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EDITORIAL COMMENTARY

Bias and precision of estimated glomerular filtration rate in children

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Abstract Determining true glomerular filtration rate (GFR) using an exogenous marker is time-consuming and cumbersome. Therefore, creatinine-based estimates of GFR are used. Recent papers using new population-specific/local parameters in their prediction equations, standardizing creatinine determination or adding other endogenous surrogate markers of GFR, like cystatin C, could demonstrate an improvement of bias inherent in the results of the prediction equations. Precision, however, is still poor. Currently, we have to accept a precision (as defined in the so-called Bland-Altman plot) of ±20% in adults and ±30–40% in children. This problem of poor precision/uncertainty is especially bothering in the higher, near normal GFR range. Caution should be exercised when applying prediction equations in individuals in need of an accurate GFR determination. In that case, a real clearance procedure has to be performed. In the long run, the true clearance procedure should be simplified using new exogenous GFR markers and developing new devices, allowing GFR measurements to be performed, for example, transcutaneously. Such a procedure would be more acceptable for both patients and physicians.

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Estimates of glomerular filtration rate (GFR) are performed in order to circumvent the expensive, time consuming and difficult to perform GFR determination using exogenous markers, like inulin or iothalamate. The well-known Cockcroft-Gault formula, mainly used in adults [1], and the Schwartz formula, devised for children [2], were published 30 years ago. Currently, there is still considerable interest in improving the old formulae or to develop new and more precise formulae as indicated by the paper by Zappitelli et al. [3], as well as recent reviews [4, 5]. Up to now, at least 46 GFR prediction equations have been published [6].

Zappitelli et al. [3] developed new parameters for the so-called Schwartz [2] and Leger [7] formulae, equations frequently used in children. Their study [3] is based on the data of 195 children and young adults. The GFR measurements had been performed between 1999 and 2004. The measured GFR was in the range between 13 and 166 ml/min/1.73 m^2. It is of note that 76 subjects had a measured GFR higher than 90 ml/min/1.73 m^2. In order to evaluate their new constants, the authors used regression analyses and Bland-Altman plots [8, 9]. They noted that the bias is close to zero, but the precision is poor (±40 ml/min).

The bias is reflected by the deviation from the line of identity in the regression analyses and the deviation from the mean in the Bland-Altman plots. Precision or limits of agreement (LOA) are defined as ±2 SD around the mean calculated for the difference between the two methods, which are compared in the Bland-Altman plot. Thus, the LOA represents the range within which approximately 95% of the predicted data could be found. In other words, if the LOA is ±40 ml/min, then a subject having a measured GFR

of 90 ml/min/1.73 m^2 may have a predicted/estimated GFR somewhere between 50 and 130 ml/min/1.73 m^2. This problem of uncertainty is especially bothering in the higher, near normal GFR range.

It is of note that the precision of the GFR prediction equation is highly dependent on the number of subjects on which the equation had been developed. Furthermore the precision decreases the higher the GFR values included. This is due to the fact, that true GFR is more variable, the higher it is (circadian rhythm, dietary habits).

The latest and probably best approach to estimate GFR in adults was the development of the formula by the Modification of Diet in Renal Disease (MDRD) Study [10]. The problem with the MDRD formula, however, is that it had been developed for lower range GFR values and is therefore not suitable for near normal values. This is true also after a modification and adjustment of this formula. In adults, this formula gives quite reasonable results, if one is willing to accept an error of ±20% (precision).

The MDRD formula had been developed on a large patient data set. The problem with paediatric formulae is that usually the sample size is much lower (about a factor of 10). Therefore, the precision of these formulae is also lower. Again the physician has to be willing to accept a low precision together with a limited GFR range up to 90 ml/min/1.73 m^2.

In general, one should keep in mind that most prediction equations were developed and validated in patients with reduced GFR. Thus, it is obvious that these GFR prediction equations can only be used in the data range for which they were developed and validated.

As already concluded in the 2002 analysis and recommendations of the K/DOQI committee [11], bias is not the problem, but precision. It was recommended to develop new methods for detecting mild and moderate kidney disease. In children, the research recommendation was: standardisation of creatinine measurement, use of "gold standard" GFR measures for reference and larger samples of children of different ages and ethnicities.

Currently, there are efforts on the way to improve the precision of GFR estimate by standardizing creatinine determination [12, 13]. Obviously there are still formulae and factors in use which are based on creatinine determinations using the so-called colorimetric picric acid method (Jaffe method) [12, 13]. This method is especially error prone and gives much higher values than the enzymatic method. The situation becomes erratic with the Jaffe method in the low creatinine concentration range/high GFR range if hemolysis occurs [14]. Thus, it is obvious that if one is willing to use prediction equations the enzymatic creatinine determination [15, 16] or an HPLC method has to be used.

Prediction equations should be adjusted to the population in which they are used. This seems to be important, as pointed out by Ma et al. [17] in adult Chinese patients. They found a fairly low bias in their large patient population, but a precision of only around ±20 to ±25 ml/min/1.73 m^2. Introducing population-specific or even local parameters, as recommended by Zappitelli et al. [3] and others [18], may reduce the bias, but will also reduce precision, as the number of subjects included in the development phase of the formula can hardly be large enough, at least in comparison to the number of patients included in the development of the MDRD formula.

Another feature of importance is body habitus, which may be interfering with creatinine production [4], e.g. growth. This is of special relevance in children. Furthermore, the formulae may result in misleading predictions in cases of malnutrition.

It is of note that in comparison to GFR, creatinine is a slowly changing parameter. Thus no acute changes can be assessed by the formulae. This is of special relevance in transplanted patients [19].

Thus, currently we have to accept a precision of ±20% in adults and ±30–40% in children, when estimating GFR from creatinine. Therefore, it would be important to either find better endogenous markers as surrogate markers of GFR. Cystatin C is currently under intense scrutiny [20–25]. For example, in a recent paper, Zappitelli et al. [26] derived and validated cystatin C-based prediction equations for estimating GFR in 103 children. In their study, the authors also devised a new equation, combining information on cystatin C and creatinine. Using this new formula and also other equations with their original as well as newly estimated parameters, they could reduce the bias to nearly 0, while the 95% LOA was still fairly high: ±30 to ±35 ml/min/1.73 m^2. Recently, Bouvet et al. [21] reported that GFR is better estimated by considering both serum cystatin C and creatinine levels. The reported minimum and maximum percentage errors were higher than ±40%. Thus, prediction of GFR in the individual is still highly variable.

Beside the search for endogenous surrogate GFR markers, it would be important to develop more convenient GFR methods by using new exogenous markers, which are either easier to determine in plasma or which could be measured transcutaneously. By labelling inulin with FITC [27, 28], it was possible to determine GFR by measuring the dye label. The problem of FITC inulin, however, is its poor solubility, which has been overcome by using sinistrin instead of inulin [29]. Recently, Rabito et al. [30] published a new GFR marker, which can be determined transcutaneously: Carbostyril124-DTPA-Eu. Thus, there are ongoing efforts to simplify the determination of real GFR.

In conclusion, the precision of GFR prediction equations based on creatinine or cystatin-C is still low, especially if

GFR is near normal [15, 16]. There might be some improvement in precision by introducing population-specific/local parameters, standardizing creatinine determination or adding other endogenous surrogate markers of GFR. Caution, however, should be exercised when applying prediction equations in individuals in need of an accurate GFR determination, as then a clearance procedure has to be performed [31]. In the long run, the clearance procedure should be simplified using new exogenous GFR markers and developing new devices, allowing GFR measurements to be performed, for example, transcutaneously. Such a procedure would be more acceptable for both patients and physicians.

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