Longitudinal Study of the National Kidney Foundation's (NKF) Kidney Early Evaluation Program (KEEP)

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Abstract. In 2000**,** the National Kidney Foundation implemented the Kidney Early Evaluation Program (KEEP 2.0) to increase awareness of kidney disease among those at highest risk, and improve outcomes through early detection and referral for care. The KEEP 2.0 screening program identified significant numbers of persons with reduced kidney function, with previously undetected kidney disease risk factors, and with inadequate risk factor control. These data support the evolution to KEEP 3.0, which will continue to identify individuals at high risk for kidney disease, and will address the educational needs of health care providers and consumers, given that preventing and managing kidney disease requires their joint effort. Consumers need to embrace lifestyle behaviors that reduce risk, and adhere to medical recommendations in managing their existing conditions. At the same time, providers need to ensure that the latest evidence-based guidelines in diagnosis and treatment are being implemented in their clinical practice. KEEP 3.0 participants will be randomly assigned to one of several educational programs that vary on whether they provide individually tailored or nontailored information, with long-term follow-up for evaluation of clinical outcomes. Tailored programs may be more successful in supporting behavioral change as these consider the individuals' "readiness to change." In addition, participant-identified providers will be randomly assigned to one of several educational protocols designed to provide evidence-based recommendations for clinical and pharmaceutical management of kidney disease and risk factors; these programs vary on whether they require active or passive participation of providers. Analytic evaluations will examine changes from baseline in participant kidney disease and risk factor status during follow-up, and estimate the influence of the various educational protocols on both process of care measures and clinical outcomes.

Kidney disease is a common, progressive health problem. In the United States, chronic kidney disease is the ninth leading cause of death (1). ESKD has an annual incidence of greater than 85,000 cases. In 1999, more than 400,000 Americans suffered from kidney failure that required dialysis and/or transplantation as treatment (2). Men are more likely to develop ESKD than women, and although African Americans comprise only 11% of the total US population, they account for more than 30% of all ESKD cases (2). In 1999, Medicare medical expenses were over $11 billion for ESKD care; inpatient and outpatient treatment costs were estimated at $4.4 billion each, and $2.1 billion was spent for physician care and/or supplier services (2).

In the United States, prevalence of reduced kidney function, based on serum creatinine measurements collected as part of a national health statistics study, was estimated at 5.6 million—25 times the number of prevalent ESKD cases (3). Most persons with CKD do not develop kidney failure. However, CKD has been linked to adverse systemic complications including anemia and cardiovascular disease (1,4). The majority of persons with chronic kidney disease die from cardiovascular complications (5–7).

Diabetes is the leading cause of chronic kidney disease and accounts for more than 42% of new cases of ESKD in the United States (2). Uncontrolled, or poorly controlled high BP is the second leading cause of ESKD accounting for 26% of new cases; diabetes and hypertension often coexist (2). There are nearly 16 million Americans with diabetes although one-third of these are unaware they have the disease (8). Diabetes is more common among minority groups (8). Furthermore, noninsulin-dependent diabetes mellitus (NIDDM) is becoming increasingly more prevalent in younger individuals across all racial groups, due to inactivity and obesity.

Diabetes causes microvascular changes in the kidneys resulting in albuminuria. The risk of developing diabetic nephropathy and ESKD increases with duration of diabetes, poor glycemic control, comorbid hypertension, hyperlipidemia, and a family history of diabetic kidney disease (9–11). Diabetic nephropathy can be prevented or delayed by consistently controlling blood glucose levels, following the prescribed diabetic diet and exercise protocols, and managing hypertension (12). At least 65% of diabetic patients have comorbid hypertension,

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and strict control of BP is an important strategy in preventing or managing diabetic nephropathy. In addition, a number of drugs, including angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB), are effective both in reducing BP and in preserving kidney function (13,14).

Hypertension is both a cause and a consequence of kidney disease. Decreased kidney function is a component of the pathogenesis of primary hypertension, and chronic kidney disease is the most common cause of secondary hypertension (15). Hypertension is associated with a more rapid progression of kidney damage regardless of the underlying etiology of kidney disease and its presence predicts increased kidney-related mortality (16,17). Hypertension is thought to induce kidney injury, at least in part, by elevating intraglomerular pressure (18). The resulting reduction in functioning kidney mass, in turn, contributes to higher BP levels by a decrease in the efficiency of elimination of dietary sodium, an increased production of vasopressors, plasma volume expansion, and increased cardiac output (18).

Loss of albumin into the urine is the hallmark of glomerular injury (19). Clinical consequences of albuminuria include hypoalbuminemia, hyperlipidemia, hypertension, hematologic abnormalities, and cardiovascular disorders. Albuminuria may also attenuate BP response to pharmacotherapy (20). Individuals with kidney disease are at risk for cardiovascular disease due to both kidney-related factors (*e.g.*, anemia, hyperparathyroidism, decreased kidney function), as well as traditional cardiovascular risk factors (*e.g.*, smoking, dyslipidemia, hypertension, heart failure). Patients with chronic kidney insufficiency have an increased risk of left ventricular hypertrophy, left ventricular dilatation, congestive heart failure, and ischemic heart disease that occur in advance of the development of ESKD (21).

The National Kidney Foundation's Kidney Early Evaluation Program (KEEP)

Central tenets of the National Kidney Foundation's (NKF) Kidney Disease Outcomes Quality Initiative are that the adverse outcomes of chronic kidney disease can be prevented through early detection and treatment, and that the early stages of kidney disease can be detected through laboratory measurements (22). Because early kidney disease may have few clinical symptoms, screening as a method of detection is necessary. Screening should target persons most at risk for chronic kidney disease, such as those individuals with a personal or family history of diabetes or hypertension, or those who belong to a minority race/ethnic group (23). In addition, screening should be carried out as part of primary health care delivery, or alternatively through community-based screenings or health fairs, to include those less likely to receive regular health care provision.

KEEP 2.0

In 2000**,** the NKF implemented the Kidney Early Evaluation Program (KEEP 2.0). This program was an outgrowth of a pilot study carried out in 1997 and was designed to increase awareness of kidney disease and to improve clinical outcomes, through early detection among high-risk groups. The specific aims of the KEEP 2.0 program included (*1*) identifying persons at increased risk for kidney disease via health screenings, and (*2*) encouraging "at-risk" persons to seek further evaluation with appropriate risk management from a health care provider.

Beginning in August 2000, KEEP 2.0 screening programs were implemented by local NKF affiliates. Eligible participants were men or women, at least 18 yr old, with diabetes or hypertension, or with a family history of diabetes, hypertension, or kidney disease. Some affiliates concentrated recruitment efforts in geographic areas with greater numbers of individuals from minority populations. Screening data were collected on participant sociodemographic characteristics and medical history; medication history data were not obtained. Systolic BP (SBP) and diastolic BP (DBP) were measured; blood and urine specimens were collected. Blood specimens were processed for determination of glucose, creatinine, and hemoglobin, and urine specimens were tested for albuminuria, hematuria, and pyuria. Estimated GFR (EGFR), an indicator of kidney function, was calculated based on published formulas that used measured serum creatinine (24,25). All screening results were made known to participants. Abnormal results were not considered diagnostic, but rather as indicative of increased risk. Participants with abnormal results were advised to contact their health care providers for follow-up evaluation. Subsequently, study personnel contacted the participants to determine if follow-up had occurred.

During the first 17 mo (August 2000 to December 2001) of the ongoing cross-sectional KEEP 2.0 program, 31 NKF affiliates conducted 135 programs in 33 states, and enrolled 6071 eligible participants. Participants were predominantly African American (43%) or Caucasian (36%); 68% were women. Mean participant age was 52 yr (range 18 to 101) and 24% of participants were 65 yr or older.

Twenty-five percent ($n = 1498$) of participants reported known history of diabetes mellitus and an additional 82 participants (2% of those without known diabetes) met the screening definition for diabetes (blood glucose >125 mg/dl if fasting, >200 mg/dl otherwise). Among participants with a history of diabetes, 35% had elevated glucose values at screening (≥ 180 mg/dl), and only 18% were controlled to comorbidity specific BP levels (BP $<130/80$) (26).

Fifty-two percent ($n = 3143$) of participants reported history of hypertension and/or hypertension medication use; an additional 847 participants (29% of those without history of hypertension) met the screening definition for hypertension (SBP >139 or DBP >89). Among participants with hypertension history, 63% were not controlled to normal limits (BP $<140/90$).

Twenty-nine percent ($n = 1778$) of participants tested positive for microalbuminuria and 16% ($n = 898$) had calculated EGFR values (<60 ml/min per 1.73 m^2) that indicated a moderate reduction in kidney function (1,24). Five percent ($n = 311$) had elevated serum creatinine values (>1.5 mg/dl in men, >1.3 mg/dl in women) (3). Only 3% ($n = 156$) of participants reported a history of kidney disease at screening;

1712 participants with microalbuminuria (29% of those without history), 839 participants with reduced EGFR (14% of those without history), and 277 participants with elevated serum creatinine (5% of those without history) were identified as a result of screening. Only 31% of participants with reduced EGFR and 27% of those with elevated serum creatinine were controlled to comorbidity specific BP levels (BP $<$135/80) (1).

The KEEP 2.0 screening program identified significant numbers of persons with reduced kidney function, with previously undetected kidney disease risk factors, and with inadequate risk-factor control. Regular screening for evidence of kidney disease and for conditions that contribute to kidney disease is critical so that appropriate interventions can be implemented. However, preventing and managing kidney disease requires joint efforts on the part of health care providers and consumers. Consumers need to embrace lifestyle behaviors that reduce their risk of disease including weight control, regular exercise, and adherence to medical recommendations regarding management of existing conditions. Health care providers need to ensure that they are implementing the latest evidence-based guidelines in the diagnosis and treatment of kidney disease and associated conditions. Data from KEEP 2.0 indicate that opportunities for improvement exist and support the evolution to KEEP 3.0, which aims to continue the identification of individuals at high-risk for developing kidney disease, while addressing the educational needs of providers and consumers.

KEEP 3.0

KEEP 3.0 will identify individuals at increased risk for kidney disease and enroll them for long-term participation in a study designed to evaluate the effectiveness of educational programs in improving process of care measures and clinical outcomes. Educational programs will be aimed at both participants and their health care providers. Eligible participants are men and women $\geq$18 yr old, with diabetes or hypertension, or with a family history of diabetes, hypertension or kidney disease. At enrollment, participants will provide data on demographic characteristics; medical history including use of medications; and lifestyle characteristics including substance use, physical activity, and medication adherence. Weight and height will be determined for calculation of body mass index (BMI). SBP and DBP will be measured according to a standard protocol. Blood specimens will be collected and processed for determination of blood glucose, creatinine, hemoglobin, lipid profile, and hemoglobin A1C. Urine specimens will be tested for hematuria and pyuria, using dipstick analyses. Microalbuminuria will be measured directly in spot urine samples. Identical data will be collected at annual follow-up visits. Participants will be randomly assigned to one of several educational programs designed to provide information on prevention of kidney disease and maintenance of kidney health; these educational protocols vary on whether they provide individually tailored or nontailored information. Health care providers, identified by participants, will be randomly assigned to various educational protocols designed to deliver evidence-based recommendations for clinical and pharmaceutical management of hypertension and diabetes, and prevention of kidney disease; these interventions differ based on whether they require active or passive participation.

The specific aims of the KEEP 3.0 program are:

- To determine baseline prevalence of kidney disease and risk factors for kidney disease in a high-risk cohort.
- To determine the cross-sectional associations of kidney disease and cardiovascular disease (CVD)-kidney risk factors.
- To determine the rate of change in kidney disease status during follow-up, and identify risk factors that determine this progression.
- To determine the long-term morbidity and mortality of individuals (*e.g.*, CVD, ESKD) with baseline evidence of kidney disease.
- To evaluate different methods for providing information to participants and their providers to optimally influence process of care measures and clinical outcomes.
- The recruitment goal for the KEEP 3.0 program is 6900 participants. Participants will be enrolled at 15 US clinical care sites in two waves during the first 2 yr of the proposed 3-yr study. Recruitment strategies will include print and broadcast advertising, and in conjunction with local NKF affiliates, annual KEEP 2.0 style health fairs will be conducted to identify eligible, interested persons. Once enrolled, participant retention will be encouraged through periodic contact between annual follow-up visits.
- Observations from KEEP 2.0 provided the basis for KEEP 3.0 sample size projections. Sample size estimates were determined to provide ample statistical power to address study objectives regarding change from baseline in kidney function (EGFR) and in process of care measures, including use of ACE inhibitors, stratified by race/ethnicity and medical status (diabetes). The estimate of 6900 participants assumes a 15% participant loss to follow-up during each study year.

Participant Interventions. Because many risk factors of kidney disease are directly attributable to personal lifestyle choices, including diet, physical activity, use of tobacco, and adherence to medical care plan, interventions to prevent or manage kidney disease should involve efforts to modify these lifestyle choices (27,28). An important objective of KEEP 3.0 is to determine the effect of different methods for providing prevention and treatment information to participants. Health education enables consumers to improve their self-care abilities by making more knowledgeable decisions, and assuming greater personal responsibility for their health. To effectively promote healthy behaviors, health concepts and self-care management strategies must be delivered to the lay public in an understandable, accessible, and cost-effective manner. In addition, educational theory, in particular the transtheoretical model of behavior change (29,30), was considered in the design of the educational intervention. This model posits that health behavior change unfolds over a sequence of six stages (precontemplation, contemplation, preparation, action, maintenance, and termination). Movement through the six stages is

influenced by an individual's decisional balance as reflected by personal beliefs and by relative weighing of the pros (benefits) and cons (costs and barriers) of change (31). In addition, tailoring intervention strategies to an individual's readiness to change increases the likelihood of successful behavior change. Educational interventions will examine the benefits of tailored print or tailored telephone counseling, compared with nontailored interventions (brochures with general risk information and health recommendations) on health behaviors and outcomes. Participants randomly assigned to tailored intervention strategies will complete a questionnaire to identify their stage of change, and tailored messages will be developed to achieve recommended health behaviors. Tailored interventions also include semiannual contact with KEEP 3.0 team members.

Provider Interventions. There is significant concern and evidence that patients with chronic diseases such as hypertension and diabetes are inadequately managed, and that the latest scientific evidence is not used in clinical practice (32,33). One way to change clinical practice and improve clinical outcomes is the dissemination of research findings. It is hypothesized that presentation of research findings and practice guidelines as participatory educational interventions will enhance provider education and produce improved clinical outcomes. The provider intervention protocol tests the educational value of passive as opposed to participatory interventions. Educational materials include copies of the NKF executive summary of guidelines, a guidelines wall chart, a pocket tool that provides clinically relevant information, an interactive CD-ROM with guidelines and case studies based on guidelines, and a KEEP 3.0 website with the latest evidence-based recommendations. Providers will be randomly assigned to the passive, active, or baseline comparison group at the time their first patient is enrolled. Providers assigned to the baseline comparison group will receive the NKF executive summary and the wall chart; those in the passive group will receive the baseline materials, plus the pocket tool and the interactive CD-ROM; those in the active group will receive baseline materials, plus access to the KEEP 3.0 website.

Longitudinal cohort studies, such as the proposed KEEP 3.0 program, are designed to investigate changes in participant characteristics over time by measuring these on each study participant repeatedly at regular intervals. These prospective studies permit assessment of outcomes using incidence rate estimates, determination of timing of outcomes in relation to exposures, evaluation of change in status from baseline, and evaluation of the effect of interventions on outcomes. As cohort participants are heterogeneous with respect to risk factors and outcomes, outcome experiences can be compared within the cohort and across subgroups defined by one or more factors (*e.g.,* race/ethnicity). In addition, using multivariate logistic or linear models, the relative contributions of risk factors (or intervention groups) with dichotomous (EGFR <60 ml/min per 1.73 m^2) or continuous (EGFR change from baseline) outcomes can be assessed. These models require appropriate adjustment for within-subject correlation across multiple observations on participants over time; however, the repeated measures nature of the study design provides increased analytic power and robustness (34).

KEEP 3.0 cohort participants will be characterized at baseline and at all follow-up visits by demographic characteristics, lifestyle characteristics, medical status, and medication use; and for evidence of kidney disease. Frequency estimates will be compared for gender, age, race/ethnicity, and medical status categories using χ^2 tests for categorical variables; estimates associated with baseline characteristics are identical to those examined in the cross-sectional KEEP 2.0 study.

Incident events during follow-up (development of EGFR <60 ml/min per 1.73 m^2, decline in EGFR of 25% or more from baseline) expressed as number of cases per 100 person-years observation, and rate ratios (for subgroups of interest) will be estimated. Risk of these incident events and the factors associated with risk will be evaluated in discrete time survival models with consideration of both time-dependent (medication use) and time-independent (race/ethnicity) risk factors. Likewise, frequency of morbidity (ESKD, CVD) and mortality outcomes during follow-up among individuals with evidence of kidney disease at baseline will be determined and evaluated in multivariate models with consideration of associated risk factors (race/ethnicity, medication use).

Outcome measures during follow-up will be used to estimate the effect of provider and participant educational interventions. The effect of type of provider educational intervention with change from baseline during follow-up in proportion of participants (*1*) at or below comorbidity-specific BP goal; (*2*) with prescription for ACE-inhibitors/ARB (when indicated); and (*3*) with glycemic control among diabetics will be examined. Likewise, the effect of participant-focused educational interventions with change from baseline during follow-up in proportion to participants who (*1*) use tobacco; (*2*) are at or below appropriate BMI; and (*3*) report adherence to medication regimens will be determined. Continuous outcomes (change in average follow-up BP from baseline, or change in EGFR values from baseline through duration of follow-up) will be estimated and compared by type of participant or provider educational interventions, with calculation of adjusted mean values for each intervention.

Summary

It is the intention that KEEP 3.0 will continue the success of KEEP 2.0 in identifying individuals at high-risk for developing kidney disease, and will also address the educational needs of health care providers and consumers. Analyses of KEEP 3.0 data will compare the benefits of various educational strategies on multiple outcomes, and will provide useful information to both health educators and providers regarding behavior change. Providers will also benefit from system support efforts introduced by the study, particularly the distribution of evidence-based guidelines. Finally, cohort participants will benefit from management of medical conditions and lifestyle decisions.

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