Cystatin C for GFR

The sensitive marker for glomerular filtration rate (GFR)

Estimation of GFR from Serum Cystatin C:

The good correlation allows close estimation of GFR

<table>
<thead>
<tr>
<th>Cystatin C in serum (mg/l)</th>
<th>GFR estimated* (ml/min)</th>
<th>GFR measured* mean ± s (ml/min)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.6</td>
<td>145</td>
<td>125 ± 34</td>
<td>14</td>
</tr>
<tr>
<td>0.7</td>
<td>119</td>
<td>111 ± 26</td>
<td>31</td>
</tr>
<tr>
<td>0.8</td>
<td>99</td>
<td>93 ± 16</td>
<td>21</td>
</tr>
<tr>
<td>0.9</td>
<td>85</td>
<td>84 ± 27</td>
<td>17</td>
</tr>
<tr>
<td>1.0</td>
<td>74</td>
<td>79 ± 15</td>
<td>21</td>
</tr>
<tr>
<td>1.1</td>
<td>65</td>
<td>68 ± 12</td>
<td>15</td>
</tr>
<tr>
<td>1.2</td>
<td>58</td>
<td>61 ± 16</td>
<td>9</td>
</tr>
<tr>
<td>1.3</td>
<td>52</td>
<td>55 ± 13</td>
<td>15</td>
</tr>
<tr>
<td>1.4</td>
<td>47</td>
<td>55 ± 14</td>
<td>12</td>
</tr>
<tr>
<td>1.5 – 1.6</td>
<td>41</td>
<td>40 ± 19</td>
<td>12</td>
</tr>
<tr>
<td>1.7 – 1.8</td>
<td>35</td>
<td>42 ± 10</td>
<td>9</td>
</tr>
<tr>
<td>1.9 – 2.0</td>
<td>30</td>
<td>32 ± 7</td>
<td>7</td>
</tr>
<tr>
<td>2.1 – 2.3</td>
<td>26</td>
<td>34 ± 6</td>
<td>7</td>
</tr>
<tr>
<td>2.4 – 2.6</td>
<td>22</td>
<td>28 ± 11</td>
<td>5</td>
</tr>
<tr>
<td>2.7 – 3.0</td>
<td>18</td>
<td>24 ± 7</td>
<td>5</td>
</tr>
</tbody>
</table>

* Inulin clearance and serum Cystatin C testing in 209 patients with a broad range of GFR, age and different pathologies yielded the following correlation function for calculation of estimated GFR:

\[
\text{GFR estm.} = \frac{74.835}{\text{Cys C}^{1.075}}
\]

Reference Range for Cystatin C: ≤ 0.95 mg/l in Men & Women

- children > 1 year show adult levels
- higher Cystatin C levels in elderly healthy subjects > 60 years reflect increased sensitivity for the age-related GFR decline
- not influenced by muscle mass or any analytical interfering factors

Cystatin C – the Ideal Marker for GFR:

- **Free glomerular filtration, without tubular secretion**
  Cystatin C, a 13,250 D, non-glycosylated protein does not bind to any other plasma protein; the only elimination route for Cystatin C is glomerular filtration.

- **Stable production rate, constant circulating levels**
  The Cystatin C expression regulating gene is of the housekeeping type, guaranteeing a stable production rate. Cystatin C is synthesized by all nucleated cells. Cystatin C is not influenced by an acute phase reaction.

- **No re-entrance into the blood circulation**
  Cystatin C is reabsorbed by the tubulus cells and thereby rapidly degraded. In the case of tubulus dysfunction, absorption is impaired and Cystatin C is eliminated with the urine. Therefore, urinary Cystatin C levels can be used as a marker of tubulus dysfunction.


- **No extra-renal elimination**
  Cystatin C is cleared only via glomerular filtration.

Cystatin C – Preferable to creatinine and creatinine clearance:

**Correlation of Cystatin C with GFR not influenced by:**
- gender
- muscle mass
- age (children > 1 year of age show adult levels)
- protein intake
- metabolic factors influencing creatinine tests; e.g. bilirubin, ketones, elevated glucose or ascorbic acid
- various drugs interfering with creatinine tests; e.g. cyclosporine A, cephalosporins, aspirin

**no urine collection**
- sensitive GFR determination with 1 serum or plasma sample

**increased sensitivity**
- to even slight impairment of glomerular filtration; already increases significantly in the creatinine blind range
Monitoring Renal Graft Function with Cystatin C:

- The baseline level is stable, uneventful transplantation is achieved by Cystatin C 6 days after surgery.
- Cystatin C decreases more steeply than creatinine during the first postoperative days, indicating graft function earlier and more clearly.
- In the absence of complications the relative change in Cystatin C during monitoring is less than 20% (90% conf. range).

**Expected range in stable renal transplant recipients:**

- Median: 1.75 mg/l
- 10.-90. percentile: 1.17 - 3.03 mg/l

*P. E. Wallemacq; Eur. Meeting on Biomarkers of Organ Damage and Dysfunction EMBODY 2000; Cambridge, UK*
Cystatin C improves discrimination between good and poor graft function

Cystatin C rapidly indicates acute rejection and therapeutic response

"Plasma Cystatin C is an alternative and accurate marker of allograft function in adult transplant patients. Increased sensitivity compared with creatinine for the detection of acute reduction in glomerular filtration rate allows in some cases a more rapid diagnosis of acute rejection or treatment nephrotoxicity."

T. Le Bricon, Clin Chem 1999
Cystatin C for GFR in Pediatrics

The sensitive marker for glomerular filtration rate (GFR)

- **No urine collection**
  
  sensitive GFR determination with 1 serum or plasma sample; no timed collection, no collection errors, assay time 6 min.
  - more reliable than creatinine clearance
  - more rapidly available than creatinine clearance

- **Increased sensitivity**
  
  to even slight impairment of glomerular filtration; already increases significantly in the creatinine blind range:
  - more sensitive than serum creatinine

- **Age-independent in children > 1 year**

- **Independent of muscle mass/height**
  
  - less complex interpretation than creatinine or creatinine clearance

![Graph showing serum Cystatin C levels across different age groups](image)

*D.J. Newman; Ann Clin Biochem 2002; 39 : 89 - 104*
Cystatin C – for Reliable and Sensitive GFR Determination in Pediatrics:

- **Sex and muscle mass independent in children > 1 year:**
  - adult reference range: 0.53 - 0.95 mg/l Cystatin C
  - also valid for children > 1 year
  
  *H Finney, Arch Dis Child 2000*

- **Cystatin C is more closely correlated to reference methods, e.g. inulin or Cr-EDTA clearance**
  - increased diagnostic accuracy
  - the diagnostic potential of Cystatin C is also superior to that of serum creatinine in children, providing better discrimination of patients with normal and reduced renal function

  *I Helin, Clin Nephrol 1998*

- **Highest Cystatin C levels are observed after birth**
  - Cystatin C levels rapidly decline in the first weeks after birth; the high levels in neonates probably reflect the degree of maturation of the glomerula

  *L Cataldi, Am J Perinatol 1999*

- **Cystatin C does not cross the placenta and thus reflects infant renal function**
  - no significant correlation between Cystatin C and maternal and neonatal variables, such as weight, BMI, age of mother, sex, diet, gestational age of neonate
  - not influenced by maternal serum level, in contrast to creatinine. Preterm infants have higher Cystatin C levels than full-term neonates

  *L Cataldi, Am J Perinatol 1999*

  - fetuses with impaired renal function have higher Cystatin C levels than healthy controls

  *A. Bökenkamp, Am J Obstet Gynecol 2001*