Measurement of glomerular filtration rate in homozygous sickle cell disease: a comparison of $^{51}$Cr-EDTA clearance, creatinine clearance, serum creatinine and $\beta_2$ microglobulin

S A J R Aparicio, S Mojiminiyi, J D S Kay, B J Shepstone, K de Ceulaer, G R Serjeant

Abstract

Glomerular filtration rates (GFR) were measured with $^{51}$Cr-EDTA in 38 patients (aged 40–75 years) with homozygous sickle cell disease and compared with serum $\beta_2$ microglobulin concentrations in 38 patients and with creatinine clearance in 21 patients. GFR estimated with $^{51}$Cr-EDTA was closely correlated with single serum creatinine measurements and the inverse of serum $\beta_2$ microglobulin. Creatinine clearance was also found to be correlated, but values were, on average, 32% below those obtained by the $^{51}$Cr-EDTA method, and this difference was significant.

It is concluded that measurements of $\beta_2$ microglobulin, single serum creatinine, and creatinine clearance are valuable indicators of GFR in homozygous sickle cell disease. Measurement of $\beta_2$ microglobulin was a useful and reliable method of estimating GFR from single plasma measurements and is therefore a useful means of screening the population.

The use of serum $\beta_2$ microglobulin, serum creatinine, and of creatinine clearance as estimators of glomerular filtration rate (GFR) has been validated against isotope methods in several populations. In homozygous sickle cell disease, however, the disordered metabolism and abnormal renal tubular function may make these techniques inappropriate. Previous studies of GFR in sickle cell disease have used creatinine clearance and serum $\beta_2$ microglobulin, although these have not been validated against the more accurate $^{51}$Cr-EDTA clearance. Impaired renal function and a lowered GFR are common in older patients with sickle cell disease, and monitoring such patients requires a simple accurate method of estimating GFR. These methods were therefore compared with $^{51}$Cr-EDTA clearance in 38 patients aged over 40 years with sickle cell disease.

Results

Estimates of serum $\beta_2$ microglobulin and of $^{51}$Cr-EDTA clearance were performed in all 38 subjects whereas creatinine clearance and serum creatinine were measured in a subset of 21 patients (table). Creatinine clearance was linearly associated with $^{51}$Cr-EDTA clearance ($r = 0.84, p < 0.010$), although creatinine clearance seems to underestimate proportionally GFR. On average, creatinine clearance values were 24.4 ml/minute (32%o) below those obtained by the isotope method, the difference between paired values being highly significant (Student’s $t$ test = 4.51, $p < 0.0002$). The
Method

<table>
<thead>
<tr>
<th>Method</th>
<th>Number of observations</th>
<th>Mean</th>
<th>Standard deviation</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{51}$Cr-EDTA (ml/minute)</td>
<td>38</td>
<td>75.9</td>
<td>30.2</td>
<td>5-132</td>
</tr>
<tr>
<td>Creatinine clearance (ml/minute)</td>
<td>21</td>
<td>51.5</td>
<td>24.7</td>
<td>5-113</td>
</tr>
<tr>
<td>$\beta_{i}$ microglobulin (mg/l)</td>
<td>38</td>
<td>3.48</td>
<td>2.67</td>
<td>1-15-5</td>
</tr>
<tr>
<td>Serum creatinine (µmol/l)</td>
<td>21</td>
<td>145</td>
<td>136</td>
<td>72-748</td>
</tr>
</tbody>
</table>

Reciprocal of serum creatinine (fig 2) and of serum $\beta_{i}$ microglobulin (fig 3) showed a good correlation with $^{51}$Cr-EDTA clearance ($r = 0.81$ and $0.79$, respectively; $p < 0.001$ for both). No sex differences were noted in any of the comparisons ($p > 0.99$).

The data as presented here are not corrected for surface area. This correction was applied in analysis and no significant differences were found between the various parameters of renal function. Furthermore, in comparisons between GFR estimates such corrections cancel out mathematically.

**Discussion**

The use of single injection isotope methods for estimating GFR has been proved for a variety of isotopes including $^{51}$Cr-EDTA. The latter is commonly used as a reference method where inulin clearance is impractical and where larger numbers of patients need to be studied. The $^{51}$Cr-EDTA method used here is believed to be robust under a variety of conditions. The major source of error occurs in the presence of moderate to severe clinical oedema, which increases the distribution time after injection, but this may be compensated for by delaying the timing of the first plasma sample. This was the case with only one patient in the study.

Endogenously produced substances are more routinely used in clinical practice and may provide good estimates of GFR. Methods based on creatinine become inaccurate when renal tubular creatinine handling is disturbed by disease and the creatinine production rate may vary with muscle mass and increased protein catabolism. Both situations may occur in patients with sickle cell disease yet studies of renal function in sickle cell disease have relied on precisely these methods. Single creatinine estimates are less reliable than creatinine clearance measurements for estimating GFR, although this study confirms that both are of use in patients with sickle cell disease. Previous studies have shown linear relations between isotope clearance methods and both creatinine clearance and the inverse of serum creatinine.

The creatinine clearance method proportionately underestimated the GFR obtained by $^{51}$Cr-EDTA. The creatinine clearance values were less than predicted in 15 of 21 (71%) of subjects and differed by a mean of 24 ml/minute ($32\%$). One possible source of error was the short period of urine collection (five hours), but although this may contribute to more variable values of creatinine clearance, it should not produce a systematic discrepancy.

$\beta_{i}$ microglobulin is a small protein of about 100 amino acids found in association with HLA-1 molecules on all nucleated cells. The endogenous production is relatively constant and the protein is filtered and fully catabolised by the kidney. Renal tubular disease does not lead to reappearance of the protein in the plasma. The production rate may be increased in some autoimmune or chronic inflammatory disorders, and the increased bone marrow...
activity in sickle cell disease could result in increased production. This possibility cannot be excluded with the available data but such increased production would tend to produce underestimates of the GFR. The β2 microglobulin values did not exceed those predicted by 51Cr-EDTA clearance (by comparison with previous studies) and in three cases the β2 microglobulin estimates were lower than expected. The strong linear relation between serum β2 microglobulin and 51Cr-EDTA clearance (fig 3) shows that the usefulness of β2 microglobulin in sickle cell disease has not been diminished, regardless of possible variation in β2 microglobulin production. Single estimates of serum β2 microglobulin have been widely used for estimation of GFR by other authors and may be more sensitive in detecting minor reductions in GFR. The efficiency of substances used to estimate GFR may be determined from the equation:

\[ \log(\text{substance}) = a \log(\text{GFR}) + c \]

in which the ideal substance has a coefficient of \( a = -1 \).\(^2\) Values of \( a \) obtained for β2 microglobulin (−0.749) and for serum creatinine (−0.588) implied that the former was a more accurate estimator of GFR. Furthermore, the strength of the relation between the inverse of serum β2 microglobulin and GFR was similar to that found by other workers.\(^1\) \(^4\) \(^5\)

If 51Cr-EDTA clearance is used as the reference method creatinine clearance seems to underestimate GFR in sickle cell disease. Furthermore, this method is technologically cumbersome, requiring accurately timed urine collections, preferably over 24 hours. Measurements of serum creatinine and β2 microglobulin are both closely related to 51Cr-EDTA clearance. β2 microglobulin seems to offer an accurate and sensitive estimate of small reductions in GFR and its measurement in urine also allows inferences about tubular function to be made.

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