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ASSESSMENT OF KIDNEY FUNCTION

Estimating GFR in children

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Abstract

In a new study, Schwartz and colleagues have investigated the best way to estimate glomerular filtration rate (GFR) in children. Having already improved GFR estimation with the use of creatinine-based equations, the investigators now propose a more precise method for cystatin C measurement. The precision of a GFR equation will strongly depend on the analytical precision of the biological variables included.

In children with chronic kidney disease, measuring glomerular filtration rate (GFR) is the best indicator of global kidney function.[1] Because measuring GFR remains relatively cumbersome and costly, however, estimating GFR using renal biomarkers remains relevant for daily practice. In 1976, Schwartz *et al.* proposed an equation where the parameter height/serum creatinine was multiplied by a constant (k) to estimate creatinine clearance.[2] This original Schwartz equation has been popular for several decades, but was based on the colourimetric Jaffe creatinine measurement method. Measuring serum creatinine levels by a precise and reproducible method is especially important in children because their mean serum concentrations are lower than those in adults and are thus more prone to interferences, for example from proteins present in the serum. Therefore, it is now recommended that serum creatinine levels should be measured by enzymatic methods in children.[3]

"By optimizing the measurements of cystatin C, they improve the estimation of GFR in children..."

Changing from the Jaffe method to enzymatic methods had a large impact on the k value in the original Schwartz equation.[3,4] In 2009, Schwartz *et al.* recalculated the k value of the estimating equation to be used with the enzymatic method and plasma iohexol clearance measurement as a reference method to assess GFR.[4] The fact that most of the enzymatic methods available in 2012 are isotope dilution mass spectrometry (IDMS)-traceable means that an identical equation can be used in all laboratories, which is very important from a practical point of view[5] However, a limitation of the 2009 study was that the equation was not validated in an independent validation cohort. In the same publication, the researchers studied the performance of the new renal biomarker cystatin C. In contrast to prior studies, Schwartz and colleagues demonstrated that cystatin C was less predictive of measured GFR than was height/serum creatinine, which resulted in a less powerful cystatin C exponent in the final equation compared with height/serum creatinine. This final equation included other variables such as blood urea nitrogen (BUN), height and sex.[4] One major issue was the turbidimetric method used to measure cystatin C, which has later been demonstrated as relatively imprecise.

In 2012, Schwartz and colleagues studied children included in the Chronic Kidney Disease in Children (CKiD) study in order to determine the best way to estimate GFR.[6] Only individuals aged between 1 year and 16 years with an initial estimated GFR of 30-60 ml/min/1.73 m^2 (by the original Schwartz equation) were included. GFR results were available for 965 patients, of whom two-thirds were randomly chosen for the training set and one-third for the validation sample. Both samples were similar in terms of age, height, sex and median measured GFR (43 ml/min/1.73 m^2).[6] In contrast to the 2009 study, cystatin C was measured by the particle-enhanced nephelometric immunoassay (PENIA) method. Measuring cystatin C by both turbidimetric and nephelometric assays in 646 individuals, Schwartz *et al.* found a better correlation between cystatin C and measured GFR with the PENIA method than with the turbidimetric assay (0.87 versus 0.74, respectively). As a result of the improved correlation, cystatin C had the same predictive power as height/serum creatinine to estimate GFR. Moreover, the performance of the univariate cystatin C equation was slightly better than the updated 2012 Schwartz creatinine equation. Indeed, in the validation dataset, the accuracy of the univariate height/serum creatinine equation and

univariate cystatin C equation— defined as the percentage of estimated GFR within 30% of measured GFR— was 80% and 83%, respectively. Accuracy of bivariate equations that included both cystatin C and creatinine (89%) was better than that of equations combining BUN and cystatin C or BUN and serum creatinine (82% and 84%, respectively). The best accuracy of 91% was observed in the equations that included cystatin C, height/serum creatinine, height, sex and BUN. Such a high accuracy is impressive and has rarely been achieved in either paediatric or adult studies of GFR estimation.

There are several explanations for such a high accuracy and precision. The precision of a GFR equation will strongly depend on the analytical precision of the biological variables included (enzymatic, IDMS-traceable method for creatinine and PENIA method for cystatin C).[5] The precision of the reference method used to measure GFR is also of high importance. The plasma iohexol clearance used by Schwartz *et al.* is precise and reproducible in children.[7] Even if plasma clearance may be considered less physiological than urinary clearance, there is little doubt regarding its precision and biological variability, especially in children in whom urological disorders and malformations are frequent and toilet training is not always fully accomplished. The last explanation for the high accuracy observed in this study is also one of its limitations. Indeed, even if the new equations have been validated in an internal validation cohort, it is obvious that equations always perform best in cohorts they were derived from. In other words, these new equations still need to be validated externally. Also, only children with CKD were studied in the CKiD cohort. Therefore, the performance in individuals with higher GFR levels should also be studied. There is actually a risk that equations (notably creatinine-based equations) underestimate measured GFR.[8,9] Accuracy of the various equations, especially the cystatin C and combined equations, should also be studied in children with abnormal muscular mass (such as spina bifida) because even the updated Schwartz equation would probably overestimate measured GFR in these children. Two other limitations of this study should be mentioned. First, the investigators included the variable BUN in their final equation. It is, however, not clear if the same type of equation (that includes height and sex) without BUN would have a worse performance. Indeed, including an additional biological variable could add potential imprecision owing to analytical and biological variation of this variable. Also, as stated by the authors, BUN measurement is not standardized.

Second, recent data, notably in adults, have indicated that standardization of cystatin C measurement by PENIA methods should be done with the new reference material (ERM-DA471/IFCC).[10] It is not clear if Schwartz and colleagues used this standard. Differences in calibration (as a result of lack of standardization) would change the cystatin C concentrations and therefore also change the values of the exponents applied to cystatin C.

Whatever the limitations of this study maybe, Schwartz and colleagues have once again added another important brick in the wall. By optimizing the measurements of cystatin C, they improve the estimation of GFR in children, which is important in daily practice. We must keep in mind, however, a fact also underlined by the authors, that measuring GFR using a reference method remains essential in specific situations.

Competing interests

The authors declare no competing interests.

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