, such as diabetes mellitus or hypertension. This finding is consistent with the observation that the same racial group exhibits the highest incidence of ESRD compared with the Chinese (262 per million population versus 216 per million) (16). Potential explanations that were not adjusted for include socioeconomic status and its attendant consequences.

The screening program also documented the increased risk for proteinuria in Asian populations with increasing age and with a family history of renal disease. Finally, we identified novel risk factors for proteinuria in this multiethnic population in that we noted the presence of proteinuria even at levels of systolic or diastolic blood pressure at the high end of the normal range of values. We observed an OR of 1.4 ($P = 0.001$) for the presence of proteinuria at systolic blood pressure levels between 130 and 139 mmHg, and an OR of 1.5 ($P < 0.0001$) at diastolic blood pressure measurements between 80 and 89 mmHg. In addition, we noted a J-shaped pattern between BMI and proteinuria, with a significantly increased OR for proteinuria at BMI values below 18.00 kg/m² and at BMI values above 25.00 kg/m². Interestingly, for the Chinese racial group, each BMI category above 25 kg/m² was associated with progressively greater OR for proteinuria, whereas for the Malay population, the relationship between BMI and proteinuria was only significant at BMI levels of $\geqslant 30$ kg/m². These findings suggest that the deleterious effects of elevated BMI values on the kidney, which are generally associated with severe obesity could occur at much lower BMI levels in the Chinese population (16).

Data from the screening program were also analyzed to determine the level of control of blood pressure among individuals with known hypertension or diabetes (16). Of the 285,126 individuals screened in the worksite program between January and December 2001, 66% of patients with diagnosed hypertension had poorly controlled systolic blood pressure, diastolic blood pressure, or both. Furthermore, for those patients with known diabetes mellitus, 64% had systolic blood pressure levels $> 130$ mmHg and 43% had diastolic blood pressure $> 80$ mmHg, above the levels recommended for nephropathy prevention in the diabetic population. As such, for these patients with either diabetes mellitus or hypertension, we observed suboptimal blood pressure control, placing the majority of these individuals at increased risk for the development of chronic kidney disease (26). Furthermore, 5.7% and 7.9% of individuals with known hypertension or diabetes, respectively, demonstrated significant dipstick positive macroalbuminuria ($\geqslant 1$) that was previously undetected (27). Finally, in an analysis of individuals 65 yr of age and older, 8.5% were identified to have previously undetected significant proteinuria (28). Altogether, these screening findings support the value of community-based screening program in this population with an apparently high rate of previously undetected disease, or poorly controlled disease.

The program's pediatric school screening initiative, developed by NKF Singapore in collaboration with the Ministry of Health and the National University of Singapore was initiated in 1999 as part of the School Health Screening Program. This targeted the early adolescent age group and was introduced as an additional component of the government's school health screening services. In a pilot study of 2083 children, the overall prevalence of proteinuria (dipstick protein $\geqslant 1$) was 2.0% and the prevalence of age- and gender-calibrated hypertension was 13.0% (29). It is important to note, however, that the normograms that were used to define hypertension were based on the U.S. population (29). An important finding in the pediatric program was the increased likelihood of significant proteinuria among children with low body weight that was not explained by other potential risk factors such as the presence of an elevated blood pressure. The analysis also identified a trend for an association between low birth weight and proteinuria, consistent with prior studies that suggest low birth weight and therefore low renal mass may be a risk factor for chronic kidney disease (29). A potential explanation for the association detected between low body weight and the presence of significant proteinuria is that the former may be a marker for environmental, clinical, and other socio-demographic factors that can predispose to chronic kidney disease (29). The pediatric program also detected a prevalence of clinically significant isolated hematuria (dipstick hematuria $\geqslant 1$) of 6.8%, arguing for the continued screening for renal disease and proteinuria among pediatric populations with a high background prevalence of kidney disease and other chronic diseases (30–32).

From these findings, we believe that these components of the screening program demonstrate the utility of surveillance and screening, not merely in identifying persons at increased risk for chronic kidney disease, but in determining population-specific risk factors unique to the Asian ethnic groups, as these may potentially be modifiable. Furthermore, that the program detected poorly controlled hypertension or previously undiagnosed diabetic nephropathy demonstrates the value of the NKF Singapore Prevention Program. Longitudinal analyses of these populations should be performed to evaluate whether interventions resulting from abnormalities identified by screening are effective in reducing the burden of chronic kidney disease in this population.

It is important to note that there have been no follow-up publications of the NKF screening program, although the actual screening initiatives are ongoing. For instance, although 167,983 individuals participated in the screening program between January and December 2005, this figure had dropped significantly by the same period in 2006, with 77,986 individuals screened (http://www.nkfs.org/statistics.php). It is apparent that a systematic downsizing of the screening program has occurred since the year 2005, which may be associated with a change in leadership at the NKF Singapore.

Early Intervention and Disease Management Program

A second component of the NKF Singapore Prevention Program for chronic kidney disease incorporates community-based comprehensive clinical services for patients with diabetes and hypertension, which are among the leading causes of ESRD in the country. Thus, the NKF Singapore program developed
such services to provide care to patients with diabetes and hypertension, even in the absence of chronic kidney disease. That a kidney focused organization incorporates initiatives that intervene at such an early stage has not been previously reported. This early intervention program aimed to elevate the standards of care for the management of diabetes and hypertension, to intervene in the progression of these chronic conditions, thereby preventing the development of renal complications. As evidenced by a study of the screening program, 73.7% of the diabetic patients studied had poor glycemic control as defined by a hemoglobin A1c of 7.0% or greater. In addition, 88.2% were found to have an elevated blood pressure, and 47% of the screened diabetics had incipient diabetic nephropathy as defined by the presence of microalbuminuria. These observations supported the design of a secondary prevention strategy, which has 2 main components. The first of these is the implementation of a diabetes disease management system by the use of an established system developed by a partner in this initiative, the International Diabetes Center (33). This program has been shown to significantly improve clinical outcomes in several populations worldwide, including the American Indian Community (33). This disease management system, known as Staged Diabetes Management, was presented to the medical community, and 10% of the total general practitioner population of the country took part in this NKF Singapore-facilitated process of incorporating clinical care algorithms in the day-to-day management of diabetes mellitus (19).

The second major component of the intervention program was the creation of a network of NKF Singapore Prevention Centers, which were designed to provide team-based comprehensive clinical services that would complement the care provided by the medical doctors. These nurse-run clinics aim to provide patient education and specialized screenings for early complications of diabetes and hypertension. Such services have been previously noted to be critical in the management of complex chronic diseases, including diabetes and hypertension (34). These Prevention Centers are currently operating in Singapore. At this point, there have been no published studies on the outcomes resulting from this aspect of the NKF Singapore Prevention Program.

Challenges Faced in the Development and Implementation of the NKF Singapore Nationwide Prevention Program

In the development of this integrated approach to addressing the burden of chronic kidney disease in the population of Singapore, several obstacles were and are continuing to be addressed. First, in dealing with the program’s design, it should be noted that studies demonstrating the effectiveness of population-based screening programs for renal disease are lacking. Indeed, although randomized clinical trials may be a potential methodology to evaluate the effectiveness of a population-based approach, these studies may not be feasible (8). Despite the lack of such data to support population-based screening programs, the NKF Singapore implemented its prevention and screening initiatives because of the high background burden of chronic diseases that lead to ESRD, particularly diabetes mellitus and hypertension.

Because the majority of incident ESRD in Singapore arises from chronic diseases that are managed primarily by general practitioners (4–6), an important component in the program is the formation of a partnership with the medical community. Indeed, this was a major hurdle given the physicians’ initial resistance of referring patients to the nurse-based Prevention Centers. The primary concern of these physicians was losing their patient pool to these Prevention Centers. For this reason, these centers were specifically designed not to have a medical doctor, and a major thrust in the educational meetings was a clarification that the services provided by the nurses served only to complement the medical care that will continue to be led by the physicians.

An obstacle that continues to confront the program is the long-term follow-up of screening participants. There is no doubt that clinical and epidemiologic tracking of the prevention program is critical, as this will provide clear documentation of its effectiveness in modifying patient and cost outcomes, including the delay in the development and progression of chronic kidney disease and reducing the cost of care. However, there has been no clear indication as to the long-term vision of the NKF Singapore Prevention Program. Since the change in the program’s leadership, there has been no published data on follow-up of either the screening program or the disease management and early intervention program (Ms. Suzie Burford, previous NKFS director of nursing training, Head Clinical Research and Education, Fresenius Medical Care - Asia Pacific, personal communication, August 1, 2007).

Ministry of Health, Singapore

Singapore’s government, in parallel with the NKF Singapore, similarly recognized the increasing burden of ESRD and the need to implement strategies that address this rising demand for dialysis (1). It proposed 3 key strategies, including: 1) an increased focus on prevention of ESRD, 2) using peritoneal dialysis as the preferred renal replacement therapy rather than hemodialysis, and 3) promoting renal transplantation. This review will focus on the first component which promotes a prevention strategy.

Similar to the NKF Singapore Prevention Program, the Ministry of Health program incorporated diabetes screening and management by standardizing care that is received by patients at the government-run polyclinics (1). The government also launched its Diabetes Management Program in 2006, which focuses on improving diabetes care and allowing the use of one’s own national medical savings account for outpatient diabetes management (35). Singapore’s government also initiated a national screening program targeted at individuals aged 50 yr and older for hypertension, hypercholesterolemia, and diabetes in 2001 (36). Notably, this program does not routinely screen for proteinuria or any evidence of chronic kidney disease (36). Published studies from this program are not available, although preliminary results have indicated that screening abnormalities are common, with up to 80% identified to have clinically significant abnormalities. Importantly, the Ministry of
Health provided funding to develop “Renal Retardation Clinics” in the country’s 2 large government-run hospitals (1). These clinics focus on the management of patients with established chronic kidney disease (chronic kidney disease stage III-IV). Preliminary findings from the clinic’s 817 patients demonstrate better blood pressure control among hypertensive patients, improved glycemic control for diabetics, and significant reduction in proteinuria (1). Published analyses of data from these clinics would be important to follow.

Singapore’s Ministry of Health has also released clinical guidelines for the screening of renal disease in Singapore (37). Although the guidelines recognize the dearth of studies that evaluate the clinical outcomes of kidney disease screening, it supports the opportunistic screening of healthy asymptomatic individuals by urine dipstick. The guidelines also propose that individuals at risk because of older age and because of the presence of risk factors, such as smoking, diabetes, hypertension, and family history, should undergo annual urine dipstick screening. These recommendations were based on a prevalence of early chronic kidney disease, which is thought to be higher than previously recognized.

Conclusion
Singapore has existing large-scale screening and prevention initiatives with a broad-based goal of early detection, screening, and intervention of chronic kidney disease. These programs pursue a multipronged public health approach to kidney disease prevention, which simultaneously implements primary and prevention strategies, including public education, screening, early intervention, provision of comprehensive clinical services, and the education of the physician community. Equally important to address would be epidemiologic research that tracks clinical and cost outcomes of these programs. Longitudinal monitoring of the program components, such as the screening elements, may eventually provide currently lacking scientific evidence as to the efficacy of such screening programs in reducing the burden of ESRD.

Disclosures
None.

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