# 4. Direct measurement of glomerular filtration rate

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**GUIDELINES**

**No recommendations possible based on Level I or II evidence**

## SUGGESTIONS FOR CLINICAL CARE
**(Suggestions are based on Level III and IV sources)**

- **Commonly used exogenous filtration markers (iothalamate, DTPA, EDTA, iohexol) provide acceptable measures of glomerular filtration rate (GFR), although they tend to overestimate inulin clearance by several mL/min (3.5–8.0 mL/min). (Level III evidence, multiple small studies, surrogate outcomes, conflicting effects)**
- **Creatinine clearance measurements have generally been shown to provide less reliable estimates of GFR than GFR prediction equations. (Level III evidence, multiple large cohort studies in community and institutional settings, surrogate outcomes, strong effect)**
- **The overestimation of GFR by creatinine clearance can be improved to a variable extent by administration of oral cimetidine or by averaging with urea clearance. (Level III evidence, several small cohort studies, surrogate outcomes, weak effect)**



## Background

The GFR is generally considered to be the best index of renal function in health and disease. Rigorous assessment of GFR requires the measurement of an 'ideal filtration marker', defined as a substance that is freely filtered by the kidney, not bound to plasma proteins, non-toxic and does not undergo metabolism, tubular secretion or absorption (Gaspari et al 1997).

Inulin, an inert polysaccharide with a molecular weight of 5200 Daltons, appears to fulfill these criteria. Inulin clearance was first proposed as a means of measuring GFR in dogs by Richards et al (1934) and in man by Shannon and Smith (1935). This method is well established and has been widely accepted as a standard against which other GFR methods are evaluated. However, inulin clearance is not practical for routine clinical purposes because of expense, limited commercial sources, restricted availability of automated laboratory methods for inulin determination, and the need for

constant supervision during the procedure (which requires intravenous infusion and sometimes bladder catheterisation of bed-resting patients).

The impracticalities associated with inulin clearance have led to the study of alternative, endogenous or exogenous clearance markers to determine their suitability for GFR measurement. The objective of this guideline is to review the evidence pertaining to the use of alternative filtration markers for the measurement of GFR.

## Search strategy

**Databases searched:** Text words for glomerular filtration rate were combined with MeSH terms and text words for measurement or iohexol or EDTA or DTPA or inulin or creatinine clearance or iodopyracet or cyanocobalamin. The search was carried out in Medline (1966 – 18 April 2005). No language restrictions were placed on the search. The conference proceedings of the American Society of Nephrology from 1994–2004 were also searched for trials.

**Date of searches:** 18 April 2005.



## What is the evidence?

No randomised controlled trials (RCTs) are available which address this issue.

### Exogenous filtration markers

The markers commonly employed for GFR measurement include radiopharmaceuticals ($^{99m}$Tc-DTPA, $^{169}$Yb-DTPA, $^{125}$I-iothalamate, $^{51}$Cr-EDTA) and radiographic contrast agents (iohexol) (Gaspari et al 1997, Rahn et al 1999, Frennby and Sterner 2002). Other markers that have been occasionally used include $^{57}$Co-cyanocobalamin (Anderson et al 1968), sodium thiosulphate (Vorburger et al 1969) and $^{131}$I-iodopyracet (Elwood and Sigman 1967). The properties of these markers are summarised in Table 1.

Validation studies comparing the clearance of filtration markers with that of inulin have generally been limited in number and poor in quality. In particular, most studies have been restricted to correlation analysis (which assesses the strength of the relationship between the two methods), but have failed to measure the actual agreement between the two variables, such as by Bland-Altman analysis (Bland and Altman 1986). This point is best exemplified by the study of Gaspari et al (1996), which assessed the reliability of multi-point iohexol clearance against the single-point method in 686 patients with a wide range of renal function. Although the two methods were highly correlated (r = 0.99), the level of agreement by Bland-Altman analysis was in fact poor with

the prediction errors ranging from -5% to -22% or +5% to +40% in 25% of patients.

Comparison of the different clearance methods is also made difficult by published differences in mode of administration and preparation of markers, comparison of urinary versus plasma clearance, use of unlabelled carrier, use of different models for plasma clearance (e.g. Bubeck's, Jacobsson and Bröchner-Mortensen models), and coadministration of adrenaline (e.g. with iothalamate).

Renal clearance of $^{125}$I-iothalamate has been shown to closely approximate GFR in most (Perrone et al 1990, Anderson et al 1968, Elwood et al 1967, Ott 1975, Maher et al 1971, Skov 1970, Malamos et al 1967, Israelit et al 1973, Adefuin et al 1976, Barbour et al 1976), but not all (Odlind et al 1985, Rosenbaum et al 1979) studies. Inconsistent results have similarly been reported for EDTA (Vorburger et al 1969, Lavender et al 1969, Lavender 1969, Chantler et al 1969, Hagstam et al 1974, Brochner-Mortensen 1973, Heath et al 1968, Rehling et al 1984, Rehling et al 1986, Garnett et al 1967, Favre and Wing 1968, Stamp et al 1970, Bailey et al 1970) and DTPA (Perrone et al 1990, Barbour et al 1976, Rehling et al 1984, Rehling et al 1986, Shemesh et al 1985, Bianchi et al 1979, Hilson et al 1976) chelates compared with simultaneous inulin clearance. In comparative studies, the plasma clearance of $^{125}$I-iothalamate was significantly higher than the clearance of $^{51}$Cr-EDTA in one investigation (Odlind et al 1985), while another paper found that the clearances of $^{125}$I-iothalamate, $^{169}$Yb-DTPA, $^{99m}$Tc-DTPA and inulin were very similar (Perrone et al 1990). The principal disadvantage of radionucleotide GFR measurements relates to the safety and inconvenience of using radiolabelled compounds (especially in children and women of child-bearing potential). They are also costly and time-consuming.

Iohexol clearance can be measured by HPLC methods with ultraviolet detection, thereby avoiding radiation exposure (Krutzen et al 1984, Back et al 1988a, Back et al 1988b). Several studies have shown strong concordance between iohexol and inulin clearances (Gaspari et al 1997, Frennby and Sterner 2002, Gaspari et al 1996, Gaspari et al 1995, Gaspari et al 1998a, Gaspari et al 1998b, Houlihan et al 1999, Brown and O'Reilly 1991).

Overall, most studies suggest that the measured clearances of the commonly used exogenous filtration markers (iothalamate, DTPA, EDTA, iohexol) provide acceptable measures of GFR, although they tend to overestimate inulin clearance by several mL/min (3.5–8.0 mL/min). Although they are too cumbersome and costly for routine clinical use, they may be useful in certain clinical situations, such as those outlined in the Suggestions for Clinical Care in the guideline titled 'Use of estimated GFR to assess level of kidney function'.

## Endogenous filtration markers

- Creatinine clearance should be considered as only a rough estimate of GFR due to a combination of:
    - Errors in serum creatinine measurement (discussed extensively in the guideline 'Use of serum creatinine concentration to assess level of kidney function')
    - Errors in urinary creatinine measurement due to inaccurate urine collections and fluctuating, unpredictable tubular creatinine secretion. The ratio of urinary creatinine clearance to urinary inulin clearance may vary from 1.14 to 2.27 in different subjects (van Acker et al 1992a, van Acker et al 1992b)
    - As discussed in the guideline 'Use of estimated GFR to assess level of kidney function', creatinine clearance has consistently been shown to be less accurate and reliable than eGFR.

Cimetidine creatinine clearance: Inhibition of tubular creatinine secretion by oral administration of cimetidine (400 mg bd to a total cumulative dose of 1200 mg) has been reported to improve the accuracy (bias and precision) of creatinine clearances (van Acker et al 1992a, Roubenoff et al 1990, Hilbrands et al 1991), although some subjects require relatively large doses to completely inhibit renal tubular secretion of creatinine (van Acker et al 1992a).

Mean urinary urea and creatinine clearance has also been suggested to improve the accuracy of creatinine clearance because the tendency of creatinine clearance to overestimate GFR due to tubular creatinine secretion is counterbalanced by the tendency of urea clearance to underestimate GFR due to tubular urea reabsorption (Levey et al 1999).

- The arithmetic mean of urinary urea and creatinine clearance has been recommended by the NKF K/DOQI for measuring residual renal function in peritoneal dialysis patients (NKF-DOQI 1997), even though there has only been 1 small validation study against inulin clearance in 10 individuals (van Olden et al 1996).
- In paediatric pre-dialysis patients, there has been 1 small study involving 15 children with severe CKD (GFR < 20 mL/min) (Manz et al 1977). Mean urinary urea and creatinine clearance was found to be strongly correlated with inulin clearance in this study.
- In adults with CKD, the largest and most rigorously performed study to date has been that reported by Levey et al involving 1628 patients enrolled in the MDRD study (Levey et al 1999). The arithmetic mean or urea and creatinine clearance underestimated iothalamate clearance and was significantly less reliable than MDRD eGFR.

## Summary of the evidence

There are no RCTs on this topic.

Despite generally suboptimal statistical analyses, the vast majority of validation assays to date suggest that measurement of the clearance of an exogenous filtration marker, such as EDTA, DTPA, iothalamate or iohexol, provides an acceptably accurate measurement of GFR. In contrast, the measurement of creatinine clearance overestimates GFR to a variable degree in individuals. The inaccuracy of creatinine clearance can be improved by the administration of oral cimetidine or by averaging with urea clearance.

## What do the other guidelines say?

**Kidney Disease Outcomes Quality Initiative:** No recommendation.

**British Renal Association:** There is no need to collect 24 h urine samples to measure creatinine clearance in primary care (Level of evidence 3 DA).

**Canadian Society of Nephrology**: No recommendation.

**European Best Practice Guidelines:** The most accurate and direct measurement of GFR requires timed blood sampling after administration of a tracer. This is often impractical for routine use in the nephrology clinic and is unrealistic as a standard for general practice.

**International Guidelines:**

**Kidney Disease Improving Global Outcomes:** No recommendation.



## Implementation and audit

No recommendations.

## Suggestions for future research

1. Future studies of GFR measurements should assess the level of agreement with the reference method by Bland-Altman analysis, in addition to evaluating precision by correlation.

2. The within- and between-method variability in GFR measurement should be assessed and agreement on protocols developed to reduce this variation.

3. Alternatives to the correction of GFR against 1.73 $m^2$ body surface area should be investigated. This process does little to reduce the between-individual scatter (and thus utility of population-based cut-offs), is based on a surface area which is no longer representative of the population, and uses a formula for body surface area developed in 1916 from which time body composition, and thus the relationships between BSA, height and weight, may have changed considerably.

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## Appendix

**Table 1** Characteristics of the commonly used exogenous and endogenous filtration markers

| Feature | Inulin | Iothalamate | DTPA | EDTA | Iohexol | Creatinine |
|---|---|---|---|---|---|---|
| MW (da) | 5200 | 614 | 393 | 292 | 821 | 113 |
| Elimination half-life (min) | 70 | 120 | 110 | 120 | 90 | 200 |
| Plasma protein binding (%) | 0 | < 5 | 5 | 0 | < 2 | 0 |
| Tubular secretion | - | + | - | - | - | ++ |
| Extra-renal elimination | - | - | + | + | - | + |