Dissecting and refining the staging of chronic kidney disease

Christopher G. Winearls[1] and Richard J. Glassock[2]

[1]Oxford Kidney Unit, The Churchill, Oxford Radcliffe Hospitals NHS Trust, University of Oxford, Headington, Oxford, UK and [2]The David Geffen School of Medicine at UCLA, Laguna Niguel, California, USA

The current Kidney Disease Outcomes Quality Initiative (KDOQI) staging system of chronic kidney disease (CKD) is simple but too rigid to accommodate variations in renal function observed in the general population. The formula most commonly used to estimate renal function is not validated in subjects without *a priori* evidence of renal disease. Their combined use results in inappropriate diagnosis of CKD and improbable estimates of prevalence rates. Although this initiative has raised the profile of kidney disease, the exaggeration of the scope of the problem could distract nephrologists from their specialist role. The nephrology community needs a revised staging system for CKD that allows accurate, effective, and timely communication with patients, primary care doctors, public health physicians, and policy makers. Its single most important function will be to identify those patients who will benefit from targeted screening and effective and safe interventions. We offer for discussion a modified definition and staging system of CKD based on the presence of unequivocal, irreversible structural kidney disease, the presence or degree of impairment of kidney function, and the consequences thereof.

Kidney International (2009) **75,** 1009–1014; doi:10.1038/ki.2009.49; published online 25 February 2009

KEYWORDS: chronic kidney disease; definition and staging of CKD; KDOQI

Correspondence: *Christopher G. Winearls, Oxford Kidney Unit, The Churchill, Oxford Radcliffe Hospitals, NHS Trust, Old Road, Headington, Oxford OX3 7LJ, UK. E-mail: Chris.Winearls@orh.nhs.uk*

Received 10 July 2008; revised 26 November 2008; accepted 7 January 2009; published online 25 February 2009

In the past, the work of clinical nephrologists was largely centered on the care of patients with 'end stage' chronic renal failure and life-threatening acute kidney injury. Attention to those patients with untreatable diseases en route to 'end stage' chronic renal failure was perfunctory until it was shown that progression could be slowed and complications of renal insufficiency mitigated. Chronic kidney disease (CKD) now receives appropriate attention in the expectation that early diagnosis will allow implementation of measures to delay the onset of, and reduce the incidence of 'end stage' chronic renal failure, and prevent presentation with advanced uremia at the eleventh hour. Treatment of complications and emphasis on the mitigation of cardiovascular risk factors should reduce the morbidity and mortality of this chronic life damaging and shortening illness.

To design a strategy to manage CKD needed a definition and diagnostic criteria. The 2002 Kidney Disease Outcomes Quality Initiative (KDOQI) staging guidelines utilizing the Modification of Diet in Renal Disease (MDRD)-derived estimate of glomerular filtration rate (eGFR) from serum creatinine concentration was a much needed start. Unfortunately both components have flaws, which undermine their laudable objectives and detract from their benefits.[1,2]

Since its publication, the KDOQI construct has been used as a two-dimensional grid to estimate the prevalence and burden of CKD worldwide.[3] The significance of these estimates were difficult to assess because the definition itself determines the prevalence, which in turn is inversely related to the thresholds of the diagnostic criteria. In practice, what has often been provided is the distribution of values for single measurements of eGFR in various populations without applying the test of chronicity. Many clinical nephrologists found the subsequent announcements that 1:10 of the citizens in the communities they served were suffering from CKD implausible.

It has also been justified as a cardiovascular risk tool. Although there is an association between kidney dysfunction (as assessed by eGFR and/or proteinuria) and cardiovascular risk, a causal relationship has not been proven; the effect is largely confined to patients with overt renal failure (eGFR < 45 ml/min per $1.73\,m^2$) and there are as yet no therapeutic implications. There is also a relationship of albuminuria with cardiovascular risk, although a direct cause

and effect relationship also remains unproven. Abnormal albuminuria may simply be a marker of a generalized disturbance of endothelial cell function and a risk factor for future cardiovascular events. A risk factor is not a disease.[4]

The next difficulty was the use of the KDOQI-CKD definition and staging system in clinical practice and its application to individual patients. It proved quite blunt and caused difficulties with the use of the word 'disease.' Reservations and dissatisfaction with this construct are growing,[4–11] and have most recently been clearly articulated by Bauer *et al.*[11] In this perspective, we rehearse the reasons for dissatisfaction. The criticisms of the KDOQI-CKD construct are directed both at the premises that underlie its design and its performance in clinical practice. Herein, we propose a modified basis for designing a staging system and offer a working option for consideration by the nephrology community.

OBJECTIONS TO THE PREMISES THAT UNDERLIE THE KDOQI DEFINITION AND STAGING SYSTEM FOR CKD

1. Although described as a staging system, it is actually a grading system based on arbitrary bands of eGFR values.

The KDOQI-CKD system is numerical,[1–5] and linear from stages 1 to 3, implying a smooth progression from one stage to the next three stages. Although there is a qualitative difference between the first two and the next three, the system relies heavily on eGFR creating overlap between stages. This is a particular problem for stage 3 (eGFR 30–59 ml/min per 1.73 m^2), which includes the steepest part of the eGFR/CKD relationship and will allocate the same stage to individuals with chronic renal insufficiency as that to individuals with inconsequential reduction in kidney function. The weakness of the staging system is that it is largely unidimensional.

2. The system asserts that the normal GFR is >90 ml/min per 1.73 m^2 in both genders and across the adult age range in all ethnic groups, and that an eGFR <60 ml/min per 1.7 m^2 is pathological. This ignores the difference between a reference and a normal range.

The KDOQI-CKD staging system is based on the premise that the lower limit of normal GFR (and eGFR) in man is 90 ml/min per 1.73 m^2. This relies on the data in the young individuals reported in the 1950 paper of Davies and Shock[12] using inulin clearance in just 72 hospitalized men (no women), and the 1969 studies of Wesson.[13] This conclusion ignores biological variation, and the redundancy and reserve in GFR with which most humans are endowed.

The staging bands of GFR are absolute and arbitrary, and are at variance with observations of both formally measured[14] and estimated GFR in the population.[15]

It declares an eGFR of <90 and >60 ml/min per 1.73m^2 as being 'mildly' reduced. In fact, in population studies the majority of individuals (younger males being the exception) have eGFRs of <90 ml/min per 1.73 m^2.[14]

3. The system ignores the age-related changes in GFR.

Population surveys have shown a consistent age-related reduction in GFR and eGFR, which is apparent before old age.[14,15] The estimates from iothalamate GFR measurements suggest a reduction beginning from the age of about 20 to 30 years, by 4.6 ml/min per decade in men and by 7.1 ml/min in women.[15] We believe that this decline in GFR with age is a natural and not a pathological phenomenon. Indeed, there are morphological and functional differences in the kidneys of the elderly compared with those of the young, which are explained in part by differences in their vasculature. As this is a generalized phenomenon observed in all circulations and in all elderly individuals, it is a semantic point as to whether this represents a natural process of tissue and organ senescence or a form of pathology.[16] The consistency of the changes supports the view that they are fundamentally related to natural organ senescence. Of course, other diseases, such as diabetes and hypertension, can be superimposed on the natural aging process and influence the decline of GFR and the prevalence of CKD. Older individuals are undoubtedly at much higher risk of suffering from CKD.

4. The system has been linked to an imprecise estimating measurement of GFR, the four-variable MDRD formula.

The MDRD formula was originally derived from studies on US patients with known CKD participating in a clinical trial. It was not validated in patients of different ages, habitus, or ancestry; yet it is now being applied to diverse populations without proven kidney disease whose serum creatinine concentrations are much lower than those used in the derivation of the formula. The laboratory method of measuring the serum creatinine concentration is also important, particularly its calibration to a known standard of reference. This imprecision in determining eGFR in patients without kidney disease has been shown to be as much as -30% of the true GFR. Although many laboratories warn clinicians of the tendency of the formula to underestimate the true GFR, the results of the calculations will be taken at face value. If eGFR is to be central to a diagnostic system it has to be more accurate. Given the serious consequences of true CKD, 'false' diagnoses are unacceptable. An additional issue is the applicability of the equation to groups with ancestry and culture divergent from the population from which the formula was derived. Studies in groups not well represented in the original sample from which the MDRD equation was derived have shown significant discrepancies, leading to 'misclassification' of those of the CKD stage.[17] For example, in a carefully performed population-based study from China, about two-thirds of patients were misclassified as having stage 3 instead of stage 2 CKD, when eGFR was compared with a reference GFR standard. A Chinese-specific adaptation of the MDRD formula was developed, which classified the CKD stage of these Chinese patients much more accurately.[18]

5. The system defines and allows diagnosis of three stages of CKD on eGFR alone.

Defining a disease on a laboratory measurement alone is at odds with the traditional clinical method, which requires

integration of a formally obtained history, a physical examination and appropriate investigation to reach a working diagnosis, and to estimate a prognosis. The designation of 'disease' also infers that the identified property conveys some material 'disadvantage' (survival, morbidity) to the individual compared with other similar individuals not showing the property. We suggest that if the level of eGFR is a sole criterion for diagnosing CKD, any choice of an absolute threshold value is bound to be diagnostically imprecise. Given the redundancy in renal functional capacity in mammals, it is reasonable and appropriate to ask what degree of GFR reduction would be patho-physiologically significant (for example, confering a unique disadvantage)? We suggest that this would be a level insufficient for maintaining homeostasis. Some of the objective evidence for 'insufficiency' would be abnormal sodium balance causing hypertension, a blunted erythropoietin axis causing anemia, disturbed vitamin D, calcium, and phosphate balance causing secondary hyperparathyroidism. These derangements are very common if not universal when the GFR is <30 ml/min per 1.73 m^2, but their prevalence is variable and unpredictable in individuals with eGFR values above this threshold.[19] At an eGFR of <30 ml/min per 1.73 m^2 the serum creatinine concentration is invariably increased above the normal range for gender even in aged persons.

PROBLEMS ARISING FROM THE USE OF THE KDOQI-CKD CLASSIFICATION SYSTEM WITH MDRD eGFR IN CLINICAL PRACTICE

The normal range of GFR implicit in the KDOQI-CKD staging system and the use of the MDRD formula to estimate it create anomalies, which challenge its validity for classifying, staging, and assessing CKD in individuals. Exceptions *prove*, by which is meant *test*, rules.

1. Examination of the data of the National Health and Nutrition Examination Surveys from the USA shows that a minority of the population >60 years of age have a 'normal' GFR (defined as >90 ml/min per 1.73 m^2) and about 25% of individuals >70 years have eGFRs <60 ml/min per 1.73 m^2 and so are automatically classified as having CKD, irrespective of the presence or absence of features suggesting 'kidney damage,' for example, proteinuria.[20]
2. Patients with very different eGFR values will be classified as having the same stage of CKD. For example, a 20-year-old man with an eGFR of 35 ml/min per 1.73 m^2, macroproteinuria, and deteriorating renal function is classified as having the same stage of CKD (stage 3 CKD) as a 70-year-old woman with an eGFR of 55 ml/min per 1.73 m^2 with no supporting evidence of kidney disease. The young male has significant renal impairment with an eGFR of $\sim$30% of that predicted for age and gender, whereas the older woman has an eGFR close to the average for her age. The implications for each of them are completely different.
3. There are inconsistencies in the differences in the prevalence rates of the stage of CKD. The prevalence rates of stages 4 and 5 CKD (unequivocal renal failure) are about the same ($\approx$0.2–0.4% of the US population), whereas stage 3 CKD is 10–20 times more common at 4.2%. This suggests that stage 3 CKD is not simply a stage in the evolution of CKD but a state that seldom progresses to kidney failure. Indeed follow-up of patients classified as having stage 3 CKD has shown this to be true.[21] In addition, in the KDOQ-CKD system patients are classified as having stage 3 CKD even in the absence of proteinuria or other features of 'kidney damage'. It is well known that when proteinuria is present along with moderately depressed eGFR (30–59 ml/min per 1.73 m^2), the likelihood of progression to later stages of CKD is greatly enhanced.[22] Similarly, it appears that it is the presence of micro-albuminuria, and not the eGFR, which is the marker of cardiovascular risk in patients with CKD stages 1–3.[23] Another paradox is that CKD stages 3–4 are found to be more common in women, but stage 5 CKD (unequivocal kidney failure) is much more common in men.
4. The unreliability of eGFR measurements >60 ml/min per 1.73 m^2 has led to a policy not to give a precise value for eGFR if it is >60 ml/min per 1.73 m^2 and to report it as such. Nephrologists have long complained that reliance on a 'normal' plasma creatinine concentration has meant that a substantial loss of kidney function of up to 50% is not appreciated. Ignoring eGFR values of >60 ml/min per 1.73 m^2 leads to making the same error. This lack of confidence in eGFR is also admitted by the fact that it is not recommended for use in individuals being considered as kidney donors who have formal measurements of GFR using isotopes or iothalamate.[24]
5. The unreliability of eGFR values $>$ 60 ml/min per 1.73 m^2 removes any justification for differentiating between CKD stages 1 and 2.
6. The majority (74% in one study) of live kidney donors will have eGFR values of <60 ml/min per 1.73 m^2 following donation of a single kidney and they will therefore be labeled as having CKD stage 3.[25]

A proposed modified staging system of CKD for debate

The purpose of this and any CKD staging system should be to inform the patient and doctor of the consequences of kidney disease, by describing its severity, its prognosis and implications for management (Table 1). The following proposal is based on a recognition of the differences among kidney disease, reduced kidney function, and kidney insufficiency. There is a need to avoid the conflation of these different states inherent in the KDOQ-CKD construct. These proposals are not novel as they have been described in principle by Poggio and Rule.[9] They may provide a structure that is more congruent with the clinical condition of the patient and avoids the adverse consequences of the simpler K/DOQI-CKD system.

Table 1 | A proposed new CKD staging system

Stage[a,b]	Description	Kidney function	Diagnostic evidence	Implications
1	Structural disease with normal kidney function	eGFR greater than fifth percentile for healthy matched patients	Macro-albuminuria and/ or glomerular hematuria Abnormal histology Abnormal imaging	Assessment for precise diagnosis and management
2[c]	Structural disease with reduced kidney function and reserve, but without clinically evident functional insufficiency	eGFR less than fifth percentile for healthy matched patients, but >30 ml/min per 1.73 m^2	Macro-albuminuria and/or glomerular hematuria Abnormal histology Abnormal imaging No complications of reduced kidney function	As above, but require monitoring of rate of change of kidney function, and testing for consequences of kidney insufficiency Awareness of lack of reserve
3[c]	Structural disease with insufficient kidney function for health (chronic renal failure/ insufficiency)	15–30 ml/min per 1.73 m^2 [c]	Structural disease present or inferred Complications of reduced kidney function	Active management of complications of insufficiency Planning for renal replacement treatment or not
4	Severe structural disease with life-threatening deficiency of kidney function	<15 ml/min per 1.73 m^2	Structural disease present or inferred	Close monitoring for triggers to start RRT or enrollment in a conservative care program
5	Advanced/complete destruction	Dialysis dependent	Not applicable	Specialist supervision

CKD, chronic kidney disease; eGFR, estimate of glomerular filtration rate; RRT, renal replacement treatment.
[a]The suffix 'P' could denote 'progression'.
[b]The suffix 'T' could denote renal transplant recipient.
[c]The distinction between stages 2 and 3 should be clinical rather than based on absolute eGFR. Patients would be tested for evidence of functional consequences of renal insufficiency (metabolic and endocrine). If present they would be placed in stage 3 irrespective of eGFR, which may be >30 ml/min per 1.73 m^2.

'CKD' is a term that should be applied only to individuals in whom there is a specific, persisting, irreversible, pathology of the kidney(s) recognized by (i) morphological abnormalities on histology or imaging and/or, (ii) persistent abnormalities in the composition of the urine, such as macro-albuminuria and/or hematuria or (iii) a reduction in kidney function causing effects attributable to functional insufficiency. So defined, CKD will also include at least a potential for progression to 'end stage' chronic renal failure. The incorporation of the word *disease* within the term CKD is justified because the described abnormalities represent a present or potential disadvantage.

'Reduced kidney function' in this concept of CKD would be established by the finding of an eGFR less than fifth percentile for healthy individuals of similar age, gender, and ancestry.

The term chronic renal failure/insufficiency is used to mean the state in which there is a reduction in overall kidney function, such that there are defects in kidney-dependent homeostasis causing clinical and metabolic consequences in proportion to the severity of the reduction.

We believe that three principles should be embodied in any staging system of CKD.

1. The stages should have a sequence that reflects the severity of renal injury, the degree of functional impairment, the risk of complications, and progression.
2. It should recognize that evidence of disease will usually be both structural (including imaging and/or pathology) and based on laboratory testing for signs of kidney injury (such as macro-proteinuria and hematuria or both), and in the later stages, functional (for example, GFR related). The degree of reduction in function should be used for staging and not diagnosing CKD
3. Any eGFR value used for staging should be referenced to age and gender percentiles, based on available data (which may ultimately be shown to differ between ancestral and geographical groups and require special adaptations of the eGFR-estimating formulas). At least two values separated by 3 months or more could be retained as the arbitrary standard for defining 'chronicity', but this requires further debate.[26]

As described below, evidence of kidney damage should be *a sine qua non* for the diagnosis of CKD, with renal function (eGFR) function conserved in stage 1; reduced but sufficient for health and homeostasis in stage 2; insufficient for health in stage 3; and a threat to life in stage 4. Stage 5 would apply to those patients receiving dialysis treatment. Whether this staging system should be applied to renal transplant recipients is debatable, as almost all of them will have a single kidney with some degree of renal injury. If it were so they could be categorized at the appropriate stage of CKD as above, but with the modifying suffix (T).

Stage 1 CKD would be applied to the early form of structural disease identified by histology, imaging, or inferred from laboratory evidence of kidney damage including, for example, persistent macro-albuminuria, but without any associated reduction in renal function. The eGFR should be greater than fifth percentile for the age and gender of the patient (preferably using an ancestrally specific estimating formula). Examples include adult polycystic kidney disease in young adults, or many forms of glomerular, interstitial, or vascular diseases.

Stage 2 CKD would also require evidence of overt kidney damage, but in addition a reduction in kidney function (eGFR less than fifth percentile for age and gender). For

consistency with K/DOQI the cutoff from stage 3 could be an eGFR of 30 ml/min per 1.73 m^2. We acknowledge that this is arbitrary. We suggest that if evidence of a clinically relevant complication or consequence of reduced kidney function (for example, anemia) is present, the patient should be placed in stage 3.

Stage 3 CKD would include patients in whom the eGFR lay between 15 and 30 ml/min per 1.73 m^2. Evidence of kidney injury would almost certainly be present, as would complications of renal insufficiency. This higher stage takes account of the higher risk of such patients progressing to stage 4 CKD. This is the stage at which there will be preparation for renal replacement treatment and the most active management of complications.

Stage 4 CKD would only require that the eGFR be less than 15 ml/min per 1.73 m^2, a GFR below which it is generally accepted that there is a significant risk to the life and health of the patient. (Common sense allows one to infer the presence of structural disease and complications.) Such patients will automatically be under the care of a nephrologist unless renal replacement treatment is not intended, in which case responsibility for palliative care should be shared or devolved.

Stage 5 CKD would be applied to patients receiving regular renal replacement therapy in the form of hemodialysis or peritoneal dialysis.

Patients with renal transplants and varying degrees of kidney damage and/or eGFR will be categorized at the appropriate stage of CKD as above, but with the modifying suffix (T). Thus, a 65-year-old patient who had received a renal transplant 5 years earlier and whose eGFR is 40 ml/min per 1.73^2 and who had 2+ proteinuria would be categorized as having stage 2 CKD (T).

Patients with an eGFR less than fifth percentile but >30 ml/min and without any evidence of structural renal disease (that is, normal imaging, no urinary abnormalities) and no evidence of complications should not be described as having chronic kidney disease but as having 'isolated reduced kidney function of uncertain significance.' This description will accommodate a significant minority of the elderly patients who have undergone unilateral nephrectomy and those who have a non-renal cause of a reduced GFR, such as heart failure or hepato-renal syndrome. They require regular re-measurement of eGFR to establish whether their renal function is stable, and they and their doctors should be aware of the lack of renal reserve when drugs are prescribed, surgery is performed, or intercurrent acute illnesses supervene.

It should be emphasized that we have specifically excluded patients with isolated urinary albumin excretion rates below that readily detected by semi-quantitative methods ('dipstick' positive proteinuria) but above the normal urine albumin excretion rate, also known as microalbuminuria, or reduced GFR (age/gender corrected) without any collateral evidence of kidney injury from the definition of CKD. The exclusion of isolated 'microalbuminuria' from the definition of CKD is bound to be controversial. However, it is our contention that such albuminuria is a manifestation of a systemic disturbance affecting all microcirculations and this does not justify it being a sufficient diagnostic criterion for chronic kidney disease.[27] Thus an obese person with a normal eGFR and 'microalbuminuria' would not be considered to have CKD in this construct unless there is histological proof.[28] Similarly, a diabetic patient with a normal eGFR and 'microalbuminuria' would not be labeled as having CKD. Both patients would be regarded as being at increased risk for developing CKD and also of manifesting cardiovascular disease at a future point in time.

FURTHER RECOMMENDATIONS

There is a clear and pressing need for a more reliable method for the estimation of GFR in individuals with serum creatinine concentrations in the upper part of the normal range. Perhaps serum cystatin C level measurements will help eventually meet this need.

Percentile charts of eGFR in healthy individuals over the full age range and in both genders and in different populations are needed.[15] These age- and gender-specific percentile charts should be made available in primary care not only to allow selection of patients requiring referral, but also to track the progress of patients diagnosed with CKD to trigger referral when a stage requiring specialist input is reached or an unpredicted deterioration is observed.

All patients with stage 1 CKD should be assessed either in person or by data review by a nephrologist, and a decision reached as to whether specialist assessment is required for appropriate evaluation such as renal biopsy, genetic testing, or additional imaging studies. All patients with stage 2–4 should be under the care of, or at the very least have access to, the advice of a nephrologist. The decision as to whether specialist follow-up is required will be based on the likely 'added value' of attendance at a specialist clinic, for example, to institute interventions that may halt the disease process, start or modify measures designed to delay progression, or mitigate complications. There would be merit in further refining the staging system with a suffix such as 'P' to indicate the risk of progression, the indicators of which have recently been discussed by Taal and Brenner.[29] This will free nephrologists of the burden of monitoring stable patients. All patients with progressive stage 3 CKD should be seen regularly by a nephrologist, in order to determine the need for and the timing of preparation for renal replacement treatment. All stage 4 CKD patients will be under the care of a nephrologist unless a co-morbidity such as advanced malignant disease makes this inappropriate.

DISCLOSURE

All the authors declared no competing interests.

REFERENCES

1. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002; **39**(Suppl 2): S1–S246.

2. Levey AS, Coresh J, Greene T *et al.* Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med* 2006; **145**: 247–254.
3. Glassock RJ, Winearls CG. The global burden of chronic kidney disease: how valid are the estimates? *Nephron Clin Pract* 2008; **110**: c39–c46.
4. Clase CM, Garg AX, Kiberd BA. Classifying kidney problems; can we avoid framing risks as diseases? *Br Med J* 2004; **329**: 912–915.
5. Couser WG. Chronic kidney disease the promise and the perils. *J Am Soc Nephrol* 2007; **18**: 2803–2809.
6. Kiberd B. The chronic kidney disease epidemic: stepping back and looking forward. *J Am Soc Nephrol* 2006; **17**: 2967–2973.
7. Kallen AJ, Patel RR. In search of a rational approach to chronic kidney disease and management. *Kidney Int* 2007; **72**: 3–5.
8. Williams B, Rodger RSC (eds). Consensus Conference On Early Chronic Kidney Disease. *Nephrol Dial Transplant* 2007; **22**(Suppl 9): ix1–63.
9. Poggio ED, Rule AD. Can we do better than a single estimated GFR threshold when screening for chronic kidney diseases? *Kidney Int* 2007; **72**: 534–536.
10. Eknoyan G. Chronic kidney disease definition and classification: the quest for refinements. *Kidney Int* 2007; **72**: 1183–1185.
11. Bauer C, Melamed ML, Hostetter TH. Staging of chronic kidney disease: time for a course correction. *J Am Soc Nephrol* 2008; **19**: 844–846.
12. Davies DF, Shock NW. Age changes in glomerular filtration rate, effective renal plasma flow, and tubular excretory capacity in adult males. *J Clin Invest* 1950; **29**: 496–507.
13. Wesson LG. *Physiology of the human kidney*. Grune and Stratton: New York, 1969 712pp.
14. Rule AD, Gussak HM, Pond GR *et al.* Measured and estimated GFR in healthy potential kidney donors. *Am J Kidney Dis* 2004; **43**: 112–119.
15. Wetzels JFM, Kiemency LALM, Swinkels DW *et al.* Age-and gender specific reference values of estimated GFR in Caucasians: the Nijmegen Biochemical Study. *Kidney Int* 2007; **72**: 632–637.
16. Darmady EM, Offer J, Woodhouse MA. The parameters of the ageing kidney. *J Pathol* 1973; **109**: 195–207.
17. Barai S, Gambhir S, Prasad N *et al.* Levels of GFR and protein-induced hyperfiltration in kidney donors: a single centre experience in India. *Am J Kidney Dis* 2008; **51**: 407–414.
18. Ma YC, Zuo L, Chen JH *et al.* Modified glomerular filtration rate estimating equations for Chinese patients with chronic kidney disease. *J Am Soc Nephrol* 2006; **17**: 2937–2944.
19. Clase CM, Kiberd BA, Garg AX. Relationship between glomerular filtration rate and the prevalence of metabolic abnormalities: results from the Third National Health and Nutrition Examination Survey (NHANES III). *Nephron* 2007; **105**: c178–c184.
20. Coresh J, Selvin E, Stevens LA *et al.* Prevalence of chronic kidney disease in the United States. *JAMA* 2007; **298**: 2028–2047.
21. Erikson BO, Ingebretsen OC. The progression of chronic kidney disease: a 10 year population-based study of the effects of gender and age. *Kidney Int* 2006; **69**: 375–382.
22. Ishani A, Grandits GA, Grimm RH *et al.* Association of single measurements of dipstix proteinuria, estimated glomerular filtration rate, and hematocrit with 25-year incidence of end stage renal disease. *J Am Soc Nephrol* 2006; **17**: 1444–1452.
23. Brantsma AH, Bakker SJL, Hillege HL *et al.* Cardiovascular and renal outcome in subjects with K/DOQI stage 1–3 chronic kidney disease: the importance of urinary albumin excretion. *Nephrol Dial Transplant* 2008; **23**: 3851–3858.
24. Rule AD, Larson TS, Bergstralh EJ *et al.* Using serum creatinine to estimate glomerular filtration rate: accuracy in good health and chronic kidney disease. *Ann Intern Med* 2004; **141**: 929–937.
25. Wan RK, Spalding E, Winch D *et al.* Reduced kidney function in living kidney donors (letter). *Kidney Int* 2007; **71**: 1076.
26. Eriksen BO, Ingebretsen OC. In chronic kidney disease staging the use of the chronicity criterion affects prognosis and rate of progression. *Kidney Int* 2007; **72**: 1242–1248.
27. Deckert T, Feldt Rasmussen B, Borch Johnsen K *et al.* Albuminuria reflects widespread vascular damage. The Steno Hypothesis. *Diabetologia* 1989; **32**: 219–226.
28. Sera A, Romero D, Lopez D *et al.* Renal injury in the extremely obese patients with normal renal function. *Kidney Int* 2008; **73**: 947–955.
29. Taal MW, Brenner BM. Renal risk scores: progress and prospects. *Kidney Int* 2008; **73**: 1216–1219.