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Definition and classification of chronic kidney disease: A position statement from Kidney Disease: Improving Global Outcomes (KDIGO)

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Top of page

Abstract

Definition and classification of chronic kidney disease: A position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Chronic kidney disease (CKD) is a worldwide public health problem, with adverse outcomes of kidney failure, cardiovascular disease (CVD), and premature death. A simple definition and classification of kidney disease is necessary for international development and implementation of clinical practice guidelines. Kidney Disease: Improving Global Outcomes (KDIGO) conducted a survey and sponsored a controversies conference to (*1*) provide a clear understanding to both the nephrology and nonnephrology communities of the evidence base for the definition and classification recommended by Kidney Disease Quality Outcome Initiative (K/DOQI), (*2*) develop global consensus for the adoption of a simple definition and classification system, and (*3*) identify a collaborative research agenda and plan that would improve the evidence base and facilitate implementation of the definition and classification of CKD.

The K/DOQI definition and classification were accepted, with clarifications. CKD is defined as kidney damage or glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 for 3 months or more, irrespective of cause. Kidney damage in many kidney diseases can be ascertained by the presence of albuminuria, defined as albumin-to-creatinine ratio >30 mg/g in two of three spot urine specimens. GFR can be estimated from calibrated serum creatinine and estimating equations, such as the Modification of Diet in Renal Disease (MDRD) Study equation or the Cockcroft-Gault formula. Kidney disease severity is classified into five stages according to the level of GFR. Kidney disease treatment by dialysis and transplantation should be noted. Simple, uniform classifications of CKD by cause and by risks for kidney disease progression and CVD should be developed.

Keywords:

chronic kidney disease, glomerular filtration rate, proteinuria, albuminuria, KDIGO

Kidney failure is a worldwide public health problem, with increasing incidence and prevalence, high costs, and poor outcomes[1]. There is even a substantially higher prevalence of the earlier stages of chronic kidney disease (CKD), with adverse outcomes, including loss of kidney function,

cardiovascular disease (CVD), and premature death. Strategies to improve outcomes will require a global effort directed at the earlier stages of CKD.

The rationale for a global initiative to address this problem is simple and self-evident. The epidemic of CKD is global. The adverse outcomes of CKD are universal, as are the underlying science and evidence-based strategies for prevention, detection, evaluation, and treatment. Although risk factors and resources for care vary locally, it is important to increase the efficiency of utilizing available expertise and resources in improving the care and outcomes of CKD worldwide.

Development, dissemination, and implementation of clinical practice guidelines are means to improve outcomes of CKD. Rigorously developed evidence-based clinical practice guidelines, when implemented, can reduce variability of care, improve patient outcomes, and ameliorate deficiencies in health care delivery[2,3,4]. Kidney Disease: Improving Global Outcomes (KDIGO) is a recently established and independently incorporated organization governed by an international board of directors with the stated mission to "improve the care and outcomes of kidney disease patients worldwide through promoting coordination, collaboration and integration of initiatives to develop and implement clinical practice guidelines"[1].

One of the initiatives undertaken by KDIGO is a series of International Controversies Conferences that examine what is known, what can be done with what is known, and what needs to be known on selected issues that impact on the care and outcomes of kidney disease patients worldwide. The first KDIGO International Controversies Conference on "Definition and Classification of Chronic Kidney Disease in Adults" was held in Amsterdam, The Netherlands, on November 16 and 17, 2004. The topics covered included the definition and classification of CKD, estimation of glomerular filtration rate (GFR), and measurement of albuminuria and proteinuria. This article has been reviewed by the conference participants and reports the recommendations of the conference, which have been reviewed and adopted as a position statement by the KDIGO Board of Directors.

Top of page

SCOPE

The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (K/DOQI) Clinical Practice Guidelines on Chronic Kidney Disease: Evaluation, Classification and Stratification of Risk published in 2002 provided the first definition of CKD independent of cause, and classification of severity based on GFR level[5]. The guidelines have been widely disseminated and generally accepted[6,7,8,9,10,11,12,13]. However, concerns have been expressed about the definition and classification, methods to estimate GFR, and ascertainment of proteinuria[14,15,16,17,18,19,20,21].

The goals for the KDIGO Controversies Conference were (*1*) to provide a clear understanding to both the nephrology and nonnephrology communities of the evidence base for the K/DOQI definition and classification of severity of CKD; (*2*) to develop global consensus for the adoption of a simple definition and classification system for CKD, clarifications and modifications to current guidelines to facilitate more widespread implementation of initiatives for patient care and physician and public education worldwide; and (*3*) to identify a collaborative research agenda and plan that would improve the evidence base and facilitate the implementation of the definition and classification of CKD

Top of page

CONFERENCE

KDIGO co-chairs (G. Eknoyan and N. Lameire) identified Conference co-chairs (A. Levey and K.-U. Eckardt) and worked together to develop the agenda and select individuals with demonstrated expertise in CKD and interest in global issues regarding guideline implementation. The Conference was attended by 60 participants from North and South America, Europe, Asia, Australia, and Africa (Appendix 1). Plenary sessions and breakout sessions were designed to provide an overview of each of the three major topics, detailed discussions, and a summary of clarifications and modifications of the K/DOQI guidelines, and suggestions for implementation, and recommendations for research. Invitees were also encouraged to submit abstracts of their work to complement the discussion. The agenda and abstracts can be found at http://www.kdigo.org/. This manuscript contains a brief summary of the survey conducted prior to the meeting, as well as the specific recommendations approved by the KDIGO Board of Directors at its meeting on December 3 and 4, 2004 in Paris.

Top of page

SURVEY

Prior to the conference, a survey was developed and disseminated to nephrologists worldwide to assess their opinion of the K/DOQI definition and classification of CKD. The survey was designed to answer the following questions:

- What is the current practice for definition of CKD, use of a classification system, estimation of GFR, and measurement of proteinuria?
- Is there agreement on the use of estimated GFR as a basis for classifying CKD?
- What is the current knowledge on parameters required for GFR estimates?
- Is there agreement on the use of spot urine samples for measurement of proteinuria?
- What are potential barriers and concerns regarding implementation?

Questions were drafted by conference planners, reviewed and amended by KDIGO Board of Directors and other experts. A "pilot" version was tested, revised, and translated from English into French, German, Spanish, and Japanese. The final version of the survey contained 25 questions and was distributed to approximately 10,000 nephrologists via electronic mail. Mailing addresses were kindly provided by the International Society of Nephrology, European Renal Association-European Dialysis and Transplant Association, Spanish Society of Nephrology, Latin American Society of Nephrology, French Society of Nephrology, and Japanese Society of Nephrology.

Responses, received from 1190 (12%) representing nephrologists in all continents Table 1, were used to formulate the issues that the Controversies Conference would address. The detailed results and analyses of the responses received will be the subject of a separate publication.

Table 1 - Survey responses by location.

Table 1 - Survey responses by location - Unfortunately we are unable to provide accessible alternative text for this. If you require assistance to access this image, please contact help@nature.

table

Definition and classification of kidney disease

In brief, respondents commented on the following with regard to definition and classification:

- K/DOQI system is frequently used already;
- Vast majority believe that it helps in identifying individuals with CKD;
- About one third find it either not useful or would prefer modifications;
- Many requested inclusion of additional information, such as cause of kidney disease, and prognosis for kidney disease progression or CVD; and
- Suggestions for revisions used inconsistent terms.

GFR estimates

The GFR estimates were evaluated as follows by the respondents:

- Many already were using equations to estimate GFR;
- Majority felt that GFR estimates should not be used alone for the detection and follow-up of CKD;
- One third considered GFR estimation from equations to be of less value than measured creatinine clearance;
- One fourth reported experience with the routine reporting of GFR estimates whenever serum creatinine is measured, but almost one half envisaged problems with routine reporting;
- Most believed that routine reporting of GFR estimates would lead to more referrals;
- Many preferred the Cockcroft-Gault formula to the MDRD Study equation, although knowledge of the determinants and validity of either equation was suboptimal; and
- There was general uncertainty about the methods for creatinine assay used in local laboratories.

Assessment of albuminuria/proteinuria

In terms of albuminuria/proteinuria, respondents responded with the following concerns:

- Testing for albuminuria for the detection of CKD and assessment of risk for CVD is underutilized;
- More use assays for total protein rather than for albumin;
- Spot urine samples are less frequently used than timed urine collections; and
- Only one third believe that spot urine samples make timed collections unnecessary.

Top of page

FRAMING THE ISSUES

Conference attendees expressed widespread agreement about the following issues:

1. The burden of illness of CKD is high worldwide, but outcomes and resources for care may vary across countries. Irrespective of location, earlier identification should improve outcome. Strategies to improve identification include increasing public awareness, professional education, changes in health care policy, changes in health care delivery systems, and basic, clinical and outcomes research related to CKD.

2. The two principal outcomes of CKD are the progressive loss of kidney function over time, and development and progression of CVD. Figure 1 shows a conceptual model of the course of chronic kidney disease, which defines stages of CKD, as well as antecedent conditions, outcomes, risk factors for adverse outcomes, and actions to improve outcomes. This representation of the course of CKD provides a framework previously lacking for the development of a public health approach to CKD.

3. "CKD risk factors" are defined as attributes associated with increased risk of adverse outcomes of CKD Table 2. The K/DOQI guidelines focus primarily on identifying susceptibility and initiation factors to detect individuals at increased risk of developing CKD, and on progression factors, to define individuals at high risk of worsening kidney damage and subsequent loss of kidney function. Because of the

older age of individuals at the onset of many kidney diseases, the slow rate of decline of kidney function, and high death rate due to CVD, most individuals with CKD do not develop kidney failure. However, decreased GFR is associated with a wide range of complications, such as hypertension, anemia, malnutrition, bone disease, neuropathy, and decreased quality of life. Therapeutic interventions at earlier stages can prevent or ameliorate most of the complications of decreased kidney function, as well as slow the progression to kidney failure. Thus, measures to improve prevention, detection, and treatment of CKD in its earlier stages could reduce adverse outcomes and improve the quality of life of individuals with CKD.

4. CVD is a complication of CKD, which deserves special consideration because (a) CVD events are more common than kidney failure in patients with CKD; (b) chronic kidney disease appears to be an independent risk factor for CVD; and (c) CVD in patients with CKD is treatable and potentially preventable. The 1998 Report of the NKF Task Force on Cardiovascular Disease in Chronic Renal Disease recommended that patients with CKD be considered in the "highest risk" group for subsequent CVD events, and that most interventions that are effective in the general population should also be applied to patients with chronic kidney disease[22]. These conclusions were affirmed by the 2003 Statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention[23] and recent guidelines by the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure[24] and the National Kidney Foundation[25].

5. It is challenging for health care providers from diverse geographic regions with varying political, cultural, and economic systems to agree with all the aspects of a definition and classification for CKD. Nonetheless, there is a need to adopt a simple definition and classification to ensure clear communication among providers. As new evidence arises, there will be continuing debate and efforts to refine and clarify the recommendations made in this document.

Figure 1.

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Conceptual model of the mourse of chronic kidney disease (CKD). Shaded ellipses represent stages of CKD. Unshaded ellipses represent potential antecedents or consequences of CKD. Thick arrows between ellipses represent risk factors associated with the initiation and progression of disease that can be affected or detected by interventions: susceptibility factors (black), initiation factors (dark gray), progression factors (light gray), and end-stage factors (white) (see Table 2). Interventions for each stage are given beneath the stage. Persons who appear normal should be screened for CKD risk factors. Persons known to be at increased risk for CKD should be screened for CKD. "Complications" refer to all complications of CKD and its treatment, including complications of decreased glomerular filtration rate (GFR) (hypertension, anemia, malnutrition, bone disease, neuropathy, and decreased quality of life) and cardiovascular disease (CVD). Increasing thickness of arrows connecting later stages to complications represents the increased risk of complications as kidney disease progresses. Modified and reprinted with permission[5].

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Table 2 - Risk factors for chronic kidney disease (CKD) and its outcomes.

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Top of page

RECOMMENDATIONS

I. Definition and Classification of CKD (Co-Chairs Y. Tsukamoto and A. Levin)

A. Definition of CKD

The K/DOQI definition of CKD Table 3 was accepted, with the following clarifications:

1. Retain the term "disease" to convey importance. It is important that the definition use terms that reflect an appropriate balance between emphasizing need for diagnosis and treatment as opposed to that of labeling a risk condition as a disease. The K/DOQI definition of CKD as a "disease" is consistent with current usage of this term. The Oxford English Dictionary (Compact Edition) defines a disease as "A disorder of structure or function in a human, animal, or plant, especially one that produces specific symptoms." Evidence in support of a disease include clinical-pathologic correlations (as defined by case series), associations with symptoms or findings (as defined by cross-sectional analyses), and associations with outcomes (as defined by longitudinal analyses). The use of the term "disease" in CKD is consistent with (a) the need for action to improve outcomes through prevention, detection, evaluation and treatment; (b) providing a message for public, physician and patient education programs; (c) common usage; and (d) its use in other conditions defined by findings and laboratory tests, such as hypertension, diabetes, and hyperlipidemia.

2. Infer chronicity from documentation or presumption of kidney disease for $\geq$3 months. This clarification allows clinical judgment about chronicity in the absence of past data on levels of GFR or markers of kidney damage. In the future, it will be important to link the definition of chronicity with definition of acute kidney disease.

3. Retain reduced GFR as a criterion for kidney disease. GFR is widely accepted as the best index of kidney function. The rationale for a threshold level of GFR <60 mL/min/1.73 m^2 is as follows:

    - It is substantially above the level associated with kidney failure leaving time for treatment of kidney disease to prevent kidney failure;
    - It is less than half the adult level of GFR;

- Lower levels are rare in young men or women (<40 years);
- Lower levels are associated with increasing complications of CKD;
- Lower levels are associated with adverse outcomes, including cardiovascular disease morbidity and mortality in individuals with and without diabetes; and
- This threshold and lower levels can be detected with current estimating equations for GFR based on serum creatinine, but not by serum creatinine alone.
- Retain albuminuria as a marker for kidney damage. Threshold values for spot urine albumin to creatinine ratio are discussed subsequently. The rationale for the recommended threshold (>30 mg/g) is as follows:
- The threshold level is two to three times greater than the normal value;
- Higher levels are infrequent in young men and women (<40 years);
- Higher levels are the earliest marker of kidney damage due to diabetes, glomerular diseases, and hypertension;
- Higher levels are associated with adverse outcomes, including progression of kidney disease and cardiovascular disease in individuals with and without diabetic mellitus; and
- Therapies that reduce albuminuria are associated with slowing the progression of diabetic and nondiabetic kidney disease.

4. Allow clinical judgment regarding the relevance of other markers of kidney damage. Other markers of kidney damage include abnormalities in the urine sediment (casts, tubular epithelial cells); abnormalities in imaging studies (polycystic kidneys, hydronephrosis, small, "echogenic" kidneys); and abnormalities in the composition of the blood and urine that defines "tubular syndromes" (renal tubular acidosis, nephrogenic diabetes insipidus, Fanconi syndrome, etc). The K/DOQI guidelines address the clinical relevance of these abnormalities based on whether they "can lead to decreased kidney function." This language is included in the definition of CKD Table 3.
5. Consider all kidney transplants recipients to have CKD, irrespective of GFR level or presence or absence of markers of kidney damage. The rationale for this is based on damage to native kidneys, presumed damage to the kidney transplant based on studies of "protocol biopsies," and need for life-long care caused by complications of prior CKD and chronic allograft nephropathy.
6. Do not include cause of kidney disease in definition of CKD. Identification of the cause of kidney disease is one of the goals of evaluation of CKD, and may lead to changes in management of CKD. However, CKD can be detected without knowledge of its cause, and ascertainment of the cause may require specialized knowledge and procedures not available to the vast majority of clinicians who encounter and can detect CKD. Importantly, the cause of CKD cannot always be determined despite extensive evaluation. Thus, it is not practical to include the cause of CKD as part of the definition. However, CKD can be classified by cause, as described below.

Table 3 - Criteria for the definition of chronic kidney disease (CKD).

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B. Classification of CKD Table 4

Table 4 - Classification of chronic kidney disease (CKD).

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In principle, CKD could be classified according to severity, diagnosis, treatment, and prognosis. Classification systems can be simple or complex. The choice of a classification system depends on answers to several questions:

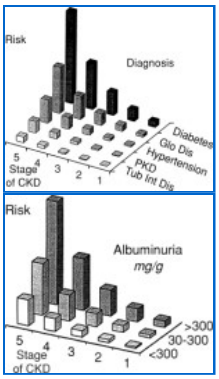
- To whom is the classification system addressed?
- Can we build a system that is useful to most clinicians, with additional complexity that is useful to some?
- Can the classification system be linked to "Action Plans"? An action plan should be evidence-based, but modifiable based on considerations for different populations, and individualized based on patient circumstances.

1. Retain classification based on severity. There was agreement with initial classification based on level of GFR, using GFR estimating equations. This initial classification is simple, and can be linked to "Action Plans." Because of imprecision of GFR estimates at higher range of GFR, it may be difficult to distinguish stages 1 and 2. Alternative terms such as "stage, class, or grade" can vary depending on local interpretation and language.
2. Add classification based on treatment by dialysis or transplantation. This is necessary to link with clinical care and policy, especially regarding reimbursement. To this end the use the following suffix: "T" for all kidney transplant recipients, at any level of GFR (CKD stages 1 to 5) and "D" for dialysis, for CKD stage 5 patients treated by dialysis. Irrespective of the level of GFR at which dialysis is initiated, al1 patients treated by dialysis are CKD stage 5D.
3. Encourage further consensus development on classification by cause of kidney disease. Clinical evaluation for CKD should include elucidation of the cause of disease. As discussed above, cause of disease cannot be ascertained in all cases. Classification based on cause

of disease would be desirable, but would require development of standard criteria for causes of CKD and a uniform taxonomy. These would be important areas for further research and consensus development.

4. Further research is necessary to allow classification by prognosis. Stratification of risk for the major outcomes of CKD (loss of kidney function and CVD) is based in part, on level of GFR (CKD stage) and cause of kidney disease Figure 2a. Other factors are also important and could be considered in risk stratification, such as magnitude of albuminuria Figure 2b. It is likely that these and other risk factors contribute differentially to the risk of different outcomes Table 5. Research is needed to elucidate risk factors and develop risk prediction instruments for CKD progression and CVD.

Figure 2.



Risk stratification in chronic kidney disease (CKD). (*A*) Relationship of stage and type of kidney disease to prognosis in CKD. Vertical axis shows hypothetical risks for adverse outcome of CKD, such as progression to kidney failure or onset of cardiovascular disease (CVD). Left axis shows stage of CKD, based on severity [glomerular filtration rate (GFR) level]. Right axis shows classification of clinical-pathologic type of CKD (diagnosis). Risk profiles differ for progression to kidney failure and onset of CVD. Abbreviations are: Glo Dis, glomerular diseases; PKD, polycystic kidney disease; Tub Int Dis, tubulointerstitial disease. (*B*) Relationship of stage of kidney disease and level of albuminuria to prognosis in CKD. Vertical axis shows hypothetical risks for adverse outcome of CKD, such as progression to kidney failure or onset of CVD. Left axis shows stage of CKD, based on severity (GFR level). Right axis shows magnitude of albuminuria, measured as spot urine albumin to creatinine ratio (mg/g). Risk profiles differ for progression to kidney failure and onset of CVD. Stratification of risk by CKD stage and albuminuria applies to patients in whom the cause of CKD is known, such as glomerular diseases or polycystic kidney disease, or in whom the cause of CKD is not known (patients with CKD stages 1 and 2 and albuminuria <30 mg/g have another marker of kidney disease, such as hematuria for patients with glomerular diseases of cysts for patients with polycystic kidney disease). Reprinted with permission[25]

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Table 5 - Risk factors for progression of chronic kidney disease (CKD), cardiovascular disease (CVD), and death.

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C. Research Questions

- What is the relationship of body surface area (BSA) or total body water (V) to measured GFR in an individual patient. What is the impact on outcomes of adjustment by BSA or V?
- Should CKD stage 3 be divided into two stages because of greater risk of CVD outcomes in patients with GFR 30 to 44 mL/min/1.73 m^2 compared to GFR 45 to 59 mL/min/1.73 m^2?
- Are different equations required for different populations and does that impact on utility of the system at the present time as a global tool?
- Do nonreferred populations with low GFR have similar outcomes as referred populations?
- Are there different predictors of progression in different populations?
- What are the predictors of risk within each CKD stage that would change the treatment plans?
- What are the implications of different levels of GFR posttransplant for CKD progression and CVD outcomes?
- If we use different or better tools to define kidney disease would we have different outcomes?
- What is the outcome of patients with increased GFR (hyperfiltration)?
- What are the long-term outcomes of patients with acute kidney disease?
- What is the time course of chronic vs. acute kidney disease?
- Should the definition of chronicity vary among diseases or populations?
- Can chronicity be inferred by rate of change of kidney function over intervals shorter than 3 months?

- Can we identify markers that will predict "rapid" progression?

II. Estimation of GFR (Co-Chairs J. Coresh and J. Rossert)

A. Standardization and Calibration of Serum Creatinine Assay

1. Serum creatinine measurements should be standardized. In the classic and modified Jaffé reaction, up to 20% of the color reaction in serum or plasma in normal subjects is due to substances other than creatinine ("noncreatinine chromogens"). Calibration of serum creatinine assays to adjust for this interference is not standardized across laboratories, such that systematic differences among laboratories account for most of the differences between observed and expected results compared to a reference standard. The lack of standardization can also cause differences in serum creatinine measurements within laboratories over time.

2. Calibration should be traceable to an international reference creatinine method. Isotope dilution mass spectrometry (IDMS) is an appropriate method. Cooperation from manufacturers is critical to this process.

B. Reporting Estimated GFR

1. Estimated GFR should be reported automatically using an equation based on serum creatinine following assay calibration and patient variables. Clinical laboratories are critical for the implementation. This recommendation does not preclude reporting GFR estimates prior to calibration, recognizing that GFR estimates >45 to 60 mL/min/1.73 m^2 are sensitive to calibration differences.

2. GFR estimates have been reported successfully using several different models.

    1. Interpretation of GFR estimates in the context of CKD definition

        - "GFR <60 mL/min/1.73 m^2 for 3 or more months is consistent with CKD";
        - "GFR $\geq$60 mL/min/1.73 m^2 and kidney damage that is present for 3 or more months is consistent with CKD; " and
        - "GFR $\geq$60 mL/min/1.73 m^2 without kidney damage is not consistent with CKD."

    2. Accounting for imprecision of GFR estimates at higher values

        - If creatinine assay is calibrated;
        - Some laboratories report a numerical value for "GFR <90" and "GFR $\geq$90" for higher values;
        - Other laboratories report numerical value for "GFR <60" and "GFR $\geq$60" for higher values;
        - If creatinine assay is not calibrated, numerical value of value of GFR can be reported for "GFR <60" and "GFR $\geq$60" for higher values; and
        - Numerical value of GFR at all GFR levels, with qualification that levels of GFR >60 are imprecise.

    3. For all of the above, GFR levels of <60 have been highlighted as abnormal. Values from 45 to 59 are estimated with less precision. Some individuals with an initial abnormal GFR in this range will have a higher estimate on subsequent testing. Averaging of multiple measurements will improve the precision of estimated GFRs as it does that of measured inulin clearance.

C. GFR Estimating Equations

1. Estimating equations for GFR should have the following characteristics:

    - Developed in a large cohort, including a variety of racial and ethnic groups for international comparisons;
    - Evaluated in an independent cohort;
    - Validated to have adequate precision and low bias against a gold standard measure of GFR (not creatinine clearance); and
    - Practical to implement taking into consideration cost, required data elements, generalizability, calibration, and reliability of the assay.

2. Abbreviated MDRD Study equation meets most of these criteria. The MDRD Study equation has been validated in patients with diabetic (type 2) and nondiabetic kidney disease and in kidney transplant recipients. It has been validated in United States whites and African Americans, European whites, but requires verification for other groups, countries and racial and ethnic groups.

3. Cockcroft-Gault formula is more difficult to implement in clinical laboratories. It requires weight (and height for body surface area adjustment), which are usually not recorded on laboratory requisitions. Furthermore, the optimal calibration of serum creatinine for this equation is uncertain.

4. Both MDRD Study and Cockcroft-Gault equations are imprecise at high values for GFR (low values for serum creatinine). This may cause misclassification in selected groups, including normal individuals, children, pregnant women, and conditions associated with hyperfiltration.

D. Clinical Circumstances in which Clearance Measurements May Be Necessary to Estimate GFR Table 6

1. Situations in which GFR estimation may be unreliable
    - Patients with grossly abnormal muscle mass (e.g., amputation, paralysis, muscular disease);
    - Low body mass index (<18.5 kg/m^2);
    - High or low intake of creatinine or creatine (e.g., dietary supplements, vegetarians);
    - Rapidly changing kidney function; and
    - Pregnancy.
2. >Situations when a high degree of accuracy may be needed
    - Potential kidney donors; and
    - Prior to dosing with medications that have high toxicity that are excreted by the kidneys.
3. Methods for measurement of GFR
    - Exogenous filtration markers including inulin, iothalamate (^{125}I-labeled or unlabeled), 51-chromium ethylenediaminetetraacetic acid (^{51}Cr-EDTA), 99-technetium diethylenetriamine pentaacetic acid (^{99}Tc-DTPA), and iohexol provide good accuracy;
    - Urinary or plasma clearance of exogenous filtration markers can be used to measure GFR;
    - Urinary clearance of exogenous filtration markers is less susceptible to error than plasma clearance;
    - Accurate clearance measurement requires cooperation among nephrology, nuclear medicine, and clinical chemistry departments to establish protocols and training of personnel for proper administration and assay of the marker, patient preparation, and sample collection. In particular, preparation of ^{99}Tc-DTPA requires careful attention to quality control; and
    - Creatinine clearance may be a useful alternative when exogenous filtration markers are not available.

Table 6 - Clinical circumstances in which clearance measurements may be necessary to estimate glomerular filtration rate (GFR).

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E. Dosage Adjustment for Drugs Excreted by the Kidneys

1. Drug dosing should be based on GFR estimates without surface area adjustment. The difference between adjusted and unadjusted GFR is largest for individuals with body size substantially different from 1.73 m^2 (children, obese, and very large or small adults).
    - Cockcroft-Gault equation provides unadjusted creatinine clearance; and
    - MDRD Study equation provides adjusted GFR.
2. Recommendations for drug dosing should be based on methods for measuring or estimating GFR that were used in pharmacokinetic studies. This is most important for narrow ranges of GFR or for drugs with significant toxicity. Otherwise, either MDRD Study or Cockcroft-Gault equation provides reasonable estimates.
3. Most studies are based on creatinine clearance. Many pharmacies use Cockcroft-Gault equation to estimate creatinine clearance before dispensing drugs. Future studies should provide drug dosing information based on both GFR and creatinine clearance. This will facilitate use of GFR estimates.

F. Research Recommendations

- Validating estimation equations for GFR in more diverse groups such as:
- Healthy populations;
- Patients with body mass index > 35 kg/m^2 and <19 kg/m^2;
- Elderly patients;
- Type 1 diabetics; and
- Specific ethnic groups and nationalities (Southeast Asians, South Asians, Native Americans, Africans, Aborigines, Latin Americans).
- Development of new equations to improve on the present equations
- Serum cystatin C alone and in combination with serum creatinine; and
- Inclusion of variables to estimate lean body mass, such as anthropometry and imaging studies.

- Determine the influence of patient referral source on estimated GFR for a given serum creatinine;
- Use of repeated measurements of serum creatinine to improve precision of GFR estimates;
- Determine the accuracy of formulas to follow progression of CKD; and
- Establish a database of research studies and clinical populations with GFR measurements and measurements of serum creatinine from a variety of countries, racial and ethnic groups to develop improved GFR estimating equations.

III. Assessment of Proteinuria (Co-Chairs D. de Zeeuw and T. Hostetter)

A. Which Urine Protein Should Be Measured and Which Measurement Method Should Be Used?

1. Albumin is the preferred urinary protein. Increased urinary excretion of albumin is the earliest manifestation of CKD due to diabetes, other glomerular diseases, and hypertensive nephrosclerosis. Albuminuria may also accompany tubulointerstitial diseases, polycystic kidney disease, and kidney disease in kidney transplant recipients.

   Albumin measuring techniques should be traceable to the CRM 470 standard. If positive, may follow up with other protein measurements, for example total protein, or low-molecular-weight proteins. Future research needs to focus on whether a urine albumin standard would be better than that of plasma albumin now used.

2. Multiple methods are available to assay albumin:
   - Turbidometry (less sensitive and specific for albumin than other methods);
   - Nephelometry;
   - Radioimmunoassay (RIA);
   - Enzyme-linked immunosorbent assay (ELISA);
   - If above unavailable, an antibody-based dipstick can be used; and
   - Conventional dipstick in spot urine specimens is acceptable, if it is the only available option.

B. Collection and Process

1. Random untimed "spot" urine samples are suitable for initial testing. A first morning urine sample is preferable, but not required if it poses substantial inconvenience compared to a random specimen.
2. Results should be expressed as albumin to creatinine ratio. Expression as a ratio corrects for variability due to hydration, diuretics, osmotic diuresis, concentrating defects.
3. For positive tests, rule out contamination from infection or menstrual blood with dipstick evaluation for leukocytes and erythrocytes.
4. Verification of increased albumin excretion requires two out of three positive tests. Patients with increased albumin excretion should be diagnosed as having CKD, and should undergo appropriate evaluation[5, 7].
5. Timed urine collection for albumin and creatinine may be performed if increased precision is required.

C. Thresholds for Abnormal Albumin to Creatinine Ratio Table 7

1. Threshold levels for diagnosis of CKD is ≥30 mg/g. This is consistent with the definition in recommendations K/DOQI, JNC-7, and 2004 American Diabetes Association (ADA). This levels corresponds roughly to various definitions of "microalbuminuria." Gender-specific threshold levels (approximately 20 mg/g in men and 30 mg/g in women) adjust for greater average creatinine excretion in men than women[26,27,28]. However, there is some reluctance to recommend gender-specific threshold levels based on greater complexity, uncertainty regarding assay precision, and effect of factors in addition to gender on creatinine excretion, such as race, ethnicity, diet, and measures of body size.
2. Levels of albumin to creatinine ratio ≥300 mg/g (>200 mg/g in men and >300 mg/g in women) correspond roughly to various definitions of "macroalbuminuria," or "clinical proteinuria," which are associated with even higher levels of risk for kidney disease progression and CVD.
3. The term "albuminuria" should be substituted for terms "microalbuminuria" and "macroalbuminuria." These terms should not be retained because they are misleading.

Table 7 - Threshold levels for abnormalities in urinary albumin.

Table 7 - Threshold levels for abnormalities in urinary albumin - Unfortunately we are unable to provide accessible alternative text for this. If you require assistance to access this image, pleas

table

D. Testing for Albuminuria in Patients at Increased Risk of CKD

1. High risk groups should be tested for presence of albuminuria: These include patients with the following:

- Diabetes;
- Hypertension;
- Family history of CKD; and
- Past or family history of CVD.

2. Frequency of testing for albuminuria in high risk groups has not been rigorously studied. Many recommendations suggest yearly testing based on opinion. This is an important area for future research.

E. Research Recommendations

- More precise definition of threshold levels of albumin-to-creatinine ratio adjusted for age, race, and sex.
- Are some ranges of albuminuria or some urinary proteins other than albumin more sensitive as a risk factor for CKD progression vs. CVD morbidity and mortality?
- How does the different range for HPLC assay for urinary albumin affect risk for CKD progression and CVD morbidity and mortality?
- Are there particular settings when point-of-care measurement of albumin is more effective for particular settings than that in a central facility?
- Does screening for albuminuria, followed by appropriate therapy, improve outcomes, in the general population, or in subgroups of elderly or obese individuals?
- What is the recommended frequency of testing for albuminuria in high-risk subgroups?
- Is reduction of albuminuria a surrogate outcome for slowing progression of CKD in clinical trials?
- Develop risk prediction equations for CKD progression and CVD morbidity and mortality, including albuminuria.
- Harmonize CKD guidelines with those of other specialties: endocrinology, hypertension, diabetes, cardiology, internal medicine, primary care, family practice, pediatrics, and clinical chemists.
- Define relationships between total protein to creatinine ratio and albumin to creatinine ratio for various ranges of proteinuria, including "clinical proteinuria" and "nephrotic syndrome."

Top of page

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Top of page

Appendices

APPENDIX 1

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Top

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