AUTOMATIC REPORTING OF CREATININE-BASED ESTIMATED GLOMERULAR FILTRATION RATE IN CHILDREN: IS THIS FEASIBLE?

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ABSTRACT

Creatinine, although widely used as a biomarker to measure renal function, has long been known as an insensitive marker of renal impairment. Patients with reduced renal function can have a creatinine level within the normal range, with a rapid rise when renal function is significantly reduced. As of 1976, the correlation between height, the reciprocal of creatinine, and measured glomerular filtration rate (GFR) in children has been described. It has been used to derive a simple formula for estimated glomerular filtration rate (eGFR) that could be used at the bedside as a more sensitive method of identifying children with renal impairment. Formulae based on this association, with modifications over time as creatinine assay methods have changed, are still widely used clinically at the bedside and in research studies to assess the degree of renal impairment in children.

Adult practice has moved in many countries to computer-generated results that report eGFR alongside creatinine results using more complex, but potentially more accurate estimates of GFR, which are independent of height. This permits early identification of patients with chronic kidney disease. This review assesses the feasibility of automated reporting of eGFR and the advantages and disadvantages of this in children.

Keywords: Estimated glomerular filtration rate (eGFR), chronic kidney disease (CKD), children, automated reporting of eGFR.

BACKGROUND

Creatinine, although widely used as a biomarker to measure renal function, has long been known as an insensitive marker of renal impairment.[1] Patients with reduced renal function can have a creatinine level within the normal range, with a rapid rise when renal function is significantly reduced. In 1976 Schwartz et al.[2] reported a correlation between height, the reciprocal of creatinine, and measured glomerular filtration rate (GFR) in children. This was used to derive a simple formula for estimated glomerular filtration rate (eGFR) that can be used at the bedside as a more sensitive method of identifying children with renal impairment. At a similar time, this association was also described by Counahan et al.[3] with an adaptation to allow use of SI units to measure creatinine. These formulae, which have been modified as creatinine assay methods have changed over time, are still widely used clinically at the bedside and in research studies to assess the degree of renal impairment in children.

With the advent of computer-generated results, there is the ability to report alongside creatinine results more complex but potentially more accurate estimates of GFR, including those which are independent of height. This would permit early identification of patients with chronic kidney disease (CKD), with evidence in adults demonstrating the benefits of this.[4] For this reason, in some countries, reporting an eGFR is mandated when a creatinine result is reported, with evidence of an increase in early referrals.[5,6]

During this review, I will assess the feasibility of automated reporting of eGFR and the advantages and disadvantages of using this in children. I will review the accuracy of established height-based formulae and more recently published height-independent formulae. After briefly discussing local optimisation of these formula and methods of calculating eGFR, which use other biomarkers (e.g. cystatin C), I will draw conclusions regarding the benefits and feasibility of automated eGFR reporting in children.

BENEFITS OF AUTOMATIC REPORTING OF ESTIMATED GLOMERULAR FILTRATION RATE

In adults, evidence-based strategies have been shown to prevent progression of CKD. In addition, CKD is a marker of increased risk of cardiovascular disease. Early detection of CKD permits early intervention to reduce the risk of cardiovascular mortality and progression to renal replacement therapy (RRT). Even in patients who progress to RRT, early detection (>12 months before onset of RRT) has been shown to reduce mortality rates. This rationale for population-based screening led to automated eGFR reporting in the UK in 2006 following publication of a National Service Framework document.[7] Automated reporting led to increased and earlier referrals,[6] although an evidence-based review suggests there is still a need for more research into the most effective interventions at early stages of CKD.[4]

The rationale for screening in children is less clear. There are multiple risk-factors for progression of CKD in children.[8] Many are amenable to treatment including conditions such as hypertension[9] and proteinuria.[10] The incidence of CKD, however, is much lower than in the adult population and the significance of anxiety caused by false positives is more of a concern. The incidence of CKD-related cardiovascular disease is also lower than in adults. However, studies have detected subclinical cardiovascular changes such as increased left ventricular mass,[11] which suggests that earlier detection and intervention may be of benefit.[12] Locally, in the Nottingham Children's Hospital, we introduced a report accompanying a creatinine result in children <18 years of age including instructions on how to calculate an eGFR based on local optimisation of the Schwartz formula. This was in response to late referrals of patients with CKD. This resulted in a moderate increase in referrals, but we have still received late referrals (unpublished). There are many theoretical benefits of early identification through automated eGFR reporting in children, though there is still a need for more research to determine the effectiveness of early interventions.

LIMITATIONS OF CREATININE-BASED ESTIMATED GLOMERULAR FILTRATION RATE

Both calculated and direct measurements of GFR have limitations that need to be considered when evaluating their use. Height-based eGFR has limitations in relation to accuracy, utility, and feasibility.

Any calculated GFR is an estimate and therefore has a degree of inaccuracy. The standard, used for adult based formulae, requires that 75% of eGFR values are within 30% of the measured GFR value.[13] When assessing the bedside height-independent formula in this way locally, we found that only 55% of measurements met this criterion.[14] This can be attributed to the changes in methods of creatinine measurement since the original studies were performed with a move towards enzymatic measurements or a corrected Jaffe measurement. This variation in creatinine measurement has been less of a concern since standardisation of creatinine methods was developed in order to facilitate automatic eGFR reporting in adults. The creatinine standardisation recommendations[15] by the National Kidney Disease Education (NKDEP) and Laboratory Working Group (LWG) Laboratory Working Group set isotope-dilution mass spectrometry (IDMS) as the reference for creatinine measurements. This significantly reduced variability in creatinine measurements between different methods and manufacturers.[16]

Height and creatinine-based eGFR formulae assume a linear relationship between height and the reciprocal of serum creatinine, although some studies have questioned this relationship.[17] Any factor that may influence this relationship will limit the accuracy of the estimate. This would include extremes of age (e.g. <1 year of age), malnutrition, and neuromuscular disorders.

eGFR formula have not been demonstrated to be reliable when altering medication doses in children with reduced renal function.[18,19] This is likely to be because the formulae are based on children with stable renal function. Children who are unwell and

require chemotherapy or antibiotics are unlikely to be stable and the equations are therefore less accurate. Where possible, drug monitoring should be used.

The derivation of many height and creatinine-based eGFRs in children has been completed in populations of patients with CKD and those post renal transplant. This has important implications for the wider application of the estimate. The calculations assume that creatinine levels are steady and less accurate in patients with acute kidney injury (AKI). Adjustments can be made to the equations to account for the rate of change of creatinine to improve the utility in this situation.[20] However, current AKI detection algorithms remain creatinine-based.[21]

Finally, the limitation of height-based formulae that is probably most significant is the need for an accurate height to be included in the data given to the laboratory that is measuring the creatinine assay. This relies on the clinician recording this data when requesting the blood test, laboratory teams or systems to input this data, and the systems available to perform the calculation. Feedback from local paediatric teams regarding a project to report the height-based formulae with creatinine measurements in children <18 years old included clinician difficulty in having a recent height available when requesting or interpreting the result (unpublished).

Table 1: Formulae discussed in this paper and accuracy expressed as a percentage (%) of values within 30% of reference glomerular filtration rate (P30).

Formulae (publication)	*eGFR (mL/min per 1.73m^2)	P30 (%)	Summary of study conclusions
Height-based formula[2,3]	=40 × height (cm)/SCr(µmol/L)	55	Measured GFR is linearly related to height divided by serum creatinine
Nottingham - optimised height-based formula[14] (Lunn et al. 2015)	=k × height (cm)/SCr(µmol/L) Where k=36 in males ≥13 years of age and k=30 in all other cases	79	Local optimisation improves performance of height-based formula
Belgium–Pottel[27,29] (Pottel et al. 2012)	=107.3/(SCr/Q) with: Q=88.4 × (0.21 + 0.057 × Age − 0.0075 × Age^2 + 0.00064 × Age^3 − 0.000016 × Age^4) for males Q=88.4 × (0.23 + 0.034 × Age − 0.0018 × Age^2 + 0.00017 × Age^3 − 0.0000051 × Age^4) for females	79.6	Equation comparable to the updated Schwartz formula
Lyon–Pottel[33] (De Souza et al. 2015)	107.3/(SCr/Q) with Q=Lyon derived median of PCR of healthy children at a specific age	87	The height-independent equation, with or without an adaptation to the local laboratory, could be used as a screening tool in a general population
BCCH2[24] (Mattman et al. 2006)	=-61.56 + [5886 × [1/SCr(µmol/L)] + [4.83 × Age] + 10.02 (if male)	Not reported	With local derivation of constants, the formula can be used where height is not available.
Modified BCCH2[25] (Zappitelli et al. 2010)	=Inverse ln of: 8.067 + (1.034 × ln[1/SCr(µmol/L)] + (0.305 × ln[age]) + 0.064 if male	74.2–80.9	Height-independent formula with local optimisation performed equally well when compared to the Schwartz formula
Nottingham - optimised Modified BCCH2[14] (Lunn et al. 2015)	=Inverse ln of: 6.064 + (0.554 × ln[1/SCr(µmol/L)]) + (0.254 × ln[age]) + 0.025 if male	85	Height-independent formula with local optimisation performed equally well when compared to the locally-optimised Schwartz formula

*all ages in years
eGFR: estimated glomerular filtration rate; PCR: protein/creatinine ratio; SCr: serum creatinine.

CURRENT HEIGHT-INDEPENDENT CREATININE-BASED ESTIMATED GLOMERULAR FILTRATION RATE FORMULAE IN CHILDREN

The advantage of height-independent creatinine-based eGFR formulae is that no extra data are required in the laboratory to allow reporting whenever creatinine is measured.[22] There is theoretical evidence that this is plausible as uncorrected GFR has a linear relationship with age between the ages of 2 and 16 years.[23] This has led to the development of height-independent formulae, the majority of which use creatinine because of the wide availability within clinical laboratories.

In 2006, Mattman et al.[24] derived two height-independent formulae (Table 1). The first (BCCH2) was a derived formula based on patients undergoing ^{99m}Tc-DTPA (diethylene triamine pentaacetic acid) GFR measurement and creatinine measured by enzymatic method. The aim of the study was to assess the sensitivity and specificity of an estimate to accurately identify patients with a GFR <60 mL/min/1.73 m^2. They also derived a method to determine creatinine cut-offs based on age and gender to serve this purpose. This performed comparably to a locally optimised Schwartz formula with a Pearson correlation coefficient of 0.72 compared with 0.83 for the Schwartz formula. The cut-off based method was also comparable with a sensitivity of 86% and specificity of 93% for the detection of a GFR <60 mL/min/1.73 m^2 (BCCH2 – sensitivity 79%, specificity 99%, locally optimised Schwartz – sensitivity 86%, specificity 97%).

The BCCH2 formula was modified in 2010 by Zappitelli et al.[25] using local data based on iothalamate GFR and enzymatic creatinine measurements in a population of paediatric patients with renal disease pre and post-transplant. Measurements were taken on up to three occasions over a median period of 1.1 years and the ability of the estimates to assess changes in measured GFR over time. The modified formula was comparable to the Schwartz formula with 75.4%, 74.2%, and 80.9% of values within 30% of measured GFR over the three different time periods compared to 76.4%, 82.8%, and 85.1% for the Schwartz formula.

Attempts have been made to apply adult derived formulae to children, the majority without a sufficient degree of accuracy. One exception may be the Lund–Malmö formula. This was originally derived in adults[26] reporting 84% of values within 30% of a measured GFR. This was assessed in a paediatric population of renal and oncology patients (pre-chemotherapy) with an iohexol GFR used as a reference and an enzymatic method used to measure creatinine. Again this was comparable to height-based formulae with 76% of values within 30% of measured GFR compared to 74% in a locally optimised Counahan–Barratt height-based estimate.

Most recently, a height-independent formula was developed based on the concept of a population-normalised serum creatinine by Pottel et al.[27] This used a ^{51}Cr-EDTA GFR as a reference. The serum creatinine measurement was obtained with an enzymatic method in children <5 years of age and a compensated Jaffe assay in children ≥5 years of age in a population of children with renal disease. They reported that 72.8% of values were within 30% of the measured GFR. This was comparable to the 69.4% for the Schwartz formula and better than the previously described height-independent measurements, although this data was not published.[28] A later publication[29] described an age-based formula for derivation of the population-normalised serum creatinine.

There are therefore a number of candidates for estimating GFR in children that are as accurate as the currently used height-based methods. They could be used to report eGFR automatically in children. The majority are tested in a population of children who have renal disease, and a concern would be that they may not be as accurate in a general paediatric population leading to an increase in false positives. The number of false positives is dependent on the definition of the lower limit of normal. Pottel et al.[30] have used large population based data to define a cut-off of 75 mL/min/1.73 m^2. This is at a higher level than recommended in adults, where in the absence of other evidence of renal disease an eGFR of 60 mL/min/1.73 m^2 is used.[31]

Local Optimisation of Results

A method often used is to apply formulae derived externally to internally verify them, and then optimise the constants to improve the accuracy of the formulae. Different methods of creatinine measurement (enzymatic, uncompensated Jaffe assay, or compensated Jaffe assay) have historically

been incomparable. Local optimisation allows adjustment for local methods of creatinine assessment. Table 2 describes different formula derived by local optimisation of the Schwartz formula and compares them with the local creatinine method used. Centres using the same creatinine method derived similar values of k.

We have done this locally in Nottingham Children's Hospital, using the Solver function of Microsoft Excel to optimise the constant k in the formula: k × height (cm)/creatinine (µmol/L) to minimise the sum of the squares of the differences. This produced a k of 36 for males 13 years or older and a k-value of 30 in all other situations.[32] We verified our data following a change in method of creatinine assay and found that the optimised formula was of similar efficacy with 49% of patients within 30% of measured GFR using the Schwartz formula (k=40) and an enzymatic assay, 55% of patients within 30% of measured GFR using the Schwartz formula (k=40) and a compensated Jaffe assay, 72% of patients within 30% of measured GFR using the locally optimised formula and an enzymatic assay, and 79% of patients within 30% of measured GFR using the locally optimised formula and a compensated Jaffe assay.[14,32] This also demonstrates the benefits of the use of the IDMS as a reference for creatinine assays.

This method has not been widely applied to height-independent eGFR formulae in children. Zappitelli et al.[25] modified the BCCH2 formula[24] using a natural logarithmic transformation rather than simple optimisation of the original formula. We applied our original optimisation technique to the Zappitelli formula and altered the constants to minimise the sum of the squares of the differences. In our population, this improved the performance of the equation from 50% of values within 30% of the measured GFR to 85%.[14]

The Pottel formula is unique in that they have introduced the concept of a Q value as a population-normalised serum creatinine.[27] They have defined a method for calculating Q values at different ages and for different genders. This value is based on normal values from their own laboratory and hence could be applied to other laboratories by calculating the local median serum creatinine for different age and gender which will be specific to the local population. This was done in Lyon and demonstrated an improvement in the accuracy of the equation from 79.6% of values within 30% of the measured GFR to 87%.[33]

Table 2: Height-based formulae and local optimisation with the method of serum creatinine assay and reference GFR.

Publication	Patient population	Age range (years)	Gender (% male)	GFR reference method	SCr	K (SCr units: µmol/L)
Schwartz et al.[2] (1976)	CKD	0.5–20	Not reported	Creatinine	Jaffe	48.6
Counahan et al.[3] (1976)	CKD	2–14	Not reported	^{51}Cr-EDTA	Jaffe (compensated)	38.0
Morris et al.[41] (1982)	CKD & normal	2–14	Not reported	^{51}Cr-EDTA	Jaffe (compensated)	40.0
Schwartz et al.[42] (1985)	CKD	3–21	63%	Creatinine	Jaffe	Males >13 years, 61.9 Others, 48.6
Vachvanichsanong et al.[43] (2003)	CKD & normal	0–19	Not reported	Creatinine	Jaffe (compensated)	41.1
Hellerstein et al.[44] (2004)	CKD	4–21	48%	Creatinine (cimetidine)	Jaffe	Males >13 years, 52.2 Others, 44.2
van Rossum et al.[45] (2005)	Tx	4–20	68%	Inulin	Enzymatic	41.2
Schwartz et al.[46] (2009)	CKD	1–16	61%	Iohexol	Enzymatic	36.5

Cr-51 EDTA: chromium-51 ethylene diamine tetracetic acid; CKD: chronic kidney disease; SCr: serum creatinine assay; GFR: glomerular filtration rate; Tx: treatment.

Table 1 summarises the main formulae discussed in this review and the accuracy as assessed by the percentage of values within 30% of the reference GFR.

ALTERNATIVES TO CREATININE-BASED ESTIMATED GLOMERULAR FILTRATION RATE IN CHILDREN

Other height-independent formulae have been derived based on cystatin C either in isolation or in combination with other measurements such as creatinine. They have been shown to be comparable to a local optimised Schwartz formula with 81–91% of values within 30% of the measured GFR[34] when tested using a compensated Jaffe assay and compared to an inulin-measured GFR. Some of these formulae also require height or weight. The use of cystatin C is promising in increasing the accuracy of eGFR measurements and has been recommended in adults,[31] particularly if the creatinine based eGFR is <60 mL/min/1.73 m^2.

NGAL (neutrophil gelatinase-associated lipocalin) has been used as a urine[35] and serum biomarker[36] for AKI in children. Serum NGAL has been shown to correlate with measured GFR, particularly at lower levels of GFR.[37] Beta-trace protein and beta-2 microglobulin have also been suggested as possible candidates for serum biomarkers of GFR but these require further research. They have not been shown to be superior to the Schwartz eGFR.[38,39] A significant limitation of these methods is that they are not yet available in all institutions.

CONCLUSION

In conclusion, automated eGFR reporting in children is now feasible with similar accuracy to currently used adult equations. It would meet accepted criteria[40] for a screening tool for the detection of CKD whenever any child has a serum creatinine measurement. An abnormal eGFR result should therefore prompt a thorough clinical evaluation of the patient and be interpreted in the light of the clinical findings. (The 'e' indicating 'estimated' should never be forgotten).

I suggest that automated eGFR should be introduced for children in conjunction with guidelines for the clinical evaluation of children who are noted to have a reduced eGFR. Either the Pottel formula[27] or the modified BCCH2 formula[25] could be used. Some studies without local optimisation favour the Pottel formula,[22,23] hence local optimisation should be used wherever possible.[14,33] It should be carefully evaluated to note the effect on early detection of CKD, the number of false positives, and the implications for service provision related to increased referrals. This will allow earlier intervention of treatments that have been shown to reduce the rate of progression of renal disease. More research is still required to determine the most effective interventions and their impact on the long-term outcomes in young children with CKD.

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