

**PROTEINURIA AND OTHER MARKERS OF CHRONIC KIDNEY DISEASE:
A POSITION STATEMENT OF THE NATIONAL KIDNEY FOUNDATION (NKF)
AND THE NATIONAL INSTITUTE OF DIABETES DIGESTIVE AND KIDNEY
DISEASES (NIDDK).**

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In recent years, chronic kidney disease (CKD) has become recognized as a major public health problem in the U.S. Until the past few years, kidney failure, the last stage of progressive kidney disease, has been the most visible outcome of CKD. The United States Renal Data Services (USRDS) maintains statistics on treatment of patients with kidney failure by dialysis and transplantation, known as end-stage renal disease (ESRD). The incidence of ESRD has doubled in the U.S. since 1990. This trend seems likely to continue, albeit at a lower rate, such that the annual incidence of ESRD will increase to 172,000 over the next seven years, and there will be 661,000 individuals receiving ESRD treatment by 2010. A much higher prevalence of earlier stages of chronic kidney disease (CKD) has been inferred. Based on data from Third National Health and Nutrition Examination Survey (NHANES III), there are 8,000,000 individuals in the U.S. with significantly decreased kidney function, who have an estimated glomerular filtration rate (GFR) of less than $60 \text{ ml/min/1.73 m}^2$. There are even more individuals with manifestations of kidney damage (particularly albuminuria) without a significant decrease in kidney function. At the current incidence rate of about 100,000 new ESRD cases per year, it is evident that most patients with CKD do not progress to ESRD, but likely succumb to cardiovascular disease, which is also the leading cause of mortality of ESRD patients on maintenance dialysis.

Poor patient outcomes and the high cost of ESRD care have been the focus of attention heretofore, and appropriately much effort has been expended to improve dialysis dose and delivery. However, it is unlikely that technical advances in dialysis can alter significantly the outcomes of existing comorbidities of patients started on maintenance dialysis. In order to improve dialysis patient outcomes it will be necessary to improve the health status of patients prior to their entering a dialysis program. Furthermore, a significant delay in progression, and even arrest, of CKD is now clinically achievable in many cases. Stated otherwise, CKD patients should be detected and treated well before the onset of kidney failure and the need for dialysis or transplantation. This is now possible because of increasing evidence that: 1) the adverse outcomes of CKD (kidney failure, cardiovascular disease, premature

death) can be prevented or delayed; 2) earlier stages of CKD can be detected through laboratory testing; 3) treatment of earlier stages of CKD can be effective in reducing progression to kidney failure and in preventing the systemic complications that develop in the course of progressive loss of kidney function; and 4) treatment of CKD related cardiovascular risk factors (diabetes, anemia, hypertension, dyslipidemia, abnormal bone mineral metabolism) at earlier stages of CKD can be effective in reducing cardiovascular mortality and morbidity of these individuals. These positive outcomes of more effective detection and treatment prompted the National Kidney Foundation to expand its Dialysis Outcomes Quality Initiative (DOQI) to encompass the entire spectrum of CKD, and the change of its acronym to K/DOQI for Kidney Disease Outcomes Quality Initiative.

The first set of clinical practice guidelines developed under K/DOQI comprised Chronic Kidney Disease: Evaluation, Classification and Stratification, which were published in February 2002 (1). These guidelines, developed over a period of two years: 1) define CKD and classify its stages independent of the underlying cause; 2) evaluate laboratory measurements for the clinical assessment of kidney function; 3) associate the level of kidney function with the systemic complications that develop during progressive CKD; and 4) stratify the risk for loss of kidney function and development of cardiovascular disease. The guidelines recommend that: 1) “All individuals should be assessed, as part of routine health encounters, to determine whether they are at increased risk for developing kidney disease, based on sociodemographic factors”; 2) individuals identified as being “at increased risk should undergo testing for markers of kidney damage”, specifically for proteinuria, and 3) to have the level of their glomerular filtration rate (GFR) “estimated from prediction equations that take into account the serum creatinine concentration and some or all of the following variables: age, gender, race and body size.”

Prompted by similar public health concerns and as part of its National Kidney Disease Education Program (NKDEP), the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) launched a series of initiatives to provide a stronger scientific basis for the adoption of these measures. As part of this effort and that of the implementation of the CKD guidelines, NIDDK and the NKF joined in hosting a conference on “Proteinuria and Other Markers of Chronic Kidney Disease” in Washington, DC, on October 8-9 2002. List of participants appended.

The objectives of the conference were to: 1) refine and clarify the requirements for the adoption of GFR estimates as a clinically useful marker of kidney function; 2) develop a consensus on the terminology and methodology for using proteinuria as a clinical marker of kidney damage; 3) explore the use of proteinuria as a valid end-point for clinical trials; and 4) delineate future research needs,

especially for markers of kidney damage other than proteinuria. Following presentations on these issues by experts in the field, three breakout groups addressed these topics and developed the following specific recommendations, which have been reviewed and approved by all conference participants.

I) CLINICAL USE OF GFR ESTIMATES AS A MARKER OF KIDNEY FUNCTION

A) Standardization of estimated GFR

1) Measurement: Clinical laboratories should measure serum creatinine accurately.

- Serum creatinine assays should be calibrated to national, and preferably to international, reference standards.

2) Laboratory reports: Laboratory reports should caution that:

- The serum creatinine value alone should not be used to estimate the level of kidney function.
- If serum creatinine is reported as mg/dl, values less than 1 mg/dl should be reported to the hundredths, i.e. two decimal points.

3) Process: Clinical laboratories should use the serum creatinine to compute GFR estimates using a prediction equation.

- Laboratories should provide GFR estimates as a regular laboratory test using a standard prediction equation
- Until a standard equation is agreed upon, it is recommended to use the MDRD equation of 4 variables (serum creatinine, age, sex and African-American or not) in individuals ≥ 18 years of age. The Cockcroft-Gault equation, which provides an estimate of creatinine clearance, is less desirable for adults but preferable to using the serum creatinine alone. The Schwartz or Counahan-Barratt equation should be used for those <18 years of age (1).
- Prediction equations should be adjusted to account for differences in creatinine calibration, between reporting laboratories and that in which the prediction equation was developed, using an international standard.
- If an international standard is not available, clinical laboratories should calibrate serum creatinine results to standards compatible with those used to develop the prediction equation.
- Laboratories should request all data needed to compute prediction equations.
If requested data cannot be provided, estimates of GFR should be provided for alternative clinical situations. For example, if using the MDRD equation, the result may be reported as the GFR estimate for African-Americans and for non-African-Americans. The clinician ordering the test can then interpret the results as necessary.

- Laboratory reports of GFR estimates should include appropriate interpretation
 - Give ‘confidence interval’ for the estimate
 - List reference values for age and sex
 - Provide an explanation for body surface area adjustment
 - Caution about conditions that affect measurements of serum creatinine, interfering substances, and extremes of body weight.
 - Explain indications for timed clearance measurements
 - Facilitate links to CKD definition, CKD guideline action plan, and drug dosing instructions
- Timed urine collections for creatinine clearance measurements are not necessary for routine estimation of GFR. However, they may be helpful in special circumstances such as cachexia, muscle atrophy, progressive weight loss, or extreme obesity.

B) Education

- 1) Clinical laboratories should provide instructions to physicians with introduction of a new laboratory test.
- 2) There should be widespread provider education about GFR estimates.
 - NKF and NIDDK should facilitate education at the undergraduate, graduate and postgraduate (i.e. CME) levels
- 3) The public, and especially individuals at increased risk for CKD, should be educated about GFR. The focus should be on individuals with hypertension, diabetes mellitus, those with a family history of CKD, the elderly and US ethnic minorities.

C) Research recommendations

- 1) Improve prediction equations for estimating GFR using serum creatinine
- 2) Develop new prediction equations using better filtration markers, such as cystatin C.
- 3) Continue to evaluate the burden of CKD.
- 4) Evaluate alternative definitions for CKD.

II) ALBUMINURIA MEASUREMENT AND TERMINOLOGY

A) Methods

- 1) For the diagnosis of CKD in adults and post-pubertal diabetic children, measurement of urinary albumin is preferred to that of total protein. Total protein is more appropriate in children in order to identify both albuminuria and low molecular weight proteinuria.
- 2) Timed urine collections should not be used. Rather, it is the ratio of the concentrations of urine albumin (in mg/dl) to that of urine creatinine (in g/dl) on a spot untimed urine specimen that should be

used. First morning spot collections are best for children and adolescents to avoid confounding the effect of orthostatic proteinuria.

- 3) Laboratories should report albuminuria as: mg albumin/g creatinine, with one reference range of ≤ 30 mg albumin/g creatinine.
- 4) Immunoassays for albumin usually have sufficient methodological sensitivity, and urine creatinine assays are fairly well standardized.
- 5) At very high levels of proteinuria (spot urine total protein to creatinine ratio > 500 to 1000 mg/g) measurement of total protein, instead of albumin, on a spot urine sample is acceptable. This should be reported as the ratio of the concentrations of total urine protein (in mg/dl) to that of urine creatinine (in g/dl), normal range < 200 mg/g.

B) Process

Use PARADE (Proteinuria, Albuminuria Risk Assessment, Detection and Evaluation) recommendations (2):

- 1) Repeat assays at later points in time, at least for patients with diabetes mellitus. Specifically, to identify persistent albuminuria repeat to confirm values above the reference range (≤ 30 mg albumin/g creatinine) in two out of three tested samples.
- 2) Patients should refrain from vigorous exercise for 24 hours prior to sample collection.
- 3) Refrigerate urine samples for assay the same or next day.
- 4) One freeze is acceptable, if necessary. Avoid repeated freeze-thaw of specimens. If the local laboratory is not equipped to handle samples, ship overnight on ice.
- 5) There is no need to acidify or otherwise treat the sample.
- 6) There is a need for standardization among laboratories for precision and accuracy into the low normal range of the assay for albumin, i.e. 2mg/L ; goal of the interassay CVs $< 15\%$
- 7) In the future, adjust creatinine for gender to provide gender independent reference range: multiply concentration in men by 0.68 (3)

C) Definitions

- Normal ≤ 30 mg albumin/g creatinine
- Microalbuminuria >30 to 300 mg albumin/ g creatinine
- Macroalbuminuria > 300 mg albumin/ g creatinine

III) ALBUMINURIA AS A CLINICAL MARKER OF KIDNEY DAMAGE

A) Process

1) Populations at increased risk for CKD (i.e. those with diabetes mellitus, hypertension or family history of CKD) should be screened for microalbuminuria, at least annually, as part of their regular health examination.

2) Individuals with documented persistent microalbuminuria (2 out of 3 measurements above the reference range), who are undergoing treatment for elevated blood pressure, lipid disorders or both, should be retested within 6 months to determine if treatment goals and reduction in microalbuminuria has been achieved.

- If the treatment has resulted in a significant reduction of microalbuminuria, annual testing for microalbuminuria is recommended.
- If no reduction in microalbuminuria has occurred, the blood pressure and lipid levels should be evaluated to determine: 1) if the targets have been achieved; 2) if specific drugs that interfere with the renin-angiotensin-aldosterone system are part of the antihypertensive therapy, and 3) the treatment regimen should be modified accordingly.

3) Recommendations for annual testing of microalbuminuria after its diagnosis and of its evaluation following institution of therapy for hypertension and dyslipidemia deserve to be better established (see Research Recommendation below). However, based on the available evidence, continued surveillance of microalbuminuria (see items 1 and 2 above) is recommended to assess progression of CKD and response to therapy.

4) Children should be screened using a standard dipstick on two occasions; once prior to starting school and then in early adolescence (as recommended by the American Academy of Pediatrics). Subsequent testing should be done as needed as recommended in the Pediatric PARADE recommendations (4).

B) Research recommendations

1) The value of testing for albuminuria in various populations at increased risk for CKD, particularly those with hypertension or with a family history of CKD or ESRD should be analyzed.

2) The value of titration of antihypertensive therapy based on changes of albuminuria needs further study.

3) Guidelines for expected reductions in albuminuria with treatment should be developed.

4) New markers of kidney damage should be developed. Among potential markers in the urine are specific kidney cells and specific mediators of injury. Patterns of urinary proteins of varying molecular weights or mRNA excretion using high throughput methods may prove valuable.

IV) ALBUMINURIA AS A SURROGATE MARKER FOR CLINICAL TRIALS

Accrued data demonstrate a strong relationship between the level of proteinuria or albuminuria and the progression of CKD to kidney failure and fatal CVD events. These associations have been useful in devising small-scale pilot and feasibility trials. However, the linkage has not been sufficiently established for use in large multicenter trials. Two exceptions exist. First, trials to prevent conversion from normal urinary albumin excretion (≤ 30 mg albumin/g creatinine) to microalbuminuria (>30 - 300 mg albumin/g creatinine) in diabetes may be justified since the time to GFR based declines is long in this condition. Second, trials to treat massive proteinuria (nephrotic syndrome) may also be justified as remission of massive proteinuria itself may yield improved prognosis for kidney and cardiovascular diseases.

Research Recommendations

1) The many available databases from previous clinical trials should be assembled and analyzed for relationships of albuminuria to usual and accepted outcome measures (doubling of serum creatinine, ESRD, CVD events, or death). The strength of the relationships should be assessed for the following subgroups and factors:

- Specific baseline levels of albuminuria or proteinuria
- Relative and absolute changes in albuminuria or proteinuria with therapy
- Specific underlying kidney diseases
- Changes in albuminuria or proteinuria as a composite along with increments of serum creatinine less than doubling, e.g. 50%
- Evaluate as an endpoint the reduction in albuminuria or proteinuria by 50%.

2) Depending on results obtained from analysis of existing databases, consideration should be given for new clinical trials to explore the potential validity of albuminuria as a surrogate marker of progression of CKD.

3) Develop and validate new markers of kidney damage using currently stored samples from completed clinical trials as well as samples from ongoing clinical trials.

REFERENCES

1. National Kidney Foundation. K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification and Stratification. *Am J Kidney Dis* 39 (suppl 1): S1-S266, 2002
2. Keane WF Eknoyan G: Proteinuria, albuminuria, risk, assessment, detection, elimination (PARADE): A position paper of the National Kidney Foundation. *Am J Kidney Dis* 33: 1004-1010, 1999
3. Jacobs DR Jr, Murtaugh MA, Steffes M, Yu X, Roseman J, Goetz FC: Gender and race-specific determinations of albumin excretion rate using albumin to creatinine ratio in single untimed urine specimens: the CARDIOA study. *Am J Epidemiol* 155:1114-1119, 2002
4. Hogg RJ, Portman RJ, Milliner D, Lemley KV, Eddy A, Ingelfinger J: Evaluation and management of proteinuria and nephritic syndrome in children: Recommendations from a pediatric nephrology panel established at the National Kidney Foundation conference on Proteinuria, Risk, Assessment, Detection, Elimination (PARADE). *Pediatrics* 105: 1242-1249, 2000