RELATIVE MERITS OF DIFFERENT CLEARANCE TESTS USED TO MEASURE GFR

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Abstracts: Merits and demerits of various renal clearance tests that are used to measure GFR are compared and it appears that the measurement of creatinine clearance tests is the best one and when GFR is less than 60 ml/min simply measuring plasma creatinine levels emphasis the prognosis.

Key Words: GFR, Renal Clearance, Plasma creatinine

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In day to day clinical practice an estimation of glomerular filtration rate (GFR) is required for various reasons a) Assessment of renal function. b) Assess the severity of renal disease c) Calculation of proper drug dosage d) Appraisal of renal involvement in systemic diseases.

Glomerular Filtration Rate

Glomerular filtration is the physiologic process of creating an ultrafiltrate of blood as it flows through the glomerular capillaries. In principle, GFR is the ultrafiltrate of the total number of nephrons in both the kidneys formed in one minute. Determinants of GFR include hemodynamic factors within the glomerular capillary network and the hydraulic properties of the capillary wall. In humans, GFR of 180 L/day is ensured by the glomeruli (1 to 1.5 million of nephrons per kidney), rich renal blood flow (25% of cardiac output, higher than in any other capillary bed), extensive total glomerular capillary surface area (0.8 m^2), and high glomerular capillary pressure 45 mm Hg. and hydraulic permeability of the glomerular capillary wall (far greater than those of other capillaries).[1] Based on a large body of evidence, mean GFR in healthy young adult individuals is ~125 mL/min/1.73 m^2, with a wide range.[2] Indexing GFR to body surface area reduces variation among healthy individuals and allows comparisons to normative values. There is some evidence that the normal level of GFR varies among ethnic groups.[3] GFR is affected by numerous physiologic and pathologic conditions and varies with time of day, age, posture, exercise, blood flow, pregnancy, obesity, hyperglycaemia, use of antihypertensive drugs, surfeit or deficit of extracellular fluid, and acute and chronic glomerular diseases.

It is not possible to directly measure GFR in humans; thus, the "true" GFR cannot be known with certainty. It can be measured indirectly as the clearance of exogenous filtration markers like Inulin, mannitol etc., or estimated from serum levels of endogenous filtration markers like creatinine, urea etc., but both measured (mGFR) and estimated (eGFR) are associated with error in their determination. In principle, true GFR could be estimated from repeated determinations of mGFR or eGFR and appropriate statistical techniques for incorporating measurement error. I suggest an operational definition of true GFR as the average level of GFR over a representative 1- to 2-day period.

Measuring GFR

GFR is measured indirectly as the clearance of exogenous filtration markers that are eliminated by the kidney only by glomerular filtration. The concept of plasma clearance of a substance is that the amount of the substance that is excreted in urine in one minute's time is present in so much volume of plasma, as it passes through both the kidneys. This amount of the substance is removed from plasma and added to formed urine. This volume cannot be collected and measured and it can be arrived at only by computation knowing urinary concentration in mg/ml, volume of urine formed/min and plasma concentration of the substance in mg/ml by the following formula

$$C_X = U_X \times V / P_X = \text{ml/min}$$

C_X: clearance of substance "x", U_X: urine concentration of substance "x" per ml of urine, V: urine formed per minute P_X: plasma concentration of substance "x".

Plasma clearance of exogenous filtration markers can be assessed when kidney function is stable or changing. The classic method of Smith for urinary inulin clearance includes a bolus dose followed by a continuous intravenous infusion at a rate that

matches the rate of its excretion, to achieve a constant plasma level, repeated blood sampling for plasma measurements of inulin, and bladder catheterization for urinary collection.

Filtration Markers

- Substances that are filtered by glomeruli that can be used to measure or estimate the GFR
- Ideal properties
  - Inert
  - Freely filterable
    Molecular weight < 20,000 Da
    Not protein bound
  - Neither reabsorbed nor secreted by the renal tubule
  - Not metabolized by the kidney
  - It should not affect the renal blood flow
  - Easy to measure
- Exogenous filtration markers , for clearance measurement (urinary or plasma)
  - Inulin (5,200 Da)
  - Iothalamate (usually with ^{125}I) (640 Da)
  - Iohexol (821 Da)
  - ^{51}Cr-EDTA (372 Da)
  - ^{99m}Tc-DTPA (938 Da)
- Endogenous filtration markers, for GFR estimation
  - Metabolites (if excreted in urine, may also be used for clearance measurements)
    Urea (60 Da)
    Creatinine (113 Da)
  - Low – molecular – weight serum proteins
    Cystatin C (13,300 Da)
    B2M (11,700 Da)
    BTP (23,000-29,000 Da)

***Abbreviations**: ^{51}Cr-EDTA, chromium 51 ethylenediaminetetraacetic acid; ^{99m}Tc-DTPA, technetium 99m diethylenetriamine pentaacetic acid; ^{125}I, iodine 125; B2M, β_2-microglobulin; BTP, β-trace protein; GFR, glomerular filtration rate.*

Estimated GFR

GFR can be estimated from serum levels of endogenously produced filtration marker whose 24 hour plasma concentration is fairly constant like creatinine an end product of muscle metabolism. GFR is related to the reciprocal of the plasma concentration of the marker, but it also is influenced by its non-GFR determinants like reabsorption/ secretion/ or both. Endogenous filtration markers in current use include low-molecular-weight metabolites, such as creatinine, and filterable serum proteins, such as cystatin C. Filtered portion of a metabolite that is excreted in urine and may be used to measure urinary clearance.

Exogenous Substances

i) Inulin: - (MW 5200 dalton), a polymer of fructose is considered to be a golden standard for the estimation of GFR. It is freely filtered by glomerulus, and is neither reabsorbed nor secreted by the renal tubules and the amount that is excreted in urine is equal to the amount that is filtered. It is metabolically inert. It requires intravenous infusion to match the rate of its excretion to maintain a constant plasma level and once a steady state has been achieved in plasma a timed urine specimen are obtained. However this procedure is cumbersome and cannot be performed in severely ill patients. 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.[4]

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. Cumbersome measurement makes it unsuitable for day to day clinical practice.[5,6]

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 [51Cr] EDTA, [125I] iothalamate, [99Tcm] DTPA, [131I] Hippuran to mention a few. 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.[7]

Endogenous Substances

i) Urea was one of the first markers for assessing GFR but at present is not used in clinical practice due to several reasons. Urea production is variable and varies with protein intake. Its reabsorption is load dependent and is readily reabsorbed by tubules and its excretion is urinary flow dependent. In addition many substances may interfere with its estimation.[8]

ii) Creatinine is an end product of muscle metabolism. The main determinant (98%) of the creatinine pool therefore is muscle mass. The only other source of creatinine is meat in the diet. Serum creatinine is commonly used to screen for renal disease. It is also used to monitor renal function after transplantation, in chronic renal disease, and in patients with glomerulonephritis. Serum creatinine can also be used to monitor the effects of nephrotoxic drugs such as gentamicin or anticancer drugs. Creatinine generation from the muscles is proportional to the total muscle mass and muscle catabolism. In people with a relatively low muscle mass, including children, women, the elderly, malnourished patients and cancer patients, the serum creatinine is lower and therefore the GFR. There is a danger of underestimating the amount of renal impairment in these patients, as their serum creatinine is also relatively low. For example, the GFR may be reduced as low as 20–30 mL/min in an elderly woman. Creatinine is an imperfect filtration marker, because it is secreted by the tubular cells into the tubular lumen, especially if renal function is impaired. This error is generally nullified by the error in estimation of plasma creatinine level by Jaffe's reaction that not only measures the creatinine level but also other chromogens thus the numerator rises through the secretion and the denominator rises through over estimation nullifying each other. Nevertheless when the GFR is low, the serum creatinine and creatinine clearance overestimate the true GFR. Some drugs (such as cimetidine or trimethoprim) have the effect of reducing tubular secretion of creatinine. This increases the serum creatinine and decreases the measured creatinine clearance. Creatinine clearance can be calculated by the well – known formula Cockcroft-Gault formula

$$\text{Creatinine clearance (ml/min)} = \frac{(140 - \text{age [yrs]}) \times \text{weight [kg]}}{814 \times \text{serum creatinine (micromol/L)}}$$

In this form the equation applies to men; the result should be multiplied by 0.85 for women to allow for the relatively lower proportion of body weight, which is muscle.[9-12]

iii) β2-Microglobulin: It is a low molecular weight (LMW) protein of 11.700 daltons composed of 100 aminoacids with one disulphide bridge[13] β2-Microglobulin can be measured in plasma, serum, urine and other human fluids like saliva, cerebrospinal or pleural fluids. It is usually measured by radioimmunoassay or enzyme—linked immunosorbent assay (Elisa). These methods are most reliable. Normal serum values are 1.1 to 2.7 mg/liter and the normal urinary excretion is <370 p.g/24 hr. About 99.9% of β2-Microglobulin all free is filtered by the normal glomerulus and subsequently almost completely reabsorbed and catabolized by the cells of the proximal tubules. By its unique property of being almost exclusively filtered by the glomerulus and most efficiently reabsorbed by the cells of the proximal tubules under diverse physiologic conditions, renal β2-Microglobulin excretion has proven to be a very sensitive method in diagnosing proximal tubular disorders. Urinary β2-Microglobulin has been shown to be the most reliable test for discriminating between upper and lower urinary tract infections. It is most useful in evaluating the results of therapy and in detecting recurrences in acute pyelonephritis by means of serial determinations. 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 β2-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.[14-16]

iv) Cystatin C: It is a 13-KD protease inhibitor which is produced by all nucleated cells and is independent of muscle mass and sex. Its production, unlike β2 -microglobulin is not affected by inflammatory states or malignancies. Cystatin C measurement has been proposed as an alternative and more sensitive marker of GFR than creatinine particularly in patients with slight to moderately decreased GFR. Cystatin C shows a high correlation with GFR, cystatin C gives a good estimate of GFR, more accurate and precise than Cockcroft and Gault. Because biological variation is low, cystatin C gives also a good assessment of GFR changes during follow-up. Cystatin C is the preferred endogenous parameter for GFR.[17-21]

Conclusion

According to the recent research work done on Cystatin C shows that it is more sensitive indicator of GFR than creatinine clearance, this is true but in my view practically Creatinine clearance is reliable, cost effective, and easy to perform the test for the patients in spite of its many disadvantages and problems. Creatinine clearance is reliable in patients who are severely ill, it is a better indicator than the others because it is endogenously produced. And as the kidney disease like chronic glomerulonephritis advances it is drastically affected along with Urea clearance. Once the GFR decreases to less than 60 ml / min simply the estimation of plasma creatinine and urea levels will give us the gravity of prognosis of the ongoing kidney disease which may be bad or good.

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