

Screening of renal function prior to administration of iodinated contrast medium

Key words: Renal function screening, contrast-induced nephropathy, eGFR, contrast medium

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Assessment of baseline renal function

Abstract

Renal impairment at baseline (estimated glomerular filtration rate [eGFR] <60 ml/min/1.73 m²) is the most important risk marker to predict the risk of contrast-induced nephropathy (CIN) in patients receiving iodinated contrast media. A number of strategies have been shown to be helpful in managing the risk of CIN in patients at risk of CIN. Hence, it is important to assess renal function before administration of contrast medium to ensure that appropriate steps are taken to reduce the risk. Serum creatinine alone does not provide a reliable measure of renal function, and thus the National Kidney Foundation Kidney Disease Outcome Quality Initiative (K/DOQI) recommends that clinicians should use an eGFR calculated from the serum creatinine as an index of renal function. eGFR should be determined prior to contrast administration, using the abbreviated Modification of Diet in Renal Disease (MDRD) formula, recommended by K/DOQI as the preferred equation for the calculation of eGFR in adults. Where a serum creatinine measurement or eGFR is not available, a simple survey or questionnaire can be used before contrast agent administration to identify patients at higher risk for CIN than the general population. In emergency situations, where the benefit of very early imaging outweighs the risk of waiting, the investigation or procedure can be undertaken without assessment of renal function.

Introduction

Contrast-induced nephropathy (CIN) is a common and clinically important complication of the use of iodinated contrast media for clinical investigations or therapeutic procedures.¹⁻⁴ The presence of chronic kidney disease (CKD) at baseline is associated with an increased risk of CIN, particularly when diabetes is also present.⁵ The evidence also supports an association between the severity of pre-existing renal impairment and the risk of CIN.⁵ The occurrence of CIN is associated with increased in-hospital mortality and a longer hospital stay, as well as being a predictor of late mortality.^{3,6} Moreover, a larger post-procedure decline in renal function is associated with an increased risk of adverse outcomes.⁶

Renal impairment is acknowledged as the most important risk factor for CIN⁵ and an independent predictor of risk in multivariate analyses.^{5,7} The evidence indicates that the risk of CIN is elevated and becomes clinically important when the estimated glomerular filtration rate (eGFR) is less than 60 ml/min/1.73 m², equivalent to serum creatinine levels ≥ 1.3 mg/dl (114.9 μ mol/l) in men and ≥ 1.0 mg/dl (88.4 μ mol/l) in women.^{1,5} Various strategies are available to reduce the risk of CIN, including adequate volume expansion, appropriate choice of contrast medium and limiting the volume of contrast medium to <100 ml.¹

Hence, it is important to identify prospectively the patients at risk so that appropriate measures can be taken. The most appropriate approach to risk prediction is a simple one focusing on renal function, the most important risk marker, and diabetes mellitus, which can be considered as a risk multiplier.⁵ This review considers the most appropriate approaches to the assessment of baseline renal function before contrast medium administration in routine clinical practice.

Estimation of renal function

The glomerular filtration rate (GFR), which is conventionally corrected for body surface area, is considered the best overall index of renal function.⁸ The most accurate method of determining GFR is to track the clearance of a marker that is freely filtered at the glomerulus and not reabsorbed or secreted in the tubule (such as inulin or a suitable isotopic marker) but this is a burdensome procedure. Clearance of creatinine, an endogenous marker, is often measured as an alternative; creatinine clearance is higher than GFR, because there is some secretion of creatinine in the tubules, but it does provide a reasonable indication of renal function.

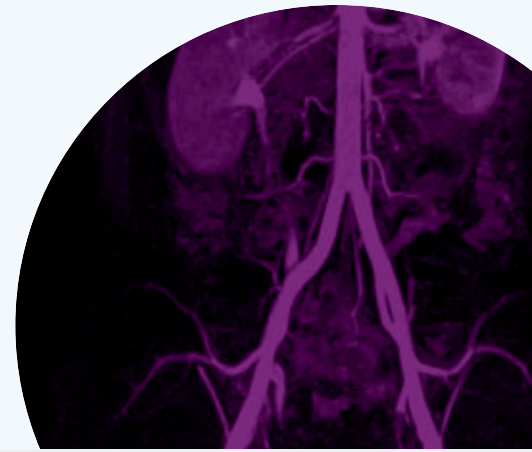
Direct measurement of renal clearance is not realistic in routine clinical practice, since it is inconvenient (24-hour urine collection required) and expensive. Consequently, the GFR is often estimated from the serum creatinine level using an equation such as the Modification of Diet in Renal Disease (MDRD) or Cockcroft-Gault formula

Serum creatinine measurements are readily available and can provide a useful indication that a patient is suffering from CKD. However, serum creatinine does not provide an accurate measurement of renal function, since the relationship with GFR is non-linear, and a substantial reduction in renal function may occur before the serum creatinine concentration is significantly elevated.⁹ The creatinine concentration in the blood is affected by a number of factors other than creatinine filtration including diet, muscle mass and gender.^{10,11} Older patients and women have a lower muscle mass and hence the renal function (GFR) may be lower than expected from the serum creatinine; for example, an elderly female may have significant loss of renal function despite having a serum creatinine in the normal range.¹²

Various methods are available for the calculation of an eGFR from the serum creatinine. The National Kidney Foundation Kidney Disease Outcome Quality Initiative (K/DOQI), with the endorsement of Kidney Disease: Improving Global Outcomes (KDIGO),¹³ recommends that laboratories should supply clinicians with a report of the eGFR with the results of serum creatinine measurement.⁹ Laboratory-reported eGFR



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may be easier for patients and physicians to interpret than serum creatinine levels.¹⁴

Equations for estimating GFR

The most widely used equations are the Cockcroft-Gault formula¹⁵ and the MDRD formula.¹²

The Cockcroft-Gault equation was originally developed to estimate creatinine clearance but has been evaluated as a predictor of GFR. It incorporates serum creatinine, age and body weight in the calculation and estimates creatinine clearance in ml/min, uncorrected for body surface area.

The abbreviated (4-variable) MDRD equation incorporates age, gender and ethnicity, but not body weight and the result is an eGFR already corrected for body surface area (ml/min/1.73 m²). This equation was developed as part of the MDRD Study¹² and the K/DOQI guidelines recommend its use as the preferred method for estimating GFR in adults.⁹ The addition of more variables (albumin, urea) adds little to its accuracy.

The modified MDRD equation is based on a validated method for measuring GFR (renal clearance of ¹²⁵I-iothalamate) and the alkaline picrate method for measuring serum creatinine and it has been validated extensively in different patient populations including Caucasians, African-Americans, patients with diabetic and non-diabetic kidney disease and renal transplant recipients.¹³ Table 1 shows the range of serum creatinine levels that correspond to an estimated GFR of 60 ml/min/1.73 m² or creatinine clearance of 60 ml/min in different patient groups using these 2 equations.⁹

The MDRD calculation is more complex than the Cockcroft-Gault one. However, calculators that compute the eGFR from serum creatinine level and patient characteristics are widely available on the internet (e.g. http://www.kidney.org/professionals/kdoqi/gfr_calculator.cfm and http://nk.dep.nih.gov/professionals/gfr_calculators/index.htm). Many laboratories now report the eGFR with the serum creatinine and this value is likely to be more accurate as it may incorporate laboratory-specific correction factors.

A recent review of the literature supported the use of the modified MDRD equation as a better estimate (than the Cockcroft-Gault formula) of GFR in people with moderate or advanced chronic kidney disease.¹⁶ The modified MDRD formula has the advantage of not requiring body weight data, which may not be available in the clinical laboratory, for the calculation of GFR. Both the modified MDRD and Cockcroft-Gault equations lack precision at high

GFR values (low serum creatinine concentrations), but this is of little relevance when screening patients for renal impairment.

If the eGFR is not available, serum creatinine levels ≥ 1.3 mg/dl (114.9 $\mu\text{mol/l}$) in men and ≥ 1.0 mg/dl (88.4 $\mu\text{mol/l}$) in women are useful cut-off values to indicate an increased risk of CIN. However, a recent study highlighted the disadvantage of relying on serum creatinine levels to assess CIN risk: among emergency patients being considered for a computed tomography scan with intravenous contrast medium, the serum creatinine was < 1.4 mg/dl (123.8 $\mu\text{mol/l}$) in 40% of those with creatinine clearance below 60 ml/min.¹⁷

Serum creatinine assay

Since the eGFR is calculated from the serum creatinine level, it is important that creatinine measurements are accurate and standardised across laboratories to allow consistent interpretation. However, this has not yet been achieved. A number of studies have documented some inter-laboratory variation and lack of precision in serum creatinine assay.^{14,18,19}

Current laboratory methods are subject to less interference from chromogens than the older alkaline-picric acid or Jaffé method and hence normal levels of serum creatinine are lower than previously. This results in higher values for creatinine clearance and overestimation of GFR.⁹ Equipment manufacturers and clinical laboratories may calibrate instruments to report higher serum creatinine values in order to minimize this overestimation of GFR but this calibration is not standardized, leading to variation within and across laboratories.⁹

Serum Creatinine Concentration Calculation (mg/dL) [†]	Age (yr)					
	30	40	50	60	70	80
MDRD formula*						
European Americans						
Men	1.47	1.39	1.34	1.30	1.26	1.23
Women	1.13	1.08	1.03	1.00	0.97	0.95
African Americans						
Men	1.73	1.65	1.58	1.53	1.49	1.46
Women	1.34	1.27	1.22	1.18	1.15	1.12
Cockcroft-Gault formula*						
Men	1.83	1.67	1.50	1.33	1.17	1.00
Women	1.56	1.42	1.28	1.13	0.99	0.85

MDRD = Modification of Diet in Renal Disease

[†]1 mg/dL = 88.4 $\mu\text{mol/L}$. [‡]Concentration corresponding to an estimated glomerular filtration rate of 60 ml/min/1.73 m².

*Concentration corresponding to a creatinine clearance of 60 ml/min

Table 1. Serum creatinine concentrations in various populations and ages corresponding to an eGFR of 60 ml/min/1.73 m² (MDRD equation) or a creatinine clearance of 60 ml/min (Cockcroft-Gault equation). Calculations assume a body weight of 72 kg and body surface area of 1.73 m². (Reprinted from Am J Kidney Dis. Copyright 2002, with permission from the National Kidney Foundation.)⁹

Screening of renal function prior to administration of iodinated contrast medium *continued*

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Risk factor questionnaires

It is strongly recommended that prior to the administration of iodinated contrast medium, renal function and hence, the risk of CIN should be assessed by calculating the eGFR from a recent serum creatinine measurement. However, in some clinical situations and particularly emergency situations, this may be impractical. Where renal function data are unavailable, a simple survey or questionnaire to determine the presence of risk factors can be used to identify patients at higher risk for CIN than the general population prior to contrast agent administration. Several groups have evaluated such questionnaires covering risk factors such as a history of kidney disease, diabetes mellitus, hypertension and advanced age.²⁰⁻²²

Choyke *et al* showed that 94% of patients giving negative answers to a simple 6-point risk factor questionnaire (covering a history of renal problems, proteinuria, hypertension, gout and diabetes) before computed tomography had normal serum creatinine levels (Table 2).²¹ Hence, the use of a questionnaire could reduce the number of patients in whom creatinine measurement was necessary prior to imaging studies.²¹ In another study in 640 emergency room patients requiring a contrast procedure, serum creatinine was measured and risk factors were assessed. Thirty-five patients (5.5%) had a serum creatinine level ≥ 1.6 mg/dl and most of these (27 patients) had recognized risk factors for renal insufficiency. The authors concluded that almost 99% of patients at risk for CIN can be identified by evaluation of risk factors.²²

The European Society of Urogenital Radiology (ESUR) recommends a risk factor analysis based on the Choyke questionnaire to identify patients with a higher risk of abnormal renal function. A history of renal disease, renal surgery, proteinuria, diabetes mellitus, hypertension, gout or the intake of nephrotoxic drugs may imply an increased probability of abnormal serum creatinine levels, and in such cases consideration should be given to serum creatinine measurement before contrast agent administration.²³

Although none of these screening methods have been validated, a survey or questionnaire may be a useful guide for identifying patients at higher risk for CIN than the general population.

Emergency situations

In the setting of emergency procedures, where the benefit of very early imaging outweighs the risk of waiting for the results of a blood test, it may be necessary to proceed without serum creatinine assessment or GFR estimation.

Six questions:
1. Have you ever been told you have renal problems?
2. Have you ever been told you have protein in your urine?
3. Do you have high blood pressure?
4. Do you have diabetes?
5. Do you have gout?
6. Have you ever had kidney surgery?

Table 2. The Choyke Questionnaire.²¹

However, where possible, an indication should be obtained of the likelihood that the patient has impaired renal function that may increase the risk of CIN, to enable suitable precautions to be taken.

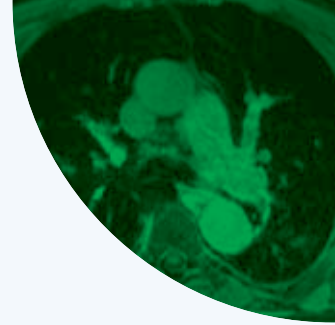
Risk management strategies

Identification of patients at risk – mainly through assessment of renal function – is an essential first step in managing the risk of CIN. Intravenous volume expansion has a well-established role in reducing the risk of CIN.²⁴ There are limited data on the most appropriate choice of intravenous fluid, but the evidence indicates that isotonic saline is more effective than half-normal saline.²⁵ The results of two studies, one comparing sodium chloride and sodium bicarbonate²⁶ and the other comparing the combination of sodium bicarbonate and N-acetylcysteine (NAC) with normal saline plus NAC²⁷ suggest that bicarbonate may be more effective than saline.

Numerous pharmacological strategies have been assessed for their potential to reduce the risk of CIN.²⁴ In particular, the use of NAC to reduce the risk of CIN in patients at risk has been extensively evaluated in clinical trials.^{24,28} These trials have given inconsistent and conflicting results, with some showing a reduction in the risk of CIN and others showing no evidence of benefit. One study²⁹ suggested that the apparent benefit of NAC observed in some trials may be a consequence of an effect on serum creatinine levels that does not reflect a real improvement in GFR, since there was no effect on serum levels of cystatin C, another marker of renal function. Other pharmacological agents that could be considered for further evaluation for CIN prophylaxis include theophylline, statins, ascorbic acid and prostaglandin E₁.²⁴

The choice of contrast medium also plays a role in reducing the risk of CIN in patients at risk of CIN. The osmolality of contrast media is a physical characteristic believed to contribute to CIN.³⁰⁻³² Clinical trials have demonstrated that low osmolar contrast media (LOCM) result in less CIN than high osmolar contrast media (HOCM).³³⁻³⁵

Use of the newer iso-osmolar contrast media (IOCM) is probably associated with a low rate of CIN compared with LOCM in high-risk patients.³⁶⁻³⁹ Similar rates have been observed with IOCM and LOCM in lower-risk patients.^{40,41} However, in these studies, some bias might have been introduced because of a higher proportion of diabetic patients in the IOCM group and use of a single non-standardised serum creatinine measurement during follow-up^{40,41} or use of larger volumes of contrast media in the IOCM group.⁴⁰ One group of researchers recently concluded that IOCM better preserves short- and long-term renal function. In 27 elderly patients with severe renal impairment (mean serum creatinine 3.0 mg/dl) receiving IOCM during elective cardiovascular catheterization, the mean serum creatinine at 6 months and the absolute and percentage increases at 3 and 6 months were all lower than in historical case-matched controls receiving LOCM.⁴²



Conclusions

The identification of patients at risk of CIN is an essential step in reducing the risk through implementation of appropriate risk reduction strategies. The eGFR provides the best indicator of impaired renal function at baseline and should be calculated using the abbreviated MDRD formula which takes into account the patient's age, gender and race as well as serum creatinine concentrations. Risk factor assessment using a survey or questionnaire can

facilitate the identification of patients at risk. Selection of contrast media is an important consideration and the use of contrast media with osmolality closest to that of blood, such as iso-osmolar agents, has been shown to be associated with low rates of CIN in high-risk patients. In emergency situations, where the benefit of very early imaging outweighs the risk of waiting, the investigation or procedure can be undertaken without determining the serum creatinine or eGFR.

Key Learning

- Renal impairment at baseline is the most important risk marker for contrast-induced nephropathy (CIN)
- Renal function should be assessed before the administration of iodinated contrast medium to identify patients at risk of CIN and enable appropriate steps to be taken to reduce the risk
- The estimated glomerular filtration rate (eGFR) is recommended as the most appropriate index of renal function
- The Modification of Diet in Renal Disease (MDRD) is the preferred equation for calculation of eGFR from the serum creatinine level in adults
- Where no measure of renal function is available, a questionnaire may be useful in identifying patients at increased risk

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