SUMMARY

Background: Chronic renal disease is common, and its prevalence is rising. Its main causes are hypertension and diabetes mellitus. An abnormally low glomerular filtration rate (GFR) often escapes medical notice in the earliest, most treatable stage, so that an increasing number of patients progress to end-stage renal failure. Early recognition of low GFR would thus be an important clinical advance.

Methods: The authors selectively review the literature retrieved by a PubMed search on the topic and also present their own clinical and laboratory data.

Results: Chronic renal failure can be detected early by direct measurement of the GFR with the aid of an exogenous filtration marker. Such techniques are costly and time-consuming and are therefore indicated only for patients at special risk. Chronic renal disease can also be diagnosed early with the aid of the endogenous filtration markers creatinine and cystatin C, which serve as indicators of a low GFR. The serum levels of these two substances are not taken as measures of GFR in themselves, but are rather entered into predictive equations for the estimation of GFR. Cystatin C-based equations seem to be more sensitive indicators of low GFR than creatinine-based equations.

Conclusions: Creatinine- and cystatin C-based equations for the estimation of GFR are valuable tools for the early diagnosis of chronic renal disease and for disease staging according to the US National Kidney Foundation criteria.

Key words: renal failure, chronic disease, nephropathy, hypertension, diabetes mellitus
reliable results and represent the gold standard. However, they are costly, time-consuming, and labor-intensive, can be performed only in specialized laboratories, and are therefore indicated primarily in patients displaying nephrological symptoms. Simpler, but less precise, is estimation of GFR (eGFR) by means of the endogenous filtration markers creatinine and cystatin C.

The aim of this review is to depict the methods used to determine GFR and—by sifting the nephrological, internal medical and clinical chemistry literature available in PubMed—ascertain their reliability in the detection and monitoring of CRD.

Measuring GFR by means of exogenous filtration markers (mGFR)

The clearance of various markers of filtration, such as inulin, 51Cr-EDTA, iohexol, iothalamate, and 99mTc-diethylenetriaminepentaacetic acid (DTPA), is determined. The GFR is either expressed in absolute terms as mL × min⁻¹ or standardized to 1.73 m², the body surface area of a person weighing 70 kg. The unit of measurement is: mL × min⁻¹ × (1.73 m²)⁻¹. Age- and gender-specific reference values for GFR can be found in Table 2 (11). The reduction in GFR correlates with the extent of functional impairment of the nephrons and thus with the degree of renal failure. A patient whose GFR falls below 15 usually requires dialysis. Nevertheless, in certain cases GFR is insensitive to the loss of functioning nephrons. In the early stage of diabetes-related kidney disease, for instance, characterized by microalbuminuria, the renal hypertrophy and hyperperfusion mean that GFR is normal or raised; thus, determination of GFR is of no value in the diagnosis of incipient diabetic nephropathy (e2). The different methods for mGFR do not show full agreement: at GFR values >80, GFRiohexol gives lower readings than GFREDTA, but below this threshold GFREDTA is lower than GFRiohexol (13).

Measuring GFR by means of endogenous filtration markers (eGFR)

Internal markers of filtration such as creatinine and cystatin C are endogenous substances that are almost completely filtered out by the glomeruli. Increasing serum levels of these parameters indicate decreasing GFR. It is recommended that whenever creatinine is determined the eGFR should be calculated and reported along with the serum value (14). Equations frequently used to ascertain eGFR based upon creatinine and cystatin C are presented in Box 2. The reduction in GFR correlates with the extent of functional impairment of the nephrons and thus with the degree of renal failure. A patient whose GFR falls below 15 usually requires dialysis. Nevertheless, in certain cases GFR is insensitive to the loss of functioning nephrons. In the early stage of diabetes-related kidney disease, for instance, characterized by microalbuminuria, the renal hypertrophy and hyperperfusion mean that GFR is normal or raised; thus, determination of GFR is of no value in the diagnosis of incipient diabetic nephropathy (e2). The different methods for mGFR do not show full agreement: at GFR values >80, GFRiohexol gives lower readings than GFREDTA, but below this threshold GFREDTA is lower than GFRiohexol (13).

Serum creatinine

Determination of creatinine in serum is the method most frequently used to evaluate renal function. Creatinine derives from the muscular metabolism of creatine and phosphocreatine. As such, the synthesis of creatinine at a daily rate of approximately 20 mg/kg body weight reflects muscle mass and varies little from day to day.
Creatinine synthesis is age-dependent. As measured by urinary excretion, it decreases with increasing age, falling from a mean 23.8 mg/kg body weight in men aged 20 to 29 years to 9.8 mg/kg body weight in men aged 90 to 99 years (e2). The essential reason is reduction in muscle mass.

When renal function is normal, creatinine is filtered out by the glomeruli and 15% of it is secreted by the tubuli (e3). There is a reciprocal non-linear relationship between GFR and serum creatinine, such that a decrease in GFR to around 40 often does not lead to an increase to above the upper limit of normal (e4). If no previously obtained values are available, a concentration within the normal range cannot be interpreted as potentially showing a decrease in GFR. In acute renal failure serum creatinine rises within 2 days as a direct result of retention within the body. In CRD the increase in serum is only 30% to 50% of what would be expected from the prevailing GFR. The reason for this is that, depending on the extent of GFR reduction, 16% to 66% of creatinine is eliminated extraglomerularly (e5). Tubular secretion and intestinal elimination reach their maximum when GFR falls to ≤15. Noteworthy extrarenal patient-related factors that influence creatinine synthesis and thus the concentration in serum include sex, age, ethnicity, muscle mass, chronic illness, and the consumption of cooked meat. Lack of standardization of methods also impacts negatively on the validity of serum creatinine for assessment of GFR. Medications such as cimetidine and trimethoprim inhibit creatinine secretion and increase the serum concentration without affecting GFR. It must also be realized that serum creatinine is not suitable for evaluation of rapid changes in GFR: The estimated GFR is too high in swiftly decreasing renal function and too low when function recovers.

### Serum cystatin C

Cystatin C is a plasma protein with a molecular weight of 13.4 kDa and belongs to the cysteine protease inhibitors. It is synthesized at a constant rate by all nucleated cells, excreted into plasma, filtered by the glomeruli, and reabsorbed and metabolized by the proximal tubule cells. In the age group from 1 to 50 years, the serum concentration is independent of muscle mass, sex, and age.

### Table 2

<table>
<thead>
<tr>
<th>Reference values for GFR (11)</th>
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<tbody>
<tr>
<td><strong>Premature births</strong></td>
</tr>
<tr>
<td><strong>Neonates</strong></td>
</tr>
<tr>
<td><strong>Children (2 to 8 weeks)</strong></td>
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<tr>
<td><strong>Children (3 to 12 months)</strong></td>
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<tr>
<td><strong>Children/adolescents (1 to 20 years)</strong></td>
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<tr>
<td><strong>Adults (age group, years)</strong></td>
</tr>
<tr>
<td>Men*</td>
</tr>
<tr>
<td>20–29</td>
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<tr>
<td>30–39</td>
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<tr>
<td>40–49</td>
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<tr>
<td>50–59</td>
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<td>60–69</td>
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<td>70–79</td>
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<tr>
<td>80–89</td>
</tr>
<tr>
<td><strong>Women</strong>*</td>
</tr>
<tr>
<td>20–29</td>
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<tr>
<td>30–39</td>
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<tr>
<td>40–49</td>
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<td>50–59</td>
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<td>60–69</td>
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<tr>
<td>70–79</td>
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<tr>
<td>80–89</td>
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</tbody>
</table>

* (mL × min⁻¹ × [1.73 m²]⁻¹)

### BOX 2

**Creatinine- and cystatin C-based equations for calculation of eGFR**

#### Children

**Counahan-Barratt equation (e14) Creatinine-based**

$$eGFR \ (\text{mL} \times \text{min}^{-1}) = 0.43 \times \text{height (cm)} \times (S_C \ [\text{mg/dL}])^{-1}$$

**Equation according to Grubb et al. (24) Creatinin C-based**

$$eGFR \ (\text{mL} \times \text{min}^{-1} \times [1.73 \text{m}^2]^{-1}) = 84.69 \times (S_{\text{cystatin C}} \ [\text{mg} \times \text{L}^{-1}]^{-1.68} \times 1.384 \ \text{(in children <14 years)}$$

#### Adults

**Cockcroft-Gault equation (19) Creatinine-based**

$$C_c \ (\text{mL} \times \text{min}^{-1}) = (140 - \text{age [years]}) \times (S_C \ [\text{mg} \times \text{dL}^{-1}])^{-1} \times (\text{BW [kg]} \times [72])^{-1}\times 0.85$$

**MDRD equation (10) Creatinine-based**

$$eGFR \ (\text{mL} \times \text{min}^{-1} \times [1.73 \text{m}^2]^{-1}) = 175 \times (S_c \ \text{standardized [mg} \times \text{dL}^{-1}]^{-1.154} \times (\text{age [years]})^{-0.203} \times 0.742 \times 1.18$$

**Equation according to Hoek et al. (25) Cystatin C-based**

$$eGFR \ (\text{mL} \times \text{min}^{-1} \times [1.73 \text{m}^2]^{-1}) = 80.35 \times (S_{\text{cystatin C}} \ [\text{mg} \times \text{L}^{-1}] – 4)^{-1.68}$$
These properties show that cystatin C is a good marker for assessment of renal function. Comparably with serum creatinine, there is an inverse, non-linear relationship between GFR and serum cystatin C. In comparison with serum creatinine, the proportional increase of cystatin C is higher when GFR falls to a level between 70 and 40 (Figure) (17). Cystatin C rises age-dependently from the age of 50 years and correlates with the decrease in GFR. Cystatin is not always a reliable marker of renal function, as its synthesis is increased in smokers, patients with hyperthyroidism, and those on glucocorticoid therapy and decreased in hypothyroidism (e6). According to a meta-analysis, however, cystatin C is a more reliable parameter than creatinine for detection of CRD (18).

**Creatinine-based eGFR**

eGFR is determined by means of equations that take account of empirically patient-related parameters and thus permit more precise and accurate assessment of GFR. All of the equations employed for estimating GFR were developed using cross-sectional data from patient collectives. The Cockcroft-Gault equation (19) and the Modification of Diet in Renal Disease (MDRD) equation (20) are recommended (Box 2). The former incorporates age, body weight, sex, and serum creatinine concentration, while the latter considers age, ethnicity, sex, and serum creatinine concentration. The Counahan-Barratt equation is recommended for children.

**Cockcroft-Gault equation**
The Cockcroft-Gault equation estimates creatinine clearance in mL × min⁻¹, but not GFR, and is not standardized to the body surface area of 1.73 m². In relation to GFR it systematically overestimates clearance because tubular creatinine secretion is not taken into account (19, 20). Because this equation includes body weight, it is particularly recommended for the monitoring of renal function during treatment with medications that influence kidney performance.

**MDRD equation**
The MDRD equation includes age, sex, and ethnicity to take account of differences among population subgroups. Therefore reductions in GFR are detected earlier than with serum creatinine. Because the MDRD equation was developed exclusively using data from patients with CRD, a GFR of >60 should be reported not as an absolute value but as eGFR >60 mL = (mL × min⁻¹ × [1.73 m²]⁻¹) (20, 21). More recently individuals without CRD have also been

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**Box 3**

Advantages of cystatin C-based eGFR over creatinine-based eGFR (examples)

<table>
<thead>
<tr>
<th>Patient category</th>
<th>Advantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children (e23)</td>
<td>Children have low levels of creatinine and determination is unreliable in the lower range of measurement</td>
</tr>
<tr>
<td>The elderly (e15)</td>
<td>Owing to physiological reduction in renal function and decrease in muscle mass, cystatin C correlates better than creatinine with inulin clearance</td>
</tr>
<tr>
<td>Myasthenics, leg amputees, paraplegics (e16)</td>
<td>Because of the lower muscle mass, creatinine synthesis is low and cystatin C-based eGFR is late to detect renal failure</td>
</tr>
<tr>
<td>Diabetics (e17)</td>
<td>Early stages of renal failure are detected more reliably with cystatin C based than with creatinine-based eGFR</td>
</tr>
<tr>
<td>Liver cirrhosis (18)</td>
<td>Creatinine methods are slow to detect the decrease in GFR because creatinine metabolism in the liver is reduced</td>
</tr>
<tr>
<td>Cytostatic treatment (e19)</td>
<td>The nephrotoxicity of cisplatin is dose-dependent and a reduction in GFR is detected earlier by cystatin C-based than by creatinine-based eGFR</td>
</tr>
</tbody>
</table>
studied. The diagnostic reliability of the MDRD equation for estimation of GFR can be summarized as follows:

- The eGFR can be 6% too high in CRD (11, e7–e9), and may be 29% too low in individuals without CRD (e10, e11).
- In 90% of cases in the MDRD study group the eGFR was within ±30% of the mGFR (21). For a GFR of 60 (mL × min⁻¹ × [1.73 m²]⁻¹) this would mean a range of 42 to 78 (mL × min⁻¹ × [1.73 m²]⁻¹). This degree of accuracy is considered acceptable provided eGFR is determined again after 3 months (22).
- The MDRD equation over-stages patients in CRD stages 2 and 3, but correctly classifies those in stages 4 and 5 (4).

This overestimation of GFR by the MDRD equation is important for the monitoring of CRD. Patients in stage 3 are expected to exhibit an annual decrease in GFR of 1.4 to 3.9. In a comparison of mGFR and eGFR, however, 41.8% of patients showed a decrease in eGFR that was less than that in mGFR by ≥2. Thus monitoring of CRD by eGFR must be viewed critically (23).

Any patient with eGFR <60 very probably has CRD. Young patients with eGFR as low as this may have a true GFR that is 29% higher, but will still probably have impaired renal function (22). In such cases demonstration of, for example, albuminuria is required for the diagnosis of renal damage (1).

To ensure comparability of eGFR among laboratories it is important to use kinetic methods such as the Jaffe reaction or enzymatic techniques to determine creatinine. To this end calibrators and controls of the tests carried out must be based on highly specific procedures for creatinine determination and specific reference materials (21).

**Cystatin C-based eGFR**

All that is needed for calculation of eGFR is the serum concentration of cystatin C. This method is particularly indicated in children (e12, e13), because the MDRD equation cannot be used in this age group (e9), and in the elderly (6). For children the equation according to Grubb (24) has proved more reliable than the Counahan-Barratt equation, and for adults the equation according to Hoek (25) is more sensitive than the MDRD equation (Box 2). In older age groups the physiological decrease in GFR from year to year is registered more sensitively with cystatin C-based eGFR than with the MDRD equation (6), and a drop of >3 is associated with a higher subsequent risk of mortality (8). Further indications for cystatin C-based determination of eGFR are listed in Box 3.

**Conclusion**

Serum creatinine and establishment of eGFR with the MDRD equation are important basic investigations for the diagnosis of CRD. The determination of cystatin C and reporting of cystatin C-based eGFR offers advantages, but on grounds of cost (determination of cystatin C is 20 to 30 times more expensive than that of creatinine) it should be reserved for certain categories of patients.

**Conflict of interest statement**

The authors declare that no conflict of interest exists according to the guidelines of the International Committee of Medical Journal Editors.

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**REFERENCES**


**KEY MESSAGES**

- The diagnostic sensitivity of serum creatinine determination is too low for early detection of CRD.
- In addition to measurement of serum creatinine the MDRD equation should be used to calculate eGFR, allowing early diagnosis of CRD.
- In individuals without CRD the MDRD equation underestimates GFR, but in CRD the agreement is acceptable.
- Reductions in GFR are detected earlier by means of cystatin C and cystatin C-based eGFR than by serum creatinine. Because of the higher costs, however, cystatin C determination should be requested only in particular indications.
- When a reduction in eGFR is found, direct measurement of GFR (mGFR) should be used to establish the exact base value of GFR and assess the progression of CRD.

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