REVIEW ARTICLE

Estimation of Glomerular Filteration Rate (GFR)

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In day to day clinical practice an estimation of glomerular filtration rate (GFR) is required for various reasons viz, a) assessment of renal function. b) severity of renal disease c) calculation of proper drug dosage and d) appraisal of renal involvement in systemic diseases. Various methods of estimating GFR are briefly described below:

I. Clearance Methods:- The concept of renal clearance was introduced as a way of expressing the relation between the excretion per unit time and the concentration in the plasma which is obviously an index of kidneys ability to clear the blood of any substance (1). Measurements of GFR are traditionally based on the renal clearance of a marker in plasma, expressed as the volume of plasma completely cleared of the marker per unit time. If the marker has no extrarenal elimination, tubular reabsorption or secretion then the clearance is given by the formula.

GFR = UV/P, where

U = Urinary Concentration of the substance

V = Urine flow rate (urinary volume)

P = Average plasma concentration

The ideal marker should be endogenous, freely filtered by glomerulus, neither reabsorbed nor secreted by the renal tubule and eliminated only by the kidney. Such a marker is not yet identified. Various markers used to measure GFR include exogenous (inulin, iothalamate) or endogenous (urea, creatinine) substances.

A) Exogenous Substances

i) Inulin:- (MW 5200 dalton), a polymer of fructose is considered the gold standard for the estimation of GFR. It is freely filtered by glomerulus, and is neither reabsorbed nor secreted by the renal tubules. It is metabolically inert and cleared only by the kidney. It requires constant IV infusion to maintain plasma level and once steady state has been achieved, plasma and timed urine specimen levels are measured. However, analysis of inulin is technically demanding, time consuming, labour intensive, costly and unsuitable for out patient use. The reference ranges for the GFR in normal individuals given by Smith are 88 to 174 ml/min/1.73m^2 for males and 87 to 147ml.min/1.73m^2 for females (2).

ii) Non-radiolabelled contrast media:- In addition to inulin, non-radiolabelled contrast media infusion (iothalamate / iohexol) have been used to measure GFR. One advantage is that urography and an estimation of GFR can be done at a single examination (3). Cumbersome measurement makes it unsuitable for day to day clinical practice.

iii) Radiolabelled compounds:- A number of radiolabelled chelates have been used to assess the GFR in man, as very small non-toxic amounts of the compound can be given and can be measured even at very low concentrations using conventional counters. Amongst these are [^{51}Cr] EDTA, [^{125}I] iothalamate, [^{99}Tc^{m}] DTPA, [^{131}I] Hippuran to mention a few (4, 5). Disadvantages are that some radiation is administered, radiopharmaceuticals are more expensive, Gamma camera and skilled personnel are needed. Hence these chelates cannot be used routinely to assess GFR.

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B) Endogenous Substances

i) Urea (MW 60 dalton) was one of the first markers for assessing GFR (6) but at present is not used in clinical practice due to several reasons. Urea production is variable and varies with protein intake. It is readily reabsorbed by tubules and again amount of reabsorption is variable. Hydration status of the individual also affects urea clearance markedly, increased plasma levels accompany decreased urine flow in patients with depleted intravascular volume. In addition many substances may interfere with its estimation.

ii) Creatinine (M.W 113 daltons) is formed by the non-enzymatic dehydration of muscle creatine. The main determinant (98%) of the creatinine pool therefore is muscle mass. The only other source of creatinine is meat in the diet. The use of endogenous creatinine clearance as an estimate of GFR first introduced by Popper and Mandal in 1937 (7) is still widely used in clinical practice. However, its performance and interpretation present formidable difficulties: Variations in the generation rate of creatinine, accurate measurement of creatinine especially in plasma, some secretion by the renal tubules and the difficulty of obtaining complete, accurately timed urine collections (8, 9).

Creatinine is usually measured by the Jaffë colorimetric reaction for more than a century, using alkaline picrate with which it forms orange red complex. Many substances interfere with Jaffë's colorimetric assay of plasma creatinine and cause falsely high levels viz ketones and ketoacids, ascarbic acid, uric acid, glucose, plasma proteins, bilirubin, fatty acids, urea cephalosporins etc.

Drugs like triametrine, spironolactone, amiloride, probenecid, cimetidine, trimethoprim, high dose salicylates or pyrimethamine inhibit tubular secretion and induce true elevation of plasma creatinine (10,11). Enzyme based assays lack this interference and have better precision similar to high performance liquid chromatographic techniques (10).

Creatinine clearance (cl_{cr}) overestimates GFR because of tubular secretion. In normal renal function this accounts for 10-40% of GFR with marked inter-individual variability. Tubular secretion can increase to more than 100% in patients with reduced renal function especially in glomerulopathic and proteinuric patients (12). Physicians need to keep these facts in mind while interpreting Clcr results. Reference values for creatinine clearance in children aged 3-13 years are 94-142 and in adults 74-162 ml/min/1.73m^2.

II. Prediction of GFR from plasma creatinine:- In clinical practice an approximation of bed side GFR is often obtained from plasma creatinine concentration alone albeit with limited accuracy (13). A number of workers have tried to develop formulae that will allow an immediate prediction of GFR from plasma creatinine.

Few pitfalls of formula derived GFR need to be kept in mind. Approximation of GFR from plasma creatinine may give unreliable results because plasma creatinine is not only dependent on GFR but also on muscle mass which varies with age, weight and gender. In cirrhosis and diseases with reduced muscle mass, plasma Creatinine is low, conversely a high protein intake can lead to 10% increase in plasma creatinine (14). Further more a marked reduction in GFR can be present before it is reflected in plasma creatinine concentration above the upper limit of normal range. The value to these formulas for GFR prediction is likely to increase when an accurate plasma creatinine assay is performed along with inhibition of tubular secretion by cimetidine. To improve the estimation of GFR from plasma creatinine concentration, formulas which incorporate variables like age, weight, height and gender can be used. Some commonly used formulas are shown in Table 1 (14-18). The most widely employed and best validated for use in adults is that of Cockroft and Gault (15).

III: GFR estimation by new endogenous markers:-

a) ß2-Microglobulin (M.W 11815 dalton) is filtered at glomerulus like water. Subsequently >99.9% is reabsorbed and degraded in renal tubule. Because it is filtered so readily, its plasma concentration in health is low(average 1.5mg/L). The plasma concentration increases as the glomerular filteration rate declines reaching about 40mg/l in terminal uremia. The logarithm of the plasma concentration is linearly related to the logarithm of glomerular filtration rate throughout the whole range so that it provides an excellent marker for renal dysfunction. The plasma concentration of ß2-microglobular is not affected by muscle mass nor by sex of individual. As its estimation involves expensive radioimmunoassay it has not yet become more useful in clinical practice. Also in patients with some tumors and inflammatory diseases there may be increase in plasma concentration due to increased production rather than reduced clearance (19).

b) Cystatin C is a 13-KD protease inhibitor which is produced by all nucleated cells and is independent of muscle mass and sex. Its production, unlike ß2-microglobulin is not affected by inflammatory states or malignancies. Cystatin C is eliminated by glomerular filtration and metabolized by proximal tubular cells. Its measurement has been proposed as an alternative and more sensitive marker of GFR than creatinine particularly in patients with slight to moderately decreased GFR (20-22).

Table 1: Formulas for rapid estimation of Cl_{cr}.

Author(s)		Formula	Units
Cockcroft & Gault (15)	♂	$\frac{(140\text{-age}).B.W.}{S_{cr}.\ 72}$	ml/min
	♀	Correction factor 0.85	
Hull *et al* (14)	♂	$\frac{145 - age}{S_{cr}} - 3$	ml/min/70kg
	♀	Correction factor 0.85	
Jelliffe (16)	♂	$\frac{100}{S_{cr}} - 12$	ml/min/1.73m^2
	♀	$\frac{80}{S_{cr}} - 7$	
Baracskay *et al* (17)		$\frac{4,420}{P_{cr}} + 88 - age$	ml/min
Salazar & Corcoran (18)	♂	$\frac{(137\text{-age}).(0.285.BW).(12.1.Ht^2)}{51.\ S_{cr}}$	ml/min/
	♀	$\frac{(146\text{-age}).(0.287.BW).(9.74.Ht^2)}{60.\ S_{cr}}$	

Scr = Serum Creatinine (mg/dl); BW=Body weight (kg): Ht=Height (m)

Conclusion

Creatinine clearance remains the most widely used test for estimating GFR in clinical practice despite its many disadvantages and problems. Appreciating the limitations, GFR can be estimated with reasonable accuracy and precision from serum creatinine alone with Clcr prediction formulas, Cystatin C could well enter the clinical field as a routine method for estimating GFR in the near future.

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