Nigerian Journal of Paediatrics 2007; 34 (3&4): 51-56

REVIEW ARTICLE

The Use of Formula Derived Glomerular Filtration Rate in Children: a Review

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Summary

Adedoyin OT, Mark F. The Use of Formula Derived Glomerular Filtration Rate in Children: a Review. *Nigerian Journal of Paediatrics* 2007; 34: 51. Facilities for investigating renal disorders in children in the developing world are still inadequate. Even when some are available as in the case of creatinine clearance determination, there is still the challenge of accurate urine collection. The newer and easier isotopic methods are unavailable, expensive and pose ethical dilemma. In view of the foregoing and after a critical analysis of its merits and demerits, the formula based glomerular filtration rate (GFR) using height/creatinine formula proposed by Schwartz *et al*, is recommended.

Introduction

GLOMERULAR filtration rate (GFR) is the most important index of renal function because it is the sum of the filtration rates of all the nephrons.[1] It determines the filtered load presented to the renal tubules and the flexibility of the renal response to homeostasis. A reduction in GFR is therefore, the principal functional abnormality underlying renal insufficiency[2] and the value makes it a critical index in the evaluation of renal function. In children, the value of the GFR is often corrected to $1.73m^2$ of body surface area to facilitate comparison between subjects of different sizes. The GFR is usually reduced prior to the onset of symptoms of renal impairment.

Standard method of measuring GFR

The GFR can be assessed by measuring the excretion and plasma level of a substance that is freely filtered through the glomeruli and is neither secreted nor reabsorbed by the tubules. The amount of such a substance in urine per unit time must have been provided by filtering exactly the number of millilitres of plasma that contained the amount. Hence, if the substance is x, GFR = UxV/Px; where Ux = concentration of x in the urine (mg/dl), V = urine flow per unit time in ml/min, and Px = plasma level of x in mg/dl. This value is called the clearance of the substance.[3] In order for the clearance rate of substance to be equal to the GFR, the substance must be freely filtered, not reabsorbed, secreted, protein bound or subject to metabolism, synthesis or storage by the kidney. It must also have a clearance over a wide range of plasma concentrations.[4] Additionally, for clinical use, the substance must be physiologically inert and non-toxic. Inulin, a fructose polymer with a molecular weight of 5200 meets all the criteria set by Smith[5] and is the standard substance used in the measurement of GFR. However, the disadvantages of using inulin in the measurement of GFR are that it is not routinely measured in clinical laboratories and several blood samples and timed urine collection usually requiring bladder catheterisation for accuracy, are necessary. Furthermore, for inulin to be used, crystalline inulin must be brought into solution and then infused intravenously at a constant rate.

Other methods of estimating GFR

In view of the difficulties involved in measuring inulin clearance, several other methods have been used to estimate GFR. The measurement of creatinine clearance is one of such methods and the most popular in the tropics. There are few other methods like the measurements of blood urea nitrogen (BUN), serum creatinine, plasma ≥ 2 microglobulin and cystatin-C. All these methods have their various shortcomings and some of them, particularly the measurement of plasma ≤ 2 microglobulin and cystatin-C, cannot yet be carried out routinely in some developing countries. Efforts have also been

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expended to develop techniques for measuring GFR that are as accurate as the inulin clearance but simpler to carry out. Some of these techniques involve using substances like Vitamin B_{12}, Ethylenediamine tetra-acetic acid (EDTA), sodium iothalamate, iohexol and sodium diatrizoate that can be labelled with radio-isotopes and can thus be measured easily both in plasma and urine. The shortcomings in the use of these techniques especially in developing countries include the non-availability, expense and ethical consideration associated with the infusion of radioisotopes.

The blood urea nitrogen (BUN) is a less satisfactory measurement of GFR because of the variability of urea with the rate of urine flow and the dependence of plasma concentration on nitrogen metabolism as well as renal functions. Serum creatinine on the other hand, is not only influenced by GFR but also by other variables including age, meat intake and muscle mass. Serum level of creatinine therefore reflects not only renal excretion but also the generation, intake and metabolism of creatinine. In the perinatal period, serum creatinine is also influenced by maternal serum creatinine. Plasma ß2 microglobulin is a very reliable measure of GFR because its plasma concentration is low and the plasma concentration only increases as GFR falls. Its major setback as a measure of GFR is that its measurement involves an expensive radio-immunoassay which is not easily available in developing countries.

While measurement of creatinine clearance remains the most popular method of estimation of GFR, the greater potential for error in its measurement rests with inaccuracies in the process of urine collection. Incomplete urine collection can result from misunderstanding by the patient or personnel about the timing directives or from incomplete emptying of the bladder at the start or end of the collection period in patients old enough to understand instructions. The problem of urine collection is more serious in children, particularly neonates, who may not pass urine at the time interval urine collection would have been preferred.

Overview of formula derived GFR

In view of the above stated difficulties and because plasma creatinine is known to correlate negatively with the GFR, several authors have attempted to derive formulae for predicting creatinine clearance from the serum creatinine and other variables including age, height and body weight which are known or thought to affect the creatinine clearance. This attempt has spanned both children and adult populations and ranged from the formula of Edward and Whyte[6] in 1959, Jeliffe[7] in 1971, Cockroft and Gault[8] in 1976 and Taylor *et al*[9] in 1982 (all used in adult populations).

Adults and children occupy different spectrums with regard to the relationship between GFR and plasma creatinine. The relationship between GFR and plasma creatinine in a growing child is not a direct relationship since at comparable levels of renal function, plasma concentration rises with age[10] whereas GFR correlated for body surface area does not vary much after the age of two years. It is therefore apparent that the relationship between plasma creatinine and GFR corrected for surface area must reflect some other aspect of body size.

Graystone *et al*[11] showed that creatinine excretion is proportional to weight and Counahan[12] utilising this information developed the formula:

$$\frac{GFR}{SA} = \frac{KHt}{Pc}$$

Where K = Constant of proportionality
Pc = Plasma creatinine in mg/dl
Ht = Height in cm
GFR = Glomerular filtration rate in ml/min/1.73m^2
SA = Surface area

Based on this assumption, it may be possible to predict creatinine clearance and hence glomerular filtration rate from plasma creatinine and the patient's height. One such relationship was derived by Schwartz *et al*.[13] They used linear regression analysis to derive the relationship between endogenous creatinine (Pcr) i.e. ^{1}/Pcr, height/Pcr and surface area/Pcr respectively, in 186 children and found that of the three, height/plasma creatinine had the strongest positive correlation with creatinine clearance [Ccr ($r = 0.893$)]. The equation derived was:

$$\text{Ccr in ml/min/1.73m}^2 = \frac{0.55 \times \text{height}}{\text{Plasma creatinine in mg/dl}}$$

They then compared the GFR derived from the formula with endogenous creatinine clearance (Ccr) in a group of 77 children and found a good correlation between the formula derived GFR and that using clearance of inulin and endogenous creatinine. The correlation was found to be stronger at Ccr less than 60mls/min/1.73m^2, i.e. at lower levels of renal function, the formula becomes reliable. Counahan *et al*[12] in a similar study arrived at the relationship:

$$\text{Ccr in ml/min/1.73m}^2 = \frac{0.43 \times \text{height}}{\text{Plasma creatinine in mg/dl}}$$

Although the Schwartz formula mentioned above has some shortcomings, it has become the gold standard as far as formula derived GFR is concerned in children. It has also become the subject of validation studies by many workers both in developed and developing world. Okoji *et al*[15] found that the

Schwartz formula gave higher GFR values in term male Nigerian neonates when compared with endogenous creatinine clearance. He however proposed that if the formula was to be applied as a bedside tool in the assessment of GFR, a factor of 10 needed to be subtracted from the derived value. Gbadegesin *et al*[14] on the other hand, found that the Schwartz formula significantly overestimated GFR when compared with endogenous creatinine clearance in healthy Nigerian children and those with renal diseases throughout all ranges of renal function. In another study, Gbadegesin *et al*[15] also found that in detecting patients with impaired renal function who might need more accurate methods of estimating GFR, Schwartz formula had a low sensitivity of 52 percent and might therefore not be useful as a screening tool. Evans and Griffiths[16] in a retrospective analysis of 314 children aged one month to 17 years, compared the height/creatinine derivation with estimation of GFR from ^{51}Cr-EDTA and endogenous creatinine clearance in another group of 225 children. A wide scatter was found with higher GFR > 60ml/min/1.73m^2 especially when they were older than three years of age (r = 0.93). He attributed the increased scatter at higher GFR to reduced analytical precision at low plasma creatinine concentration seen at this level of renal function and noted that this was even worse in infants where plasma creatinine is lower than in older children and adults. He concluded that ^{51}Cr-EDTA was a reliable indicator of GFR and that formula derived GFR gives a large error at higher levels of GFR measured by ^{51}Cr-EDTA. Similar findings were documented by Davies *et al.*[17] Guignard *et al*[18] found that formula derived GFR underestimated inulin clearance value at GFR > 80m1/min/1.73m^2 and concluded that there was little merit in the use of height/plasma creatinine formula in predicting glomerular function in children older than one year. Morris *et al*,[19] while studying children aged two to 14 years, compared height/plasma creatinine with ^{51}Cr-EDTA in the measurement of GFR and found that the formula derived GFR was adequate in more than half of the children in the estimation of GFR for routine clinical work and that the formula could be used for screening; that is, to separate children with normal GFR from those with abnormal GFR. He also found that the accuracy of the prediction was greatest in children with reduced renal function, especially those with GFR <80ml/min/1.73m^2 where it is of particular value to detect changes in renal function. Szefld and Mehes[20] applied the formula derived by Counahan *et al* to 128 apparently healthy children aged one month to 14 years as a group, and found a good correlation with endogenous creatinine clearance. However, when they analysed their results in children less than one year of age, they obtained a very low correlation coefficient. They therefore concluded that 24 hour creatinine clearance study should still be the method of choice in assessing GFR in this age group. Zacchelo *et al*[21] however found a good correlation between GFR derived by the Schwartz formula and GFR obtained from endogenous creatinine clearance in 13 neonates, although the formula derived GFR showed higher values when compared with values obtained by endogenous creatinine clearance. They concluded that renal function can be monitored using the Schwartz formula in neonates especially in asphyxiated neonates who are at risk of developing renal failure.

As part of further efforts at obtaining a more reliable formula derived GFR, van Rossum *et al* [22] who obtained a K of 40 in their study, recommended that the optimal value for K be assessed locally in view of the variability of K obtained by various workers.[12,15,19] Thai workers, while attempting to evaluate the accuracy of using the Schwartz formula in sick Thai children (aged 0-19years) concluded that modification of the Schwartz formula in which the coefficient equals 0.465, was more reliable in sick children.[23] Mattman *et al* [24] working in Canada, concluded from their findings that if local laboratory constants are derived and a height is known, then the Schwartz formula offers the most accuracy with least mathematical complexity in clinical settings. More recently, cystatin C was found to be a superior and better marker of GFR than serum creatinine.[25-26] Using multiple stepwise regression analysis on log/log transformed data, a relationship between cystatin C concentration and GFR was derived. Using the Bland and Altmann analysis to test agreement between the Schwartz formula and gold standard GFR, there was considerable bias with a mean difference of +10.8 percent and a trend towards overestimation of the GFR by the Schwartz formula with lower GFRs. In contrast, the Bland and Altmann analysis applied on the GFR estimate derived from cystatin C showed the mean difference to be negligible at +0.3 percent and no trend towards overestimation of the GFR with lower GFRs. In the regression analysis of the estimate and the GFR, the Schwartz estimate showed significant deviation from linearity, whereas the cystatin C estimate did not. It was therefore concluded that the cystatin C based GFR estimate shows significantly less bias and serves as a better estimate of GFR in children.[25] Corderon found that although GFR estimated by creatinine and cystatin C had a significant correlation, the Bland Altmann analysis showed greater differences between GFR estimated by the two methods with a mean difference of 50 ml/min. Moreover, >50 percent of the patients with a reduced

cystatin-C estimated GFR had a normal GFR when analyzed by the Schwartz formula. It was therefore concluded that cystatin C based GFR was more sensitive.[27]

Demerits and limitations of formula derived GFR

1. In patients with advanced chronic renal failure, creatinine synthesis may be reduced as a result of reduced muscle mass such that plasma creatinine will be falsely low and thus give a gross overestimation of GFR.[28]
2. It is not reliable in acute renal failure when there is rapidly changing plasma creatinine since formula derived GFR is only valid in a steady state.[28-30]
3. Due to variations in the body habitus of children used to derive the formula, it may not be useful in grossly obese and wasted subjects.[29,31]
4. If the subject has just eaten a high animal protein meal, plasma creatinine values may be elevated especially if estimation is done within eight hours following the meal. It is therefore advisable to measure fasting creatinine concentration which is relatively constant.[31]
5. Some studies[15] have consistently shown that it is a poor predictor of GFR in children in some environments due to differences in the constant K in the formula. Hence, in a given environment, the formula has to be tested and validated for accuracy and possibly establish a specific constant K for the environment before it is used in a clinical setting.
6. Studies have also shown that in patients with impaired renal function who have low GFR, the Schwartz formula has a low sensitivity and may therefore not be useful as a screening method.[15,21]

Merits of formula derived GFR

1. It is a quick way of obtaining a rough estimate of the GFR at the bedside. Hence, it provides quick information on whether GFR is normal or not once the serum creatinine is known.[31]
2. It does not need any urine collection before an estimate of GFR is known.[31]
3. The use of the formula is superior to depending on plasma creatinine alone to determine renal function. This is because the creatinine value is critically dependent on the percentage of muscle mass in addition to renal function.[31]
4. It is easier to grasp clinically significant changes when dealing with large (GFR) rather than small serum creatinine numbers or values. For example, a change in GFR of 40ml/min/1 .73m^2 would corresponds to a change in Pcr of 0.2mg/dl.[31]
5. The formula derived GFR is very useful in monitoring the trend of renal function rather than just depending on serum creatinine and BUN for the purpose.[31]
6. It is also useful for screening children for any abnormality in renal function since GFR estimation represents the best index of renal function.[19]

Current use of formula derived GFR in research and clinical practice in Nigeria

The acceptability of a formula is judged by its applicability in research and clinical practice. Despite the fact that the Schwartz formula has been the subject of intense validation study, its use both in research and clinical setting has continued to rise. In 1991, Okoro & Onwuameze[32] used it to determine GFR in healthy Nigerian children and children with sickle cell anaemia in steady state. In 2000, Adedoyin *et al* [33] reported the use of the formula to determine GFR of clinically stable newborns, and Anigilaje in 2005[34] also used the same formula derived GFR to determine GFR in sickle cell patients in crisis and in steady state.

A critical element of GFR estimation is to provide the trend of renal function which the formula derived GFR adequately does. Furthermore, serum creatinine which is a critical component of the estimation of GFR remains, like in the endogenous creatinine clearance determination. The constant K which has been derived for normal children is also there and may not change even if the body mass reduces due to chronic renal failure, malnutrition and obesity, as it is age dependent. Hence, length remains the main confounding factor which is liable to change or remain static with chronic illnesses such as chronic renal failure. Even then, it is expected to cancel out, since these changes will occur in all children with chronic illnesses. It may therefore not be significant when all children with chronic illnesses are compared.

While the creatinine clearance determination remains the gold standard, the formula derived GFR can be a feasible and easy alternative. Therefore, while efforts are being made to fine tune the constant K for children in this environment, formula derived GFR is hereby recommended for use in clinical practice in children in the tropics. The effort of Gbadegesin *et al* [14] in establishing a mean value of K of 0.45 for children in the south-west geo-political zone of Nigeria is quite commendable. Similar studies are

suggested in different geopolitical zones of the country to help arrive at a consensus K. Furthermore, while most of the controversy generated by formula derived GFR are sound and valid, it seems that there is a need to distinguish between GFR measured for the purpose of scientific and physiological research where maximum accuracy is required and GFR measured in clinical situations where according to Chantler *et al*,[35] two questions are of vital importance: is the GFR normal? and has the GFR changed? Any simple method of GFR estimation that can answer these questions will be adequate in a clinical setting as it will give an indication of when intervention is needed. The Schwartz formula with all its limitations enumerated above and tested by various workers appears to fit the bill. It must be realized that in the search for a method of GFR determination, inulin clearance was the most ideal method of GFR determination but endogenous creatinine determination was then the most clinical feasible.

Conclusion

Since urine collection for the purpose of GFR estimation remains a difficult task in children, the formula based GFR (KL/Pcr) is proposed as an easy, feasible and reliable approach to estimate GFR. Meanwhile, researchers should intensify efforts at deriving a consensus and accurate K value for healthy children and children with renal disease in their various localities.

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