Cystatin C as a marker of renal function in older adults


Summary
This article looks at the value of cystatin C in assessing renal function in older people. While it appears to be reliable and accurate, it is still relatively untested in most clinical settings and there is much to learn before its value in the day-to-day assessment of renal function can be determined.

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MARKERS OF GLOMERULAR filtration rate (GFR) are used to assess kidney function. Knowledge of GFR is crucial in the management of patients with chronic kidney disease. GFR not only provides a general evaluation of kidney function, but also allows ‘correct dosage of drugs cleared by the kidneys, to detect early impairment of renal function, to prevent further deterioration, to manage renal transplant patients, and for the use of potentially nephrotoxic radiographic contrast media’ (Grubb et al 2005).

There are five main markers used to measure or estimate GFR: inulin clearance, serum creatinine, urinary creatinine clearance (CrCl), the 4-variable modification of diet in renal disease (MDRD) (Levey et al 2000) formula and the Cockcroft-Gault formula (Cockcroft and Gault 1976).

Both creatinine tests—serum creatinine and CrCl—are cheap and convenient, but questions over their accuracy have led to the need to find a more reliable marker of renal function. The plasma or serum concentrations of endogenous substances, for example creatinine, have been used as markers of GFR for more than a century (Grubb et al 2005). Serum creatinine is most commonly used and is produced almost exclusively by muscle (Macdonald et al 2006). Muscle mass decreases with age, therefore creatinine production also declines, and this may contribute to the inaccuracy of creatinine tests in older people. Serum creatinine is also affected by diet. A high intake of cooked meat may cause short-term elevated levels of serum creatinine (Preiss et al 2007). Given the sensitivity of the analytical methods of measuring creatinine, interference from other substances in the plasma, such as bilirubin, may occur and distort results.

The use of CrCl to measure GFR has limitations. Urine collections are often difficult to achieve, especially in older people. Difficulties with voiding, manual dexterity and the need to collect the entire urine output over a 24-hour period often lead to incomplete collections and inaccurate results (Burkhardt et al 2002, Van Den Noortgate et al 2002, O’Riordan et al 2003).

Inulin clearance is the gold standard used for measuring GFR, but this procedure is expensive and cumbersome (Chantrel et al 2000). It involves an intravenous injection of inulin and several timed blood and urine collections to determine the time taken for the kidneys to remove inulin from the body. It is labour intensive and carries the risk of an anaphylactic reaction (Grubb et al 2005).
The two formulae commonly used to estimate GFR—the MDRD and the Cockcroft-Gault formula (Box 1)—have been found to be inaccurate. The MDRD formula slightly overestimates renal function in older individuals (Grubb et al 2005), despite generally being more accurate than the Cockcroft-Gault formula in estimating GFR (Carter et al 2008). Therefore, more research is needed before the MDRD formula is used to estimate GFR in older people (Van Den Noortgate et al 2002).

In contrast, the Cockcroft-Gault formula underestimates renal function in older people because of the effect of age on the formula itself (Van Den Noortgate et al 2002).

Studies into the use of cystatin C

Because of the problems associated with the aforementioned markers of GFR, cystatin C has been proposed as a new marker of renal function. Several studies have been carried out to determine its accuracy and value in various demographic groups (as discussed later in this article).

Cystatin C can be measured from only a single blood test. It is a protein produced by most human tissues. As it has a relatively low molecular weight and is produced at a constant rate, its serum concentrations are determined mainly by GFR (O’Riordan et al 2003). Small molecular weight proteins have long been proposed as markers of GFR as they are almost freely filtered through the glomerular membrane (Jung 1987). In a normally functioning kidney, these small molecular weight proteins should then be almost reabsorbed completely and degraded by proximal tubular cells (Filler et al 2005). It has been suggested that cystatin C is unaffected by height, body mass, gender or age (Filler et al 2005). However, this has been questioned in a number of studies (Burkhardt et al 2002, Knight et al 2004, Macdonald et al 2006). There may also be other factors, which are yet to be determined, that may affect the reliability of cystatin C.

Although GFR generally decreases with age, this is not inevitable, and in about one third of the population, renal function appears to remain stable over time (Lindeman et al 1985). Therefore, there is a need for an accurate marker of renal function in older people, and it is important that clinicians do not assume that an older individual with a low GFR has decreased renal function purely because of his or her age.

An accurate method of measuring GFR could enable better management of renal function and potentially enhance the individual’s quality of life. It is especially important to measure renal function accurately in older individuals because of the decrease in the renal excretion of potentially nephrotoxic drugs (Finney et al 1999). Failure to appreciate renal insufficiency commonly results in antibiotic drug dosage errors in older people (O’Riordan et al 2003) and gives rise to antibiotic resistance (Van Den Noortgate et al 2002).

Van Den Noortgate et al (2002) calculated the GFRs of 48 older inpatients on an older people’s ward with a wide range of renal function, using the five main markers described earlier and cystatin C. No significant difference between the tests, including cystatin C, was found. However, in older people with moderate to severe renal impairment, the Cockcroft-Gault formula was useful. Van Den Noortgate et al (2002) suggested that GFR should be estimated by at least two different methods and, if there is a discrepancy between the results, a more invasive marker, such as inulin clearance, should be used. Van Den Noortgate et al (2002) were unable to confirm the superiority of serum cystatin C in detecting early renal impairment in this population.

Chantrel et al (2000) also questioned the value of cystatin C, comparing serum cystatin C, serum creatinine and estimated GFR (eGFR) (using the Cockcroft-Gault formula) with inulin clearance as the gold standard. The study concluded that cystatin C is no more sensitive than serum creatinine for detecting renal failure, but that it could be used as a confirmatory test for the diagnosis of renal failure for patients with elevated serum creatinine. However, the study involved only a small number of older people and findings cannot be generalised to the wider population.

Cystatin C has been identified as a sensitive marker of GFR (Finney et al 1999, Coll et al 2000, O’Riordan et al 2003) (Box 2). Coll et al (2000) demonstrated that cystatin C was better...

**Box 1**

**The two most commonly used formulae for estimating glomerular filtration rates**

<table>
<thead>
<tr>
<th>Formula</th>
<th>Description</th>
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<tbody>
<tr>
<td>eGFR (ml/min/1.73m²)</td>
<td>eGFR = 186.3 x (serum creatinine/88.4) – 1.154 x age – 0.203 x (0.742 if female) x (1.21 if black)</td>
</tr>
<tr>
<td>Cockcroft-Gault formula</td>
<td>Estimated creatinine clearance = (140 – age) x weight x 12 x (0.85 if female) / (serum creatinine x height²)</td>
</tr>
</tbody>
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Serum creatinine is expressed in umol/L, age in years and weight in kg (Cockcroft and Gault 1976).
at detecting small changes in renal function than serum creatinine.

O’Riordan et al (2003) stated that ‘serum cystatin C is a simple and sensitive screening test for kidney dysfunction in older people’. While Coll et al (2000) found that, because of its sensitivity, cystatin C may be particularly useful in the detection of early renal insufficiency from a variety of causes. Coll et al’s (2000) study is significant because it compared cystatin C with iothalamate labelled with iodine, which is a ‘gold standard’ method of assessing GFR. However, not all of the research studies compared cystatin C with a gold standard method (Keevil 1998, Herget-Rosenthal et al 2000, Van Den Noortgate et al 2002, Knight et al 2004, Koenig et al 2005), which raises questions about the validity, reliability and generalisability of the findings.

Fliser and Ritz (2001) and Hoek et al (2003) found serum cystatin C to be a better marker than plasma creatinine concentration for the detection of subtle changes in GFR in older people. However, Fliser and Ritz (2001) did not include very old adults in their study, the oldest recruit being 73 years, while the ages of the participants in Hoek et al’s (2003) study is unclear.

Cystatin C measurement is expensive. O’Riordan et al (2003) acknowledged the high cost of cystatin C measurement compared with the cheaper serum creatinine measurement, but claimed that its use could be justified when the wider clinical benefits to the patient, such as enabling better management of chronic kidney disease based on a more accurate result, are examined.

Several studies identified cystatin C as a precise marker of GFR. Hoek et al (2003) found that, with adjustment from a simple formula (GFR= 4.32 + 80.35 x 1/cystatin C), cystatin C gave a precise estimate of GFR when compared with the Cockcroft-Gault formula. Herget-Rosenthal et al (2000) compared the sensitivity of cystatin C to that of serum creatinine in detecting reduced GFR, and found it to be potentially superior. They studied a cohort of patients from adolescents to the very old, referred to hospital for assessment of renal function, and compared them with a group of healthy subjects. They also looked at whether cystatin C was affected by either glomerular (vascular) or tubular (collecting tube) impairment, and found that it was in fact independent (Herget-Rosenthal et al 2000). A major flaw of this study was that it used creatinine clearance as a reference method for GFR instead of a gold standard method such as inulin clearance.

Hojs et al (2006) found that there was no difference in cystatin C results between the sexes except that, in females, cystatin C had higher diagnostic accuracy in distinguishing mild to moderately impaired kidney function than serum creatinine or the MDRD formula. The majority of available studies in adults to date indicate that cystatin C is a superior measure of GFR compared to other methods (Coll et al 2000, Hoek et al 2003, O’Riordan et al 2003, Hojs et al 2006). In these studies it was found to be more sensitive than serum creatinine, although this was not the case in other studies (Keevil et al 1998, Chantrel et al 2000, Knight et al 2004, Grubb et al 2005).

In the authors’ opinion, cystatin C does appear to be useful as a confirmatory test for the diagnosis of chronic kidney disease. However, there is a need for studies to be undertaken in specific populations where creatinine is known to be a poor marker of GFR.

Factors affecting cystatin C

There is debate about whether cystatin C is affected by age. Filler et al (2005) claimed that cystatin C is unaffected by age or muscle mass. In a study of 401 healthy older people, Finney et al (1999) concluded that serum cystatin C levels offer a more sensitive screening assay for early changes and decreases in GFR than serum creatinine levels using commercially available assays. The results show cystatin C values increasing with age and then becoming steady at about 80 years. However, creatinine ‘does not show any changes with age except a small increase in the upper limit of normal, while still retaining the gender differences caused by muscle mass’ (Finney et al 1999).

It is possible, however, that the continued increase in cystatin C levels with age makes it less reliable than serum creatinine, the level of which remains relatively stable and could therefore provide a more accurate GFR estimation. Finney et al (1999) suggested that there is no need to apply a formula to the cystatin C result to achieve an accurate estimate of GFR, unlike Hoek et al (2003), as discussed.
earlier. Creatinine measurements, on the other hand, have to be adjusted by formulae to take into account different patient variables.

Burkhardt et al (2002) conducted a study comparing insulin clearance, creatinine clearance, creatinine serum, cystatin C and eGFR (using the Cockcroft-Gault formula). They found that cystatin C estimates of GFR have slight advantages compared to creatinine-based estimates, especially in older people where a reduced muscle mass can lead to imprecise creatinine results. However, cystatin C showed poor precision when compared with iothalamate labelled with iodine. This was attributed, in part, to unknown factors that may influence cystatin C results in older individuals. It was concluded that overall there is no precise formula for GFR estimation in older adults (Burkhardt et al 2002).

Body mass may affect cystatin C levels. In their study of 77 participants, Macdonald et al (2006) concluded that cystatin C levels are not independent of body composition (mass). If cystatin C levels were dependent on mass, this might help to explain why Knight et al (2004) found cystatin C to be affected by demographic and anthropometric variables. However, in Macdonald et al’s (2006) study, more than half the patients had either muscle wasting or were obese and therefore may not be representative of the general population. Caution is recommended when using the current cystatin C-based GFR equation for patients with altered body composition (Macdonald et al 2006).

It has been suggested that cystatin C levels are affected by many factors other than renal function, thus contributing to its unreliability. These factors include age, weight, height, C-reactive protein (a commonly used marker of inflammatory states), gender and smoking (Knight et al 2004). A study by Knight et al (2004) found no evidence that serum cystatin C is superior to multivariate serum creatinine-based estimates. However, a major limitation of the study is that it did not directly measure GFR. Instead, 24-hour creatinine clearance was used to estimate renal function; this is not a recognised gold standard test. The study also only examined a Caucasian population and so the results are not generalisable to other ethnic groups. The results suggest that even after accounting for other influences that may affect cystatin C, it is not superior to serum creatinine-based measurements (Knight et al 2004).

Chantrel et al (2000) recommended that studies are carried out on specific populations where creatinine is known to be a poor marker of GFR (for example, people with oedema, cirrhosis, acute renal failure and acute hypercatabolic states) to determine if there is a place for cystatin C as a marker of renal function in clinical practice.

Cystatin C concentration has been shown not to vary in the presence of malignancy (Randers and Erlandsen 1999, Finney et al 2001), diabetes (Wasén et al 2003) or inflammation (Grubb et al 1985, Abrahamson et al 1990). However, cystatin C results were high in male recruits with rheumatoid arthritis (Wasén et al 2003). Cystatin C levels were also found to be affected in recruits with asthma after using methylprednisolone (Wasén et al 2003). This suggests that there are clinical factors that may affect the general clinical use of cystatin C, and therefore it can not replace the gold standard (Grubb et al 1985).

Cystatin C levels have also been found to be a strong predictor of all-cause and cardiovascular disease mortality in older patients with advanced chronic kidney disease (Menon et al 2007).

From the studies available to date, it seems that more research is needed to identify how cystatin C results are affected in the presence of other co-morbidities to determine the actual value of cystatin C as a marker of renal function in clinical practice. Cystatin C was, however, found to be accurate in measuring the decreasing GFR that occurs with increasing age (Finney et al 1999). It is unclear whether body mass complicates the measurement of cystatin C and so it should be used with caution in older adults, who often have reduced muscle mass.

**Conclusion**

An alternative marker of GFR is necessary as the current methods of measuring renal function are all affected, to varying extents, by age, gender and muscle mass. The lack of accuracy in the measurement of renal function may then lead to poor clinical decision making about the care of patients with chronic kidney disease. Cystatin C appears to fulfil many of the criteria required for a marker of GFR, particularly because it can be obtained from a single blood test. Many of the available studies have confirmed a strong correlation to serum creatinine in healthy cohorts and in those patients with a degree of renal dysfunction.

Cystatin C appears to be useful as a confirmatory test for the diagnosis of renal failure. However, it does have limitations, including being an expensive test. This cost, however, can be offset by the convenience of the test compared with conventional methods of testing GFR. It is also not clear whether a formula...
needs to be applied to the cystatin C result to make it an accurate estimation of GFR and to account for differences between patients, such as co-morbidities, age, sex, height and weight. Cystatin C is relatively untested in most clinical settings and not enough is known yet about how it is affected by different co-morbidities and medical conditions. It appears that it can be affected by asthma medications, muscle mass, smoking, rheumatoid arthritis and gender.

Cystatin C may be reliable and accurate in assessing GFR in older adults, but there is still much to learn about this particular protein and its value in the management of renal patients.

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References