The advantage of a uniform terminology and staging system for chronic kidney disease (CKD)

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Chronic kidney disease is an epidemic facing most western countries, with annual dialysis growth rates ~6–8% per annum. There is an increasing awareness of the immense size of the patient group with kidney disease who do not require dialysis, as derived from analysis of population databases [1]. In a recent publication, the National Kidney Foundation sponsored Kidney Disease Outcomes Quality Initiative (KDOQI) working group proposed a set of guidelines regarding the definition, classification and evaluation of chronic kidney disease [2]. Using large representative databases of both referred and non-referred patients, and evidence-based examination of the literature, five stages of kidney disease have been defined. These stages correspond to the severity of kidney function loss and the prevalence of co-morbidities associated with kidney disease. Importantly, the classification system describes the stages according to level of estimated glomerular filtration rate (GFR), not serum creatinine levels, and advocates for the use of estimated GFR values to be used in evaluation of all patients. The new classification system does not suggest that all persons with kidney disease will require dialysis, nor that they will all progress through each stage; instead, the evidence reviewed suggests that patients with sustained low GFR are at increased risk for acute deterioration in function, and will have higher health resource utilization and death rates than the general population.

A recent set of international studies [3–5] and previous publications have demonstrated that there continues to be late referral to nephrologists by both primary care physicians and specialists, and that the majority of patients are referred with advanced kidney disease, often at average GFR levels of ~30 ml/min/1.73 m² (stage 3/4 CKD) [6–8]. Given the accumulating data regarding the increasing prevalence of risk factors for cardiovascular and progressive kidney disease at lower levels of GFR, current referral practices preclude the nephrology community’s attempt to prevent or delay progression of disease. Furthermore, and perhaps even more unsettling, is the finding that despite numerous guidelines to screen patients at high risk for CKD (diabetics and those with hypertension of cardiovascular disease) many patients remain unscreened or poorly characterized with respect to the extent of kidney disease [5,9,10].

There are numerous consequences of kidney disease prior to dialysis including hypertension, anemia, cardiovascular disease, mineral metabolism abnormalities and nutritional impairment [11–14]. Strategies for prevention of these consequences, which are associated with a high burden of illness and resource utilization, include public and professional education, policy change and influence, and increased research effort (basic, clinical and outcome based) [15,16]. Numerous barriers exist to implementation of intervention strategies, which include (i) continued late referral, (ii) paucity of data for some interventional strategies at all levels of kidney function, (iii) problems with measurement of the marker/screening tool for kidney function (serum creatinine) and (iv) unawareness of the problem due to confusing communication with patients, physicians and policy makers. The inaccuracy of serum creatinine as a marker for kidney function, and the confusing terminologies and approaches to kidney disease have undoubtedly contributed to the late referral, which in turn has contributed to the lack of large clinical trials in early kidney disease populations.

The purpose of this paper is to describe the advantages and rationale for a common terminology of CKD and its stages, as proposed by the NKF Working group in AJKD, February 2002 [2]. Many in the nephrology community may wonder if such a system is necessary, and have chosen to question the specific guidelines regarding estimation of GFR, and thus challenge the essence of the classification system [17–19]. This article attempts to contextualize the discussion within the current era of increasing awareness of kidney disease, describes the importance of the proposed system, the value of adopting objective and clear definitions, and the advantages of this approach. However, it also recognizes that there are limitations to any classification system. These limitations should be viewed as appropriate for research and refinement.
rather than immeasurable obstacles that preclude
the adoption of the classification system with many possible
advantages.

General issues: the value of precise definitions?
Definitions and terms are important in all aspects of
medicine to aid in communication and acquisition of
knowledge. Without precise definitions for diseases,
for stages of diseases or for treatment strategies the
study of medicine and ongoing research would be
chaotic. Imagine the treatment of Hodgkin’s lymphoma,
breast cancer or heart disease in the absence of
clear definitions, and staging and classification systems. The ability to describe with some precision,
irrespective of patient demographics, the extent of an
illness or condition, permits rational clinical action
plans to be developed and implemented. Furthermore, and perhaps most importantly, the development of
clear definitions and classification systems, allows the
systematic study of disease processes and by so doing,
Improves research clarity and applicability of results.

As much of the co-morbidity of dialysis patients
occurs prior to dialysis, interest in identification and study of this patient group has increased [11,20,21].
However, the lack of uniform terminology and
classification system for patients before dialysis has
led to problems in both identification and study interpretation for investigators. The imprecision in
clinical language has been mirrored in research studies,
which look at ‘chronic renal insufficiency’ (CRI)
patients, ‘pre-ESRD’ patients, ‘progressive renal insuf-
ficiency’ (PRI) patients and ‘CKD’ patients. Closer
examination of publications using these terms reveals a
range of kidney function from just below normal values
for GFR, to 10 ml/min/1.73 m² (truly, just prior to
dialysis). (The reader is referred to even this short
paper’s bibliography for an example of this). Results
and findings from such studies need to be interpreted
with caution, and the use of the term pre-ESRD or -PRI
refers to such a heterogeneous group of patients, that
there is clearly a need to define the terms in absolute,
and measurable ways; or else we should abandon the
words as imprecise and unhelpful.

Definitions should improve communication and clarity amongst health care professionals their patients
and public bodies. While the concept of GFR may appear ‘sophisticated’ it actually corresponds well to
percentage of kidney function: a concept that is
relatively simple for patients, non-specialists and lay
people. Operational definitions and staging of disease
permit clear and consistent classification of disease
states and action plans, which can be appropriately
tested and evaluated.

What is chronic kidney disease and why is it
important?
Chronic kidney disease is defined primarily as an
abnormality of kidney function or structure, as
determined by laboratory tests, urinalysis or imaging
tests which has been present for 3 or more months [2].
Kidney disease is characteristically asymptomatic, and
is often not diagnosed until relatively advanced.
Evidence is accumulating that chronic kidney disease
at any level is associated with poor outcomes [21–25].
Long-term outcomes are impacted by conditions and
risk factors that are present long before the initiation
dialysis. Given the modifiable risk factors identified in
patients with CKD (anaemia, hypertension, dyslipidae-
mia, abnormalities of calcium and phosphate, and
nutritional deficiencies) it would seem that accurate
identification of CKD populations would be important
[26–30]. The treatment of modifiable risk factors
depends on accurate screening of high risk populations:
thus, the need to identify those high risk populations at
appropriate time points in the continuum.

Essential aspects and components of the new
classification system
In order to appropriately study and intervene, a
clear terminology, applicable by patients, clinicians
(primary care providers, specialists and nephrologists)
and researchers is required. The proposed recent
terminology should ensure both a clear definition of
chronic kidney disease and a staging system, which is
simple, clear and differentiates groups of patients.

The essential components of the proposed new
system are based on a rigorous evidence review process,
database analysis (population and referred patient
groups) and public review process of international and
multidisciplinary breadth. The essential components to
the guidelines included the following.

(i) Kidney function should be estimated using
formulae, from serum creatinine, given that
serum creatinine is so imprecise that errors in
patient identification and assessment occur using
it as a sole assessment of kidney function.
(ii) Urine sediment abnormalities (such as albumin:
creatinine ratios) are an important component of
the evaluation of patients with CKD.
(iii) The severity of staging (1 through to 5) is based
on increasing prevalence of abnormalities asso-
ciated with kidney disease, and the stages can be
described relatively clearly, according to levels
based on ranges of GFR.

Details of the generation of the staging system
The findings and conclusions of the work group/task
force were based on an analysis of NHANES III data
supplemented by data from other large databases
including the MDRD study and the Canadian study
of patients prior to dialysis [31,32]. Using the
databases, rigorous analyses were conducted to
describe the prevalence of abnormalities based on
categories of GFR, which had been determined by
transformation of serum creatinine using an abbreviated MDRD formula. This strategy led to a set of proposed categories, based on cut points, which were based on population data obtained from the NHANES sample in the US. The categories appear consistent when applied to independent samples, in that they define different prevalences of co-morbidities associated with kidney disease [3].

A few caveats, and areas of controversy

Accuracy of serum creatinine

First, the use of serum creatinine is widely acknowledged as an inaccurate measure. It is well known that > 50% of functioning nephron mass must be lost prior to a perceivable change in serum creatinine [33], and that the absolute levels need to be interpreted within the context of muscle mass and gender. Thus, serum creatinine alone as a measure of kidney function (GFR) is a poor tool. Since as early as 1976, this has been acknowledged and attempts at prediction equations for GFR or creatinine clearance have been developed [34]. The new staging system recommends use of specific formulae; and warns about potential problems with actual creatinine assay measurements. However, as none of the formulae have been validated on the heterogeneous populations in which they will be used, this recommendation has fostered some debate [17–19,35].

With respect to the measurement issue, Coresh et al. [36] have nicely addressed this issue in a recent paper, and call for laboratory standardization and calibration of creatinine measurement techniques in the laboratory. This will avoid further bias when using the serum creatinine value to estimate GFR.

Irrespective of the formula used [i.e. Cockcroft–Gault, or modified MDRD (Modified Diet in Renal Disease), Nankivell or Schwartz formulae, the important issue is that any calculation is a better estimate of kidney function that serum creatinine alone. The purpose of the guidelines emphasis on estimated GFR is to improve the identification of kidney disease by transforming serum creatinine into a more meaningful measure. The implications of this approach and improvement in identification of significant kidney impairment were demonstrated in a recent paper [37]. The authors demonstrated not only that a single time point measurement of creatinine when transformed could be interpreted as significantly abnormal, but of those patients with abnormal kidney function, previous values tabulated up to 4 years demonstrated previously a steady decline in kidney function, despite normal range values for serum creatinine; this was true for over 20% of the population in whom there was available data.

The advantage remains that standardized methods of describing the level of kidney function by using estimates of GFR, allows a categorization of patients into definable groups for future clinical care or research study. Furthermore, the educational potential of contextualizing the raw number of serum creatinine into kidney function (which is associated with so many adverse outcomes) is critical to increasing awareness of the problem of kidney disease.

Validation of stages

The stages of CKD are defined by using ranges of estimated GFR, based on analysis of NHANES III data which examined the prevalence of abnormalities associated with kidney disease (causes or consequences: anaemia, hypertension, abnormalities of calcium and phosphate, physical exercise, quality of life, etc.) (Table 1 and Figure 1). The stages are defined currently using the best data available from these large population-based cohorts of patients.

While it is possible that some refinement in the exact cut points may occur as more data accumulates, there is some clarity that the current staging brings to this disease process. Furthermore, the implementation of the staging system permits more observations to be made, so that testing of the hypothesis that specific characteristics which define the state of simply ‘low GFR’ vs important, clinically relevant disease can be undertaken.

It is important to recognize that the data analysis and staging system generated thereby, did not test whether all patients in specific stages would progress

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<th>Table 1. Chronic kidney disease: a clinical action plan</th>
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*aActions are not confined to specific stages, and should be additive. Adapted from Reference [2].
to ESRD, but simply described the presence of abnormalities related to CKD, and the prevalence of each of these as increasing at lower levels of kidney dysfunction.

In so doing, a series of long-term research questions for investigators may be more clearly defined: what is the impact of specific interventions in stage 2 vs 3 CKD on progression of CKD or morbidity; what is the outcome of patients identified but not referred to specialists at specific stages; what is the current prevalence of 'CKD' as defined with the current system in high risk groups, and does this portend a worse outcome. Research agendas can now be articulated around understanding key components of modifiable risk factors and their impact on patient outcomes, using a clear and reproducible system.

Mislabelling

The potential impact of mislabelling of individuals who have low GFR but not disease (i.e. no associated abnormalities, low risk of progression, etc.) has further fuelled the discussion as to the utility of adopting the philosophy of insisting on new laboratory standards to estimate GFR, and thus questions whether the proposed staging system should be adopted worldwide. There are implications for individuals (labelling, insurance coverage issues, adoption of sick role) for being labelled as having reduced kidney function if indeed they do not have any other abnormalities. However, given the accumulating evidence supporting the adverse prognostic effect of low GFR, independent of other factors known to impact outcomes [22,25] the level of GFR appears to be important, and the risks of mislabelling outweigh the potential benefits from a disease awareness perspective. The guidelines do define chronic kidney disease as abnormalities in existence for >3 months, and thus the mislabelling of patients whose GFR levels are transiently decreased, is avoided. It may be that those patients in whom low GFR occurs during illnesses have less good outcomes (the reduction in GFR may be construed as a ‘stress’ test), but, rather than discarding the proposed new system, this particular issue could be studied in a systematic manner.

The identification of low GFR states may allow the implementation of simple measures to prevent worsening of GFR (e.g. use of nephrotoxic drugs, radiocontrast dye, excessive diuresis). For these reasons, it may be prudent to adopt the system of defining kidney disease according kidney function, not serum creatinine values.

Predicting outcomes

Furthermore, and perhaps most importantly, given the paucity of data regarding predictors of progression at different stages, impact of interventions at different stages of disease, the staging system allows the design and execution of clinical trials and long-term observational studies. The value of the KDOQI analyses and proposed classification system, in conjunction with the review of other existing data,
is the heightened awareness of all to the consequences of kidney disease, and the need to identify it early.

Summary

The need for clarity of definition, common terminology and a simple staging system lies in its immense potential to aid in the earlier identification of kidney disease. In so doing, there will be a heightened awareness of the prevalence of CKD (already identified to be much higher than that identified by elevated serum creatinine measures alone). That recognition, and the action plan identified with the staging system will lead clinicians to screen for risk factors for cardiovascular disease and progressive kidney disease, and ideally to institute appropriate therapies in a timely manner. The issues of mislabelling of the elderly patients needs to be assessed in more detail. It will be important to develop an explicit research agenda to understand the implications of these guidelines on physicians, patients and the health care system. This in itself could be considered an advantage of adopting the system at this point in time.

The outcomes of patients on dialysis as changed little over the past decades, despite improvements in technology and awareness of the complexity of CKD. Recent awareness of need for earlier identification, and thus referral to nephrology teams is predicated on more accurate tools (i.e. estimated GFR formula). Understanding of disease processes requires well-designed clinical trials, using easily applicable patient demographic descriptors. The proposed new staging system and uniform terminology allows both clinicians and researchers to understand, treat and explore the spectrum of kidney disease.

The advantages of a uniform technology for the definition and staging of CKD are numerous in the realms of public education, clinical care, observational and interventional research. Despite the perceived shortcomings or nuances of specific formula, issues with calibration of serum creatinine, the proposed system may well allow a more accurate assessment of the true implications of abnormal kidney function, the prevalence of associated illness with CKD within and between countries, and foster strategies which allow the implementation of strategies to delay progression or treat the co-morbidity associated with abnormalities of kidney function. Failure to agree upon a common terminology, while recognizing its limitations, may retard our ability to pursue important clinical questions.

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**Editorial note**

We would like to draw the attention of our readership to the fact that more and more nephrologists are using the term ‘CKD’ in place of the well-known and long used term ‘CRF’ (chronic renal failure), in accordance with recent K/DOQI guidelines. In so doing, patients with renal disease but still normal GFR may be confused with those who have reduced GFR. For the sake of clarity therefore, when using the term ‘CKD’, it is indispensable to indicate the precise stage.