Monitoring renal function in children with Fabry disease: comparisons of measured and creatinine-based estimated glomerular filtration rate

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Abstract

Background. Studies on renal function in children with Fabry disease have mainly been done using estimated creatinine-based glomerular filtration rate (GFR). The aim of this study was to compare estimated creatinine-based GFR (eGFR) with measured GFR (mGFR) in children with Fabry disease and normal renal function.

Methods. Eighty-two examinations were done in 42 children (24 boys, 18 girls) with Fabry disease from three different centres. The mean age was 12.3 years. GFR was measured with iohexol, Cr51-EDTA or iothalamate, and the mean mGFR was 108 ml/min/1.73 m2.

Results. The widely used original Schwartz formula (1976) overestimated GFR substantially by 50.6 ml/min/1.73 m2 with a very low accuracy, whereas the new abbreviated Schwartz formula (2009) showed relatively good performances with a mean GFR overestimation of 5.3 ml/min/1.73 m2 and 79% of the eGFR calculated within 20% of mGFR, thus being only slightly superior to the Cowan–Barratt formula. However, less than half of the eGFR calculated by the new abbreviated Schwartz equation were within 10% of the mGFR. When repeated measurements were performed, mGFR showed less variation than eGFR.

Conclusions. The new abbreviated Schwartz formula should replace the original Schwartz formula in the routine follow-up of children with Fabry disease. The current creatinine-based GFR formulas are all hampered by low accuracy in the ‘creatinine-blind’ GFR range, and early progressive disease may be missed. Supplemental mGFR is, therefore, recommended in patients where changes in GFR have potential impact on important treatment regimens. Cystatin C-based GFR formulas remain to be validated in Fabry children.

Keywords: child; chronic kidney disease; estimated glomerular filtration rate; Fabry disease; measured glomerular filtration rate

Introduction

Fabry disease is an X-linked lysosomal storage disease due to deficient activity of α-galactosidase A, resulting in the accumulation of glycosphingolipids, mainly globotriaosylceramide (GL3), in various tissues [1]. Kidney involvement has been reported early in life, and tubular, glomerular, vascular and interstitial cells are affected in children with Fabry disease [2,3]. Overt nephropathy usually develops in hemizygotes in the third to fourth decade, but proteinuria and reduced glomerular filtration rate (GFR) may occur in adolescents [4–6]. Although short-term and medium-term studies of enzyme replacement therapy (ERT) have demonstrated clearance of GL3 from renal cells [7], early initiation of ERT and adequate monitoring of kidney function are important to avoid progressive decline of GFR [8].

In most clinical studies in Fabry disease, estimated GFR (eGFR) has been used to monitor renal function [9–14], mainly by the Modification of Diet in Renal Disease formula in adults [15] and the Schwartz formula [16–18] in children. Measured GFR (mGFR) techniques are only scarcely used [3,19,20] due to the more complicated and invasive procedures. In general, creatinine-based eGFR is thought to underestimate true GFR in the normal range, and considerable variation is seen in various subgroups [21]. Recent reports demonstrate that creatinine-based eGFR may result in a substantial overestimation of the mGFR in adult male patients with Fabry disease [19,22,23]. The lack of precision of eGFR in children has for long been a matter of dispute. The introduction of isotope dilution mass spectrometry (IDMS) traceable enzymatic serum creatinine analysis as well as the compensation of the Jaffe analysis results in lower creatinine levels, which further augment the overestimation of the commonly used paediatric GFR formulas [24,25]. Schwartz et al. recently reported the development of a
A new complex eGFR formula and a modification of different existing eGFR formulas (Counahan–Barratt formula, Leger formula and others) applicable to serum creatinine measured with the enzymatic method in chronic kidney disease (CKD) children in the GFR range 15–75 ml/min/1.73 m² [26]. The new complex Schwartz formula incorporating serum creatinine, serum cystatin C, blood urea nitrogen (BUN), height and sex achieved 79.4% of the eGFR values within 30% of mGFR and 45.6% within 10% of mGFR. For bedside use, the new abbreviated Schwartz formula (Schwartz09) based on serum creatinine and height was demonstrated to have 79.4% of the eGFR values within 30% and 37.0% within 10% of mGFR. The Schwartz09 formula was only slightly superior to the nearly similar Counahan–Barratt equation (Counahan76) [26,27].

It has been shown that both paediatric and adult Fabry patients may have significant morphologic renal involvement in spite of normal GFR [2,3] as well as reduced GFR without significant proteinuria [6,20]. Precise assessments of GFR are, therefore, essential for adequate diagnosis, monitoring and treatment of nephropathy in these patients. To our knowledge, the different eGFR formulas have not been previously evaluated in this population. The aim of our study was to compare the creatinine-based eGFR and mGFR in children of both genders with Fabry disease and normal renal function.

### Materials and methods

A total of 42 patients, 24 girls and 18 boys, from three Fabry centres in Norway, UK and The Netherlands were recruited for the study (Table 1). The GFR measurements were performed on a consecutive basis according to the clinical follow-up programme of Fabry patients in each centre. The baseline studies were performed in the period from 2003 to 2008. Each patient had from one to six (mean 1.9, median 1.0) mGFR measurements with concomitant serum creatinine analysis. In total, 82 examinations were performed. The mean follow-up time was 3.1 years (range 1.3–5.4 years) for the 13 patients that had three or more GFR measurements.

True GFR was measured according to the local practice, and each centre used different methods. In the Norwegian cohort, iothalamate single-point method at 4 h (high-performance liquid chromatography analysis) was used, calculated according to the method reported by Jacobsson [28]. The body surface area (BSA) was calculated by the Dubois–Dubois formula [29] in the children who were 12 years or older. In younger patients, the distribution volume was calculated according to Stake [30] and BSA by the Haycocks formula [31]. Serum creatinine was measured with the IDMS traceable enzymatic method in all Norwegian patients except in three early measurements where Jaffe alkaline picrate (calibration traceable to IDMS) was used. In the UK cohort, GFR was measured by Cr⁵¹-EDTA (three-point method; 2, 3 and 4 h) and serum creatinine was measured by Jaffe alkaline picrate (calibration traceable to IDMS). ESA was calculated in the Haycocks formula in the Dutch cohort. GFR was measured by iohalamate (four-point method; 1, 2, 4 and 6 h) and the IDMS traceable enzymatic serum creatinine method was used. BSA was calculated by the Dubois–Dubois formula. Albuminuria was measured as albumin–creatinine ratio (ACR) and values >2.5 mg/mmol creatinine was defined as pathological.

### Calculations and statistics

The eGFR was calculated by five different formulas:

- **Counahan76:** \( k \times \text{height} (\text{cm})/\text{serum creatinine (mg/dl)}, k=0.43 \) [27];
- **Schwartz76:** \( k \times \text{height} (\text{cm})/\text{serum creatinine (mg/dl)}, k=0.55, \) boys 213 years \( k=0.70 \) [17,18];
- **Schwartz09:** \( k \times \text{height} (\text{cm})/\text{serum creatinine (mg/dl)}, k=0.413 \) [26];
- **Leger02:** 0.641 (weight (kg)/serum creatinine (mg/dl)) + 16.063 (height (m)²/serum creatinine (mg/dl)) [32];
- **Leger09:** 0.542 (weight (kg)/serum creatinine (mg/dl)) + 9.948 (height (m)²/serum creatinine (mg/dl)) [26,32].

Baseline data such as age, body mass index (BMI), serum creatinine and mGFR were compared between the three patient cohorts (n=42 patients) using one-way ANOVA, and a P value of 0.05 was considered statistically significant. All 82 GFR examinations were included when the performances of the equations were evaluated. Bias was calculated as the mean value of eGFR–mGFR for the different equations and the standard deviation and interquartile range (IQR) for the difference between eGFR and mGFR was calculated as a measure of precision. Accuracy was calculated as percentages of the eGFR results within 30%, 20% and 10% of the mGFR results (P30, P20 and P10, respectively) [33]. To evaluate longitudinal changes in individual consecutive measurements, we used the concept of critical difference (CD). The CD is defined as the minimal difference needed between two consecutive results to conclude (with a specified level of confidence) that the results are truly different, i.e. the difference is not due only to analytical imprecision (CVa) and intra-individual biological variation (CVi) [34]:

\[
\text{CD(95\%CI)} = 2.77 \times \sqrt{\text{CVa}^2 + \text{CVi}^2}.
\]

Adopting a CVi of 5.4% [35,36] and a CVa of 4.0% for iohexol clearance (Haukeland University Hospital, Norway) and a CVi of 7.4% [37] and a CVa of 3.4% for Cr⁵¹-EDTA (Addenbrookes University Teaching Hospital, UK), a CD of 19% and 22% could be calculated for iohexol clearance and Cr⁵¹-EDTA clearance, respectively. For serum creatinine (analytical variation of 2% and intra-individual biological variation of 5.3%) [38], a CD of 16% was calculated. Baseline mGFR and serum creatinine results were used as initial values and CD values were calculated.

### Table 1. Baseline data for 42 Fabry children at the time of inclusion (first examination) and stratified by country

<table>
<thead>
<tr>
<th></th>
<th>Norway (n=14)</th>
<th>UK (n=15)</th>
<th>The Netherlands (n=13)</th>
<th>Total (n=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>13.5 (11.6, 15.4)</td>
<td>10.9 (8.5, 13.2)</td>
<td>12.7 (11.2, 14.2)</td>
<td>12.3 (11.2, 13.4)</td>
</tr>
<tr>
<td><strong>Gender (F/M)</strong></td>
<td>5/9</td>
<td>8/7</td>
<td>11/2</td>
<td>24/18</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>21.6 (18.2, 24.9)</td>
<td>18.0 (16.6, 19.3)</td>
<td>18.8 (16.9, 20.7)</td>
<td>19.4 (18.1, 20.7)</td>
</tr>
<tr>
<td><strong>Bmi range (n≥±2 SD&lt;±2 SD)</strong></td>
<td>10/4</td>
<td>14/0</td>
<td>12/0</td>
<td>36/4</td>
</tr>
<tr>
<td><strong>Serum creatinine (μmol/L)</strong></td>
<td>57 (50, 65)</td>
<td>50 (41, 59)</td>
<td>48 (43, 53)</td>
<td>52 (48, 56)</td>
</tr>
<tr>
<td><strong>mGFR (ml/min/1.73 m²)</strong></td>
<td>107 (100, 114)</td>
<td>103 (98, 109)</td>
<td>118 (109, 127)*</td>
<td>108 (105, 113)</td>
</tr>
<tr>
<td><strong>Microalbuminuria</strong></td>
<td>5</td>
<td>1</td>
<td>2</td>
<td>8</td>
</tr>
</tbody>
</table>

Confidence intervals (95%) in brackets.

*Number of patients with a urinary ACR of >2.5 mg/mmol; five children were missing results of urine test at baseline (one from Norway, two from UK and two from The Netherlands).

*P=0.01 vs UK.*
was seen between microalbuminuria and renal function, nor age or gender.

### Results

Baseline data at inclusion are given in Table 1. Normal BMI was found in 86% of the 42 patients and there were no significant differences in BMI and serum creatinine across the three cohorts. The mean mGFR in all patients was 108±13.5 ml/min/1.73 m², range 87–147 ml/min/1.73 m². The mean mGFR was significantly higher ($P = 0.01$) in the Dutch group compared to the UK patients; 19% of the patients had microalbuminuria. No correlation

### Bias, precision and accuracy

The mean eGFR differed from mGFR in all five equations; the Schwartz76, Counahan76, Schwartz09 and Leger02 formulas overestimated GFR, and the Leger09 formula underestimated the GFR values (Table 2, Figure 1). Similar findings were seen when the first examination of each patient was analysed separately ($n=42$, data not shown). The median values of the differences between eGFR and mGFR for the various equations were similar in all centres ($n=82$ examinations) and the same pattern of differences were seen when repeated examinations were compared, for example, first vs second (data not shown).

Large standard deviations and IQR were seen for the mean calculated differences between eGFR and mGFR for all equations (Table 2). The highest precision was found using the Schwartz09 formula, whilst Leger02 showed the largest variance. The Schwartz09 formula showed the best accuracy of all GFR estimates, followed by the Counahan76 formula, whereas the Schwartz76 showed very low P30–P10 values (Table 2). The uncertainty for the five different equations is shown as Bland–Altman plots in Figure 2.

### Repeated measurements and CD

No significant clinical deterioration was noted in the 13 patients that had three or more consecutive mGFR mea-

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**Table 2. Bias (mean eGFR–mGFR), precision (IQR) and accuracy (P30, P20 and P10) for the five different eGFR equations ($n=82$ measurements)**

<table>
<thead>
<tr>
<th>Equation</th>
<th>Bias ± SD</th>
<th>IQR</th>
<th>P30 (%)</th>
<th>P20 (%)</th>
<th>P10 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Counahan76</td>
<td>9.9±20.0</td>
<td>22.4</td>
<td>87</td>
<td>76</td>
<td>41</td>
</tr>
<tr>
<td>Schwartz76</td>
<td>50.6±26.1</td>
<td>31.5</td>
<td>27</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Schwartz09</td>
<td>5.3±19.4</td>
<td>21.7</td>
<td>87</td>
<td>79</td>
<td>49</td>
</tr>
<tr>
<td>Leger02</td>
<td>12.1±27.1</td>
<td>35.3</td>
<td>72</td>
<td>54</td>
<td>24</td>
</tr>
<tr>
<td>Leger09</td>
<td>−21.9±21.7</td>
<td>31.7</td>
<td>71</td>
<td>50</td>
<td>24</td>
</tr>
</tbody>
</table>

IQR, interquartile range; P30, P20, and P30, percentage of eGFR within 30%, 20% and 10% of mGFR.

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**Fig. 1. Error bars showing the mean difference between eGFR and mGFR for the different equations ($n=82$ measurements): Counahan76, Counahan–Barratt formula [27]; Schwartz76, original formula modified in 1985 [17,18]; Schwartz09, new abbreviated formula [26]; Leger02, original formula [32]; Leger09, formula modified by Schwartz et al. in 2009 [26,32].**
measurements. Both mGFR and eGFR showed substantial variability by repeated measurements (Figure 3). For 10 patients, the variance of mGFR was within the limits of the defined CD, one patient (Patient 5) showed a temporary decrease in renal function, probably due to measurement error, whilst two patients (Patients 6 and 10) showed improved mGFR. Estimated GFR results showed larger variations; five patients (Patients 1, 2, 7, 8 and 10) showed substantial increases of eGFR compared with the expected values, whilst two patients (Patients 3 and 11) showed deteriorating values. Only one patient (Patient 10) showed concordant changes (increased GFR) of both mGFR and eGFR. Estimated GFR falsely signalled changes of renal function (either decrease or increase of GFR outside the limits of CD) in six of 13 patients and did not detect an improved function for one of the two patients that had such findings by mGFR.

Patient 3 had a substantial discrepancy between the first mGFR and eGFR, whereas higher muscle mass due to more physical activity after ERT may explain the lack of discrepancy at the second and third GFR measurements.

Discussion

We demonstrate that both the Schwartz09 formula [26] and the Counahan76 formula [27] have relatively good performances in Fabry children. Both formulas showed a slight overestimation of GFR in contrast to the minor underestimation demonstrated in the study of Schwartz et al. [26] which evaluated the formula in non-Fabry patients with mild to severe CKD (median GFR 41.3 ml/min/1.73 m², range 16–93 ml/min/1.73 m²) and mild growth retardation. Even though a relatively high degree of accuracy (high numbers within P30) was found using the Schwartz09 formula in our cohort, it is important to pay attention to the fact that, in the normal GFR range (GFR >90 ml/min/1.73 m²), a 30% deviation of GFR equates to a large absolute difference. Although the mean overestimation of the Leger02, Counahan76 and Schwartz09 formulas were similar (Figure 1, Table 2), the uncertainty of the Leger02 formula was much larger and accordingly lower values for accuracy was demonstrated (Figure 2, Table 2). The Leger02 formula should, therefore, be avoided in clinical practice. We observed that the older Schwartz76 formula, which has been used in many clinical trials and is still used in international observational registries for Fabry patients, had very low accuracy (Table 2) and overestimated mGFR by as much as 50.6 ml/min/1.73 m² (Figure 1). As a consequence, we suggest that eGFR data from the Fabry registries should be recalculated with the new formula to avoid false conclusions regarding kidney function (i.e. hyperfiltration) which may have an impact on staging of the kidney disease or decisions to commence ERT [14,23,39].
A major problem in Fabry disease is the precise diagnosis of early decline in GFR, since the progression of renal disease carries a more serious prognosis if ERT is initiated at a later stage, especially when GFR is <60 ml/min [8]. It is well known that serum creatinine and all creatinine-based formulas are hampered by lower precision in the ‘creatinine-blind window’ (GFR 90–60 ml/min). This is the main reason for using mGFR to disclose early renal progression from CKD stage 1 to stage 2. Although creatinine-based eGFR equations used in children and adults are different, it is an interesting observation that these formulas overestimate mGFR in both children and adult Fabry patients with normal or near-normal kidney function [19,22,23]. It is not known whether this pattern relates to abnormal creatinine metabolism, changes in muscle mass or other factors specific for Fabry disease.

Hyperfiltration in Fabry patients has mainly been shown in adults by eGFR, but has also been recently demonstrated in a limited number of patients with mGFR [19,20]. In children, using the Schwartz76 formula, Ries et al. reported nine out of 25 boys with eGFR >140 ml/min/1.73 m² and thus assumed hyperfiltration in a high number of patients [19,22,23]. It is not known whether this pattern relates to abnormal creatinine metabolism, changes in muscle mass or other factors specific for Fabry disease.

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Fig. 3. Pairs of individual mGFR and eGFR [results for all patients who had more than two repeated measurements (n=13)]; horizontal lines mark the point outside which repeated test results exceed the CD for the analysis; pairs of mGFR (left) (Patients 1–6, iothalamate clearance; Patients 7–13, Cr²⁵⁺-EDTA clearance) and eGFR (right) (Schwartz09 formula) are shown; seemingly missing corresponding measurements are due to overlapping results (Patient 9, mGFR1=mGFR3; Patient 10, eGFR2=eGFR3; Patient 11, mGFR2=mGFR3).

Cystatin C has been suggested as more accurate in the near normal GFR range, especially in children [41]. Schwartz et al. found that the eGFR equations based on cystatin C alone did not score better than the creatinine-based Schwartz09, whereas the combined equations containing both creatinine and cystatin C in general had better scores [26]. Feriozzi et al. demonstrated that serum cystatin C and cystatin C clearance, but not serum creatinine and creatinine-based eGFR formulas, indicated deterioration of GFR after 1 year of ERT in a group of 21 proteinuric adult Fabry patients treated with ERT for 3 years [42]. However, they did not include exact GFR measurements, and pitfalls in the cystatin C metabolism caused by ERT itself (i.e. changes in thyroid or proximal tubule function) cannot be excluded. Differences of 10–40% have been shown between cystatin C values measured by different laboratory methods [43]. The lack of standardization of methods and the higher costs are among the reasons that cystatin C-based eGFR has not been introduced in international general guidelines for clinical practice [43,44].
many centres, including the centres in the present study, cystatin C is still not a routine measurement. In addition, cystatin C is not available in the follow-up of Fabry patients included in the international Fabry registries (Fabry Outcome Survey and Fabry Registry) and different clinical trials. The new complex Schwartz formula that includes cystatin C and BUN needs validation also in Fabry patients where changes in BMI and muscle mass, as well as potential influence of ERT itself, may have an impact on the precision of new formulas. Further studies should be performed to validate cystatin C-based GFR formulas in Fabry children.

During repeated measurements of GFR, we found a larger variability and a tendency for eGFR (Schwartz09) to suggest changes in GFR that could not be confirmed by mGFR in about 50% of the patients. The robustness of GFR methods is an important issue in Fabry disease where valid early clinical prognostic markers are missing and subtle changes in GFR may raise concern on the efficacy of individual therapy [8,19]. Repeated GFR measurements will always show some degree of variance due to analytical and biological variation, and the concept of CD is, therefore, a valuable reminder that should preclude premature or false conclusions on improvement or deterioration of kidney function. Our study, therefore, supports the routine use of exact GFR measurements in detecting clinically relevant changes in kidney function. In clinical practice, we recommend mGFR annually or once every 2 years in all children on ERT and/or with manifest microalbuminuria/proteinuria and once every 3–5 years in patients not on ERT. We suggest yearly calculation of eGFR in all children with Fabry disease over the age of 5 years. The new abbreviated Schwartz formula is feasible and recommended for routine use, bearing in mind the shortcomings of all creatinine-based formulas in the ‘creatinine-blind window’. Furthermore, all unexpected decreases or low levels of eGFR or mGFR should be confirmed with a repeat measurement of mGFR within 3 months.

Limitations

Different methods for mGFR measurements and serum creatinine analyses were used in the three different centres. Variable methodology, as well as variable patient characteristics, may influence the difference found between measured and estimated GFR results, but the finding that similar bias (median values) was observed for all equations in the different centres in spite of the use of different methodology strengthens our results. It should be noted that the slightly higher mGFR values in the Dutch cohort compared to the UK patients may be due to many female patients (Table 1) and the finding reported by Vedder et al. that 78% of the Dutch female Fabry patients showed signs of hyperfiltration [20]. The one-point iohexol procedure is assumed to have a higher risk of outliers than the multiple point procedure. On the other hand, the method is shown to correlate well with multiple point methods [45–48]. The short follow-up time and the low number of patients with three or more GFR measurements limit the value of the comparison of repeated measurements. Potential interlaboratory variations of GFR estimations might have been attenuated by utilizing a modified k for each site. This was not available in the study. On the other hand, our results are strengthened by the fact that five different eGFR calculations for each paired GFR measurement all showed the same pattern of differences in all three centres.

Conclusions

In our study of children with Fabry disease and normal kidney function, GFR estimated by the Schwartz09 formula or the Counahan76 formula showed relatively good performances with a minor overestimation of the mean GFR and a high percentage of the eGFR within 20% of the mGFR. However, less than half of the eGFR measurements were within 10% of the mGFR and demonstrate that the eGFR may lead to an unacceptable high failure rate in the diagnosis of early decline in GFR from the normal GFR range. This may lead to delay of appropriate initiation of ERT. Estimated GFR (Schwartz09) showed greater variation for repeated examinations than mGFR. We recommend the use of the mGFR to disclose early decline of GFR in the ‘creatinine-blind window’. The original Schwartz formula should be replaced by the superior new abbreviated Schwartz formula in the general follow-up of children with Fabry disease. The latter formula should also be used to re-calculate the eGFR values in the international Fabry registries. The new complex Schwartz formula and other cystatin C-derived formulas need validation in Fabry children.

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Renal function in Fabry children


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