Is Combined Cystatin C and Creatinine Based Equation Better in Predicting GFR?

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Accurate assessment of glomerular filtration rate (GFR) is critical to estimate degree of renal impairment, intervening early to prevent end-stage renal failure, and dose adjustment of drugs in renal impairment. An ideal renal function marker is one which is produced at a constant rate, is filtered freely in the glomeruli without any tubular secretion, and is completely catabolized in the tubules. Conventionally, renal inulin clearance is the gold standard for GFR estimation, but the method is flawed by difficulty in collecting timed urine samples, especially in children with vesico-ureteral reflux or bladder dysfunction and lack of availability outside a research setting [1].

Creatinine clearance-based estimates of GFR are widely used in children but are inaccurate because of influence of various factors such as age, gender, muscle mass and its catabolism and hydration status. Schwartz formula that takes into account height compensates for increase muscle mass with age but leads to overestimation of moderate to severely reduced GFR (<50 mL/min/1.73 m^2) [2]. Though it obviates the need of tedious urine sampling, plasma creatinine values may change with dietary intake of protein, nutritional status, hepatic disease and increased tubular creatinine secretion [3]. Moreover, creatinine is actively secreted by proximal tubules and tubular secretion increases at lower GFR.

Besides this, radio-isotopes like ^{51}Cr-EDTA, ^{99}Tc-DTPA, ^{125}I-iothalamate and Iohexol are exclusively excreted by glomerular filtration, and are precise and accurate in measurement of GFR [4]. In patients with significant edema or ascites, tracer disappears into the expanded extra-cellular volume leading to GFR overestimation. Although accurate and precise, the methods are relatively cumbersome, invasive, and expensive.

In search of an ideal marker of renal function, researchers have found serum cystatin C (s-cysC) an endogenous low molecular weight protein of cysteine proteinase family which is freely filtered in the glomeruli, completely reabsorbed by proximal tubule and is produced at a constant rate [5]. S-CysC has been proposed as a more sensitive marker of renal function than plasma creatinine as subtle changes in GFR are readily detected due to shorter half life of cystatin C and its level is not affected by age, gender, race and muscle mass. By analyzing data from 536 children with various renal disorders, Filler and Lepage proposed a novel cysC-based GFR estimate [6]. Studies comparing cystatin-based formulas to Schwartz formula have shown contradictory results. While some have shown superiority in terms of precision and accuracy [6,7] others did not prove any advantage [8]. For cysC, Knight, *et al.* [9] showed in a multivariate analysis adjusted for the level of renal function in a general population (8058 subjects) that s-cysC levels may be influenced by multiple factors independent of the renal function, especially high C reactive protein levels. Serum cystatin levels are also influenced by corticosteroid therapy, thyroid dysfunction and ketonuria in diabetic children [4]. Hence, combined serum cystatin C and creatinine based formulas might increase accuracy and precision to estimate GFR to overcome the disadvantages of individual marker.

Bouvet, *et al.* [10] prospectively studied 100 children and compared ^{51}Cr-ethylenediaminetetraacetate (actual GFR) with estimated GFR by combined creatinine and serum cystatin C based equation. The estimation of GFR using the final equation based on the four covariates (cysC, SCr, BW, and age) was less biased and more precise than the Schwartz formula. However for patients with GFR <50 mL/min/1.73 m^2, there was an overestimation of GFR.

Hari, *et al.* [11] have studied 100 children with early CKD (GFR between 60-90 ml/min/1.73 m^2) with ^{99m}Tc-diethylenetriamine penta acetic acid estimated GFR (dGFR) and by applying regression analysis derived equation with creatinine, height and serum cystatin C as covariates. The derived new equation for cystatin alone when compared with actual GFR was found to overestimate, while combined creatinine and cystatin equation underestimated GFR. Cystatin C-based equation [GFR=96.9 -30.4 x cystatin C] had significantly less median bias (1.9 *vs* -12.4 mL/min/1.73 m^2) (Sign rank test, P=0.05), higher precision (13.1 *vs* 25.6 ml/min/ 1.73 m^2) and accuracy (92.1% *vs* 75.7%) as compared to creatinine-based equation. The authors concluded that

cystatin C-based equation was significantly better than creatinine-based equation in terms of bias, precision and accuracy in children with early CKD. Authors also found that adding creatinine to the cystatin C-based formula did not improve the accuracy of predicted GFR. The major strength of this study is its methodologic rigor. The authors have rightly used Bland-Altman plots in the data analysis which strengthened the study conclusions and provided a more precise evaluation of agreement. Further research is required – on a large, well-defined pediatric population with carefully matched controls – to confirm the usefulness of cystatin based estimation of GFR in patients with early CKD.

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Estimating Accurate Glomerular Filtration Rate in Children

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A reliable and accurate assessment of glomerular filtration rate (GFR) is critical for diagnosing acute and chronic kidney impairment, intervening early to prevent end-stage renal failure, prescribing nephrotoxic drugs and drugs cleared by a failing kidney, and monitoring for side effects of medications. Estimation of GFR using exogenously administered substances is well established and precise, but these methods are cumbersome and time consuming [1].

Plasma creatinine is the most commonly used index for estimating renal function in the clinical practice. Due to its small size and lack of protein binding, it is freely filtered through the glomerulus. However, it is also actively secreted by the proximal tubules at unpredictable rates. Moreover, with decreasing GFR, the fraction of tubular secretion increases, leading to an over-estimation of 10-40% when compared to that of inulin clearance [2]. Especially in children, estimation of creatinine is difficult, as there is a muscle mass related increase in plasma creatinine in children after 2 years of life. Moreover, plasma creatinine may change in cases of excessive dietary intake of meat, malnourished children and anorectic adolescents [3]. On the other hand, cystatin C is produced endogenously at a constant rate, is freely filtered by the glomerulus, and is completely reabsorbed and catabolised by the renal tubule cells. Blood levels of