# LABORATORY INVESTIGATION OF CHRONIC KIDNEY DISEASE

*Reduction in kidney function is associated with considerable morbidity and mortality.*

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The kidney plays an essential role in the maintenance of homeostasis in the human body and therefore a reduction in kidney function is associated with considerable morbidity and mortality. The consequences of kidney disease include decreased kidney function, the development of kidney failure and a high incidence of cardiovascular disease in these patients. The high prevalence of diabetes mellitus and hypertension in the developed and developing world contributes significantly to the high incidence of kidney disease, making it a common health problem. Early identification of kidney disease is important to prevent or lessen complications, as well as to delay the progression to renal failure. It is important for the family doctor to identify and treat the risk factors in the development of kidney disease, to diagnose and stage chronic kidney disease and to have an appropriate plan for the management of chronic kidney disease.

## CLASSIFICATION AND STAGING OF RENAL FAILURE

Renal failure is divided into either acute renal failure (ARF) or chronic kidney disease.

### Acute renal failure

ARF is diagnosed when renal function declines rapidly over hours to days. Types of ARF include prerenal renal failure, intrinsic renal ARF and postrenal ARF (Table I).

Table I. **Types of acute renal failure**

| Types | Example |
|---|---|
| Prerenal ARF | • Hypovolaemia, e.g. dehydration, gastrointestinal fluid loss, renal fluid loss<br>• Decreased effective plasma volume, e.g. sepsis, shock, sequestration into extravascular space<br>• Decreased cardiac output, e.g. congestive cardiac failure, pulmonary embolism<br>• Renovascular obstruction, e.g. atherosclerosis, stenosis |
| Intrinsic renal ARF | • Glomerular and small-vessel disease, e.g. glomerulonephritis and vasculitis<br>• Acute tubular necrosis, e.g. post-ischaemic, nephrotoxins, rhabdomyolysis<br>• Interstitial nephritis, e.g. infections, infiltrations, drugs |
| Postrenal ARF | • Bladder outflow obstruction, e.g. prostatism<br>• Ureteric obstruction, e.g. prostatic carcinoma, stones |

Adapted from Burtis CA, *et al.* and Braunwald E, *et al.* (see Further Reading).

## Chronic kidney disease

The National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) guidelines define chronic kidney disease as either:

- Kidney damage for 3 or more months. Kidney damage is defined as structural or functional abnormalities of the kidney, with or without decreased glomerular filtration rate (GFR), manifest by either pathological abnormalities or markers of kidney damage, including abnormalities in the composition of blood or urine or abnormalities in imaging tests.

or

- Decreased kidney function (GFR < 60 ml/min/1.73 $m^2$) for 3 or more months with or without kidney damage. Decreased kidney function is assessed as decreased GFR, which is a reflection of the number of functioning nephrons and is generally accepted as the best overall measure of kidney function.

The NKF-K/DOQI guidelines recommend the staging of chronic kidney disease according to calculated GFR into 5 stages (Table II).

A GFR below 60 ml/min/1.73$m^2$ is associated with a loss of more than one half of normal renal function.

Kidney disease needs to be diagnosed early. Staging of chronic kidney disease allows the doctor to have a clear action plan in the management of chronic kidney disease and also improves patients' understanding of chronic kidney disease, disease progression, management of risk factors and early identification and treatment of complications (Table III).

## RISK FACTORS

The family doctor needs to identify patients at increased risk for developing kidney disease, because early treatment may prevent complications and progression of disease. Diabetes mellitus is the largest single cause of chronic kidney disease and accounts for 45% of dialysis patients in the USA. Hypertension is another common important underlying cause of chronic kidney disease.

The NKF-K/DOQI guidelines divide risk factors for chronic kidney disease into susceptibility factors, initiation factors, progression factors and end-stage factors (Table IV).

Lowering blood pressure, reducing proteinuria and improving glycaemic control in diabetics will slow down the rate of progression of chronic kidney disease.

## COMPLICATIONS

Kidney disease is associated with a wide range of complications, including hypertension, anaemia, malnutrition, bone disease and neuropathy. Early identification and treatment of kidney disease can prevent or lessen complications, as well as slow down the progression to kidney failure (Table V).

## DIAGNOSIS OF KIDNEY DISEASE

Everyone should be assessed routinely to determine whether they are at increased risk for developing chronic kidney disease. People at increased risk should be tested to identify markers of kidney damage and to assess GFR. The diagnosis of kidney disease is based on history, examination, screening and special investigations.

Screening for kidney disease:

- dipstick analysis – detection of proteinuria and haematuria are of most significance
- assessment of urinary sediment for casts, cells and crystals, which supports the diagnosis of intrinsic renal disease.

Special investigations:

- creatinine measurement to estimate GFR
- proteinuria detection as a marker of kidney damage
- ultrasonography plays an important role in visualising the size of the kidney, as well as in identifying possible evidence of obstruction
- percutaneous kidney biopsy is a confirmatory test.

Table II. **NKF-K/DOQI guidelines staging of chronic kidney disease**

| Stage | Description | GFR (ml/min/1.73 $m^2$) |
|---|---|---|
| 1 | Kidney damage with normal or increased GFR | > 90 |
| 2 | Kidney damage with mildly decreased GFR | 60 - 89 |
| 3 | Moderately decreased GFR | 30 - 59 |
| 4 | Severely decreased GFR | 15 - 29 |
| 5 | Kidney failure | < 15 |

Table III. **Action plan**

| Stage | Action plan |
|---|---|
| 1 | Diagnosis<br>Treatment of co-morbid conditions<br>Intervention to slow disease progression<br>Cardiovascular disease risk reduction |
| 2 | Estimating disease progression |
| 3 | Evaluation of disease complications<br>Treatment of disease complications |
| 4 | Preparation for possible kidney replacement therapy |
| 5 | Kidney replacement therapy if appropriate |

Adapted from: National Kidney Foundation Document (see Further Reading).

Table IV. **Risk factors for chronic kidney disease**

| Risk factor | Examples |
|---|---|
| Susceptibility factors – increased susceptibility to renal damage | • Older age<br>• Family history of chronic kidney disease<br>• Low birth weight<br>• Low income or education |
| Initiation factors – directly initiate kidney damage | • Diabetes<br>• High blood pressure<br>• Autoimmune disease<br>• Systemic infections<br>• Urinary tract infections<br>• Urinary stones<br>• Lower urinary tract obstruction<br>• Drug toxicity |
| Progression factors – cause worsening kidney damage and faster decline in kidney function after initiation of kidney damage | • Higher blood pressure<br>• Higher levels of proteinuria<br>• Poor glycaemic control in diabetes<br>• Smoking |
| End-stage factors – increased morbidity and mortality in kidney failure | • Lower dialysis dose<br>• Temporary vascular access<br>• Anaemia<br>• Low serum albumin<br>• Later referral for dialysis |

Adapted from: Johnson CA, *et al.* (see Further Reading).

Table V. **Complications associated with chronic renal failure**

| Stage | GFR (ml/min/1.73 $m^2$) | Possible complications |
|---|---|---|
| 1 | > 90 | |
| 2 | 60 - 89 | • Increased parathyroid hormone (PTH) |
| 3 | 30 - 59 | • Decreased calcium<br>• Malnutrition<br>• Onset of left ventricular hypertrophy<br>• Onset of anaemia (decreased erythropoietin) |
| 4 | 15 - 29 | • Increased triglyceride concentration<br>• Hyperphosphataemia<br>• Metabolic acidosis<br>• Hyperkalaemia |
| 5 | < 15 | • Uraemia |

Adapted from: Burtis CA, *et al.* (see Further Reading).

## Glomerular filtration rate

GFR is generally accepted as the best overall measure of renal function. GFR can be assessed using endogenous or exogenous markers. The ideal marker is freely filtered, not secreted, not reabsorbed, and not metabolised by the renal tubules and exclusively eliminated via the kidneys. Exogenous markers such as Inulin, $^{51}$Cr-EDTA, $^{99m}$Tc DTPA and iohexol are accurate in assessing GFR, but are costly and impractical for routine clinical use.

Creatinine clearance is used as an indicator of GFR. Creatinine clearance is measured by means of a 24-hour urine collection. Measuring creatinine clearance is a cumbersome process prone to error. Urine sample collection (24-hour) is inconvenient and patient compliance is poor and it is therefore frequently inaccurate. The NKF-K/DOQI guidelines have not found the collection of a 24-hour urine sample for creatinine clearance to be more reliable than that of s-creatinine-based prediction equations in the assessment of GFR. A 24-hour urine collection for creatinine clearance appears to provide superior information under the following circumstances:

- exceptional dietary intake – vegetarian diet, creatine supplementation
- extremes of age or body size
- severe malnutrition or obesity
- disease of skeletal muscle
- paraplegia or quadriplegia
- rapidly changing kidney function
- prior to the use of nephrotoxic drugs
- determining the need to start dialysis.

The NKF-K/DOQI guidelines recommend the estimation of GFR using prediction equations based on s-creatinine. The two formulas used most commonly in the adult population are the Cockroft Gault formula (formula 1) and the modification of diet in renal disease (MDRD) formula (formula 2).

Formula 1 – Cockroft Gault formula:

$$\text{GFR} = \frac{(140 - \text{age}) * \text{weight (kg)}}{0.814 * \text{serum creatinine (µmol/l)}}$$

* O.85 if patient is female

Formula 2 – Abbreviated MDRD formula:

$$\text{GFR (ml/min/1.73 m}^2) = 186 * [\text{s-Creat (µmol/l)} * 0.011312]^{-1.154} * [\text{age}]^{-0.203}$$

* [0.742 if patient is female]

* [1.212 if patient is African American]

The MDRD formula has been shown to be more accurate and simpler to implement in the clinical laboratory, as the weight of the patient is not required. To date the correction factor of 1.212 used for the African American population has not been verified in the South African black population.

For the measurement of GFR using s-creatinine-based prediction equations accurate measurement of creatinine is essential. However, there are differences in the calibration of creatinine depending on the

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autoanalyser and method used. Efforts are now under way to standardise creatinine measurement using an international standard.

### Cystatin C

Cystatin C is a novel marker for the evaluation of chronic kidney disease. Cystatin C is produced by all nucleated cells at a constant rate and functions as a cysteine protease inhibitor. Cystatin C is relatively unaffected by muscle mass, diet, gender and age. It is freely filtered by the glomerulus due to a low molecular weight (12.8 kDa) and a high isoelectric point (pI = 9.2). Cystatin C is not secreted by the renal tubules. Although it is reabsorbed by the renal tubules, it is metabolised and does not return to the bloodstream. Cystatin C therefore meets the criteria for an ideal GFR marker. Cystatin C is currently not routinely used in South Africa for the evaluation of renal function. Its role as a possible early marker of decreased GFR needs to be evaluated further.

### Proteinuria

Persistent proteinuria is usually a marker of kidney damage. The glomerulus acts as an ultrafilter. Proteins with a high molecular weight, such as IgM (MW 970 kDa) pass through the glomerulus only in trace amounts. Albumin (MW 66 kDa) passes through the glomerulus in small amounts due to high plasma concentration and a relatively low molecular weight. Smaller proteins such as $B_2$-microglobulin (MW 12 kDa), pass through the glomerulus easily but are reabsorbed in the proximal tubule. Normally urine protein consists of small amounts of albumin and Tamm-Horsfall protein secreted by the distal tubule.

Proteinuria is defined as a protein excretion of > 300 mg/24 h. However, 24-hour urine collections for protein estimations are prone to poor patient compliance. Using a spot urine sample as a ratio to creatinine corrects for variations in urinary protein concentration and is more convenient for the patient. The ratio of protein to creatinine or albumin to creatinine is an accurate estimation of the urinary protein or urinary albumin excretion rate.

In most circumstances spot or untimed urine samples may be used for the detection and monitoring of proteinuria. It is preferable to use an early-morning urine sample, but a random urine sample is also acceptable.

### Albuminuria

Albuminuria refers to increased urinary excretion of albumin. Albuminuria reflects glomerular proteinuria. Increased excretion of albumin is an indication of chronic kidney damage due to diabetes, glomerular disease or hypertension.

### Microalbuminuria

Microalbuminuria is defined as an increased U-albumin too subtle to be picked up by urine dipsticks, an albumin excretion rate of 30 - 300 mg/24 h (20 - 200 µg/min). The identification of microalbuminuria is important because angiotensin-converting enzyme (ACE)-inhibitors can significantly reduce the progression to albuminuria.

Current recommendations according to the NKF-K/DOQI guidelines for detection and monitoring of proteinuria include:

- **Screening of adults without kidney disease**. Perform a urine dipstick for protein measurement. A positive urine dipstick protein result (1+ or greater) requires follow up with quantitative measurement, protein-to-creatinine measurement or albumin-to-creatinine ratio.
- **Screening adults at increased risk for chronic kidney disease**. Evaluation of random spot urine sample with albumin-specific dipsticks. A positive test needs to be followed up with a quantitative measurement. Alternatively, adults at increased risk can be evaluated with a random urine evaluation of albumin-to-creatinine ratio. Albumin measurement is technically more difficult and more expensive than that of total urine protein and therefore total protein-to-creatinine measurement is an acceptable alternative.
- **Monitoring adults with chronic kidney disease**. Albumin-to-creatinine ratio.

## CONCLUSION

The new definitions and staging of chronic kidney disease should allow for improved and earlier identification of chronic renal disease. It is anticipated that the use of prediction equations to estimate GFR will make the diagnosis of chronic kidney disease simpler and thereby improve patient care and treatment.

### *Further reading*


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## IN A NUTSHELL

Kidney disease is a common health problem. The early identification of kidney disease is important to prevent and delay the onset of complications as well as the progression of chronic kidney disease.

Risk factors and complications should be identified and treated early. Diabetes mellitus and hypertension are common causes of chronic kidney disease and need to be identified and treated early. Cardiovascular risk identification and risk reduction are extremely important in patients with renal disease.

GFR is a reflection of the number of functioning nephrons and is generally accepted as the best overall measure of renal function. Creatinine-based prediction equations, such as the MDRD equation, can be used to estimate GFR.

Proteinuria is an indicator of kidney damage. The early identification of microalbuminuria is important because ACE-inhibitors slow down the progression of albuminuria.

The family doctor plays an important role in the early identification of renal disease, as well as in establishing an appropriate action plan, together with the patient, for the management of renal disease.