Glomerular Filtration Rate Estimation With The Diethylene Triamine Pentaacetic Acid (dtpa) Camera Method In Indian Healthy Donors And Comparison With Modified Diet In Renal Disease Formula (four Variable) - Our Experience

[1]Dr Rajeev Kumar, [2]Dr MS Chauhan, [3]Dr Amit Sharma and [4]Dr Anurag Jain,
[1,4]Graded Specialist,[2] Professor & Head,[3] Resident Doctor,
Department of Nuclear Medicine, Army Hospital R&R, Delhi Cantt-110010, New Delhi, India.

ABSTRACT:
Background: Chronic kidney disease (CKD) encompasses a spectrum of different path physiological processes associated with abnormal kidney function and a progressive decline in glomerular filtration rate (GFR). Due to increasing in the number of cases of Chronic kidney disease Stage-V, there is higher demand of renal transplantation for which there is a need of healthy donors. Presently the criteria for renal donor is a globally accepted creatinine based GFR estimation method which are mostly accepted globally as a marker, however, there is a lack of an easily available, cheap, reliable and reproducible GFR marker. Diethylene Triamine Pentaacetic Acid (DTPA) camera method is a potential method to be used in place of modification of diet in renal disease method (MDRD) of GFR estimation. **Aims & Objectives:** The present study was undertaken to know the comparison of DTPA method and the MDRD formula of GFR estimation in healthy individuals of Indian origin.**Methods:** The present study is a prospective and observational study, which was conducted in the Department of Nuclear Medicine, Army Hospital R&R Delhi Cantt. All the cases of renal donors, which were brought to us for GFR estimation during the two year period from January 2011 to December 2012, were selected for this study to find out the GFR.**Results:** In our study most of the donors were mostly female in their 4th decade of life because of the fact that our hospital is military hospital and most of the families are nuclear family which are very far from their native place and most of the female mostly wife are willing to donate the kidney for their husbands. G**FR estimation by MDRD formula i**n healthy donor GFR ranged from 51 to 161 ml/min with a mean GFR 99.40± 25.14 ml/min, while **GFR estimation by DTPA** in healthy donor ranged from 72.3 to 141.9 ml/min with a mean GFR 99.97± 16.45ml/min. There was a significant positive correlation between DTPA and MDRD (r = 0.372 with p: 0.002) method.**Conclusion:** Our study shows that the DTPA renogram using Gamma Camera will give not only the measured GFR but also it will help clinician to know the other valuable information like size and outline of kidney, relative function and excretory performance of the kidney.

Key-words: GFR, MDRD, DTPA and Gamma camera.

Corresponding Author: Dr Rajeev Kumar, [4]Graded Specialist, Department of Nuclear Medicine, Army Hospital R&R, Delhi Cantt-110010, New Delhi, India

INTRODUCTION:

The kidneys perform an incredibly wide array of functions in the body, which are essential for homeostasis and these functions can be divided into excretory and secretary. Chronic kidney disease (CKD) encompasses a spectrum of different pathophysiologic processes affecting both types of functions. Decline in excretory function represented by a progressive decline in glomerular filtration rate (GFR), is relatively easier to quantify and serve as a surrogate marker of decline of other types of renal function as well. Transplantation of the human kidney is the treatment of choice for advanced chronic kidney disease. Donors can be deceased or volunteer living donors. Decision of suitability of living donor is based on

ascertaining normal renal function in the donor for which GFR is one of the main parameters.

Glomerular Filtration Rate

The Glomerular Filtration Rate (GFR) is the volume of the blood plasma filtered through glomerulus in per unit time. GFR is expressed as the milliliters per minute and it is similar for male and female (Normal GFR is 90- 120 ml /min). It is most often calculated comparative for the average person's Body Surface Area (BSA) of 1.73 m^2 that is, a person's GFR is expressed as ml/min/1.73 m^2. There are many different formulae available to calculate BSA, but all use the person's weight and height as parameters.[1]

GFR less than 90 is defined as chronic kidney disease. The severity of chronic kidney disease (CKD) is described by six stages; the most severe three are defined by the MDRD-EGFR value, and first three also depend on whether there is other evidence of kidney disease (e.g., proteinuria). GFR is widely accepted as the best index of kidney function in health and disease, and accurate values are needed for optimal decision making in many clinical settings. Estimated GFR (eGFR) based on serum creatinine is now widely reported by clinical laboratories and is available in most clinical encounters as a "first line" test of kidney function. First line tests are followed by more accurate confirmatory tests when needed. Measured GFR (mGFR) using urinary or plasma clearance of exogenous filtration markers is considered the gold standard for evaluation of kidney function but is not routinely available because of the complexity of measurement protocols. Instead clinicians usually rely on endogenous creatinine clearance. However, timed urine collections are difficult to obtain and fraught with error. Despite the complexity, GFR should be more often measured as a confirmatory test in clinical practice.

The level of GFR is only one parameter by which kidney disease is evaluated. Clinical decisions are also based on the cause of kidney disease, presence or absence of complications, risk factors for rapid progression and co-morbid conditions, and the presence of albuminuria. Nevertheless, the level of GFR and its magnitude of change over time are vital to the detection of kidney disease, understanding its severity and for making decisions about diagnosis, prognosis, and treatment. Recognition of the strengths and limitations of any estimating equation, and the clinical settings when GFR estimates are likely to be inaccurate, will enable identification of those patients in whom a measured GFR should be considered.

Radio-Nuclide Evaluation of GFR

To evaluate GFR in Nuclear Medicine a radiopharmaceutical is required, which is excreted purely by glomerular filtration. It should not be secreted or reabsorbed within the renal tubules, or excreted by any other means. It should not be bound to protein, which inhibits glomerular filtration. Tc^{99m}-DTPA (Diethylene Triamine Penta Acetic acid) is the most commonly used radiopharmaceutical for GFR studies, although up to 10% of the preparation may be bound to protein, therefore slightly underestimating the GFR. Despite this, it is the most suitable radiopharmaceutical readily available at present. Several techniques have been applied in clinical practice, because of technical simplicity and requirement for less time for the patients. The Gate method introduced by Gates has been more common in the routine setting. Although the diagnostic accuracy of the gamma camera methods is debated, the program is provided as a software package by manufacturers in commercially available computer systems dedicated to nuclear medicine. In Gates, 24-hour creatinine clearance was chosen as a reference. The equations for predicting the GFR are based on the linear relationship of the renal uptake of Tc-99m- DTPA in the Gates.

Inulin clearance is proved as the gold standard for GFR determination. However, this method is not performed in clinical practice, because of technical complexity and limited availability. The intrinsic creatinine clearance has been widely performed as the only alternative to inulin clearance in routine practice. This method, however, is not accurate compared to inulin clearance.

Therefore, simple and accurate determination of the GFR is still a challenge clinically. Creatinine clearance remains the most widely used tests 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 CrCl prediction formulas, Cystatin C could well enter the clinical field as a routine method for estimating GFR in the near future. Two creatinine based equations also have been extensively studied and widely applied are the Modification of Diet in Renal Disease and Cockcroft and Gault study equations in adults.

Modification of Diet in Renal Disease (MDRD) Study equation

MDRD (6-variable): GFR (ml/min/1.73m2) = 170 x (S Cr/88.4) $^{-0.999}$ x (age) $^{-0.176}$ x (BUN x 2.78) – 0.170 x (Alb) 0.318 x (0.762 if the patient is female) x 1.180 (if African American).

Abbreviated MDRD (4-variable): GFR (ml/min/1.73m2) = 186 x (S Cr/88.4) $^{-1.154}$ x (age) $^{-0.203}$ x (0.742 if the patient is female) x 1.210 (if African American). It has shown to be more accurate than the Cockcroft Gault equation or the creatinine clearance even after adjustment for body surface area and correction for systemic bias owing to the overestimation of GFR by creatinine clearance.[2]

MATERIAL & METHOD:

This study was conducted in the Department of Nuclear Medicine, Army Hospital (Research and Referral) Delhi during the period of January 2011 to December 2012 and 64 healthy individuals were included in the present study.

Inclusion Criteria

1. Healthy individuals who do not have any history of renal disease and individuals having serum creatinine less than 1.2 mg/DL. Most of these are prospective renal donors. Normal range of creatinine in our lab is < 1.4 mg/dl

2.Patients who gave informed consent.

Exclusion Criteria

1. Chronic kidney disease patients or individuals having serum creatinine more than 1.5 mg/dl persisting for more than three months in the absence of reversible factor.

2. Renal transplant recipient.

3. Patients with obstructive uropathy, acute kidney injury, gross edema, significant pleural or abdominal effusion, hypertension, diabetes mellitus, and patient who has not given informed consent were excluded.

Each subject was examined in detail clinical history and thorough physical examination with a serum creatinine examination was done at all on the same day.

RESULT:

There are total 64 healthy persons included in this study, out of which 28 were males (43.8%) and 36 were females (56.2%). Proportion of females was higher in the whole study population. Healthy group age ranged from 18 to 70 years with a mean age of 46.34 ± 12.4 years. Overall maximum subjects were from 41 to 50 years age group that is 24 individuals (37.5%). Creatinine of the males and females ranges from 0.50mg/dl to 1.10mg/dl in males and 0.4 mg/dl to 1.2 mg/dl in females with mean creatinine in male 0.77 mg/dl ± .14 and in female 0.78 ±0.16 **GFR by DTPA (normalized) in** healthy donor GFR ranged from 67.4 to 144.8 ml/min with a mean GFR 104.39 ± 17.26 ml/min.

Table-1 Comparison of GFR by Different Methods

	Healthy
DTPA(ml/min) (MEAN ± SD)	99.97 ± 16.45
MDRD (ml/min/1.73 m^2) (MEAN ± SD)	99.40 ± 25.15
Normalized DTPA (ml/min/1.73 m^2) (MEAN ± SD)	104.39 ± 17.26

GFR by MDRD formula in healthy donor GFR ranged from 51 to 161 ml/min with a mean GFR 99.40± 25.14 ml/min. **GFR by DTPA** in healthy donor GFR ranged 72.3 to 141.9 ml/min with a mean GFR 99.97± 16.45ml/min.

Correlation of GFR by DTPA GFR and MDRD in Healthy Group

In studies, it has been observed that in healthy group DTPA significant positive correlation with

MDRD. (r = 0.372 with p: 0.002). In our study it has been observed that in Normalized GFR significantly positive correlation with MDRD (r = 0.384 with p: 0.002).

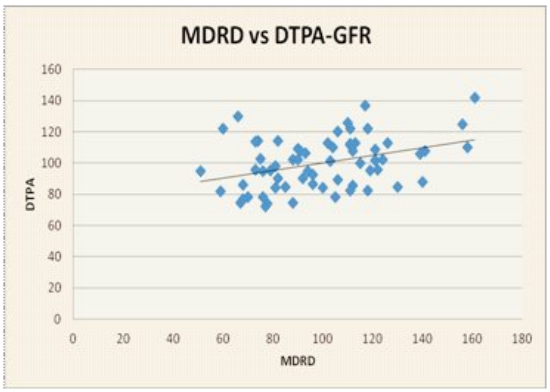

Figure 1. Correlation of Normalized GFR and MDRD GFR in Healthy group

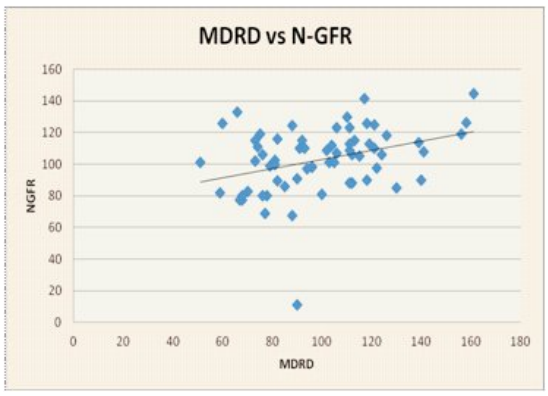

Figure 2. Scatter plot of GFRs determined by DTPA (normalized) against that by MDRD formule in healthy study group.

DISCUSSION:

Chronic kidney disease (CKD) encompasses a spectrum of different path physiological processes associated with abnormal kidney function and a progressive decline in glomerular filtration rate (GFR). DTPA camera method is a potential method to be used in place of MDRD method for GFR estimation and with this background this study was carried out in the Department of Medicine at Army Hospital (R&R) to correlate measured radio isotope GFR (mGFR) with serum creatinine based estimation of GFR (EGFR) in healthy individuals. Total 64 healthy individuals who are prospective renal donors are included in our study, out of which majority 36 (56.2%) were females and 28 (43.8%) were males, which is contradictory to the prevalent sex ratio in our country (M/F:50/45.7).

In our study lower mean age and female predominance might be because of the fact that our hospital is military hospital and most of the families are nuclear family which are very far from their native place and most of the female mostly wife are willing to donate the kidney for their husbands. GFR estimated from the abbreviated MDRD formula shows significant negative correlation (p value >. 001) among the separate group of male and female donors. The mean GFR of males was 113.96 ml/min/1.73m^2 as compared to females 88.56 ml/min/ 1.73m^2, which may be due to differences in body surface area. GFR estimated from the abbreviated MDRD formula among the donor age group shows that the GFR decrease as the age increases both among males and females. The mean GFR in age group < 30 yrs is 124.89 ml/min/1.73m^2 with comparison to age group >60 yrs is 91.95ml/min/ 1.73m^2. GFR measured by DTPA (Gate's method) shows no significant difference (p value.304) among the separate group of male and female donors. The mean GFR of males is 105.90 ml/min/1.73m^2 with comparison to females 100.46 ml/min/1.73m^2.

GFR measured from DTPA (gate's) method among the donor age group does not show any correlation both among males and females. The mean GFR in <30 yrs is 100.97 ml/min/1.73m^2, in 31–40 yrs is 111.95 ml/min/1.73m^2 in comparison to >60 yrs group is 81.42ml/min/ 1.73m^2 with mean GFR is 102.84 ml/min/1.73 m^2. However the GFR in >30 yrs age group is more than the group of >60 yrs age group, suggest GFR measured by DTPA method is decreased with increase in age. We estimated GFR with the mGFR (^{99m}Tc DTPA by Gates method) in all cases and compared with abbreviated MDRD formula. In donor, mean normalized GFR by DTPA is 104.39 ± 17.26 (range 67.4-144.8) ml/min/1.73m^2, whereas mean GFR by Abbreviated MDRD is 99.40 ± 25.14 (range 51-161) ml/min/1.73m^2. In our study GFR by DTPA method is significantly positive

correlation with GFR by MDRD (p value: 0.002). No doubt that in present days MDRD formula is the best indicator of GFR estimation, but till date there are limited studies to validate the accuracy of the MDRD formula in healthy donors. [3]

oggio et al[5] and Froissart et al[3] have reported that the MDRD formula was less accurate and less precise in patients without CKD. They reasoned that the MDRD formula, which was developed in a population with CKD, had limited application in a population without CKD. Lin et al[6] had verified the high bias and poor accuracy for abbreviated MDRD compared to DTPA. The other reason is that the Asian subjects were not included in the MDRD study, and previous work found that this equates to EGFR underestimated RGFR in upper-normal kidney function and over estimated GFR in advanced renal failure. Indian studies such as Mahajan et al[6] has also observed poor agreement of EGFR with mGFR in healthy Indian transplant donors. A similar study was done by Shrinivas et al, in South Asian healthy renal donors and they also observed higher bias and low accuracy in stage 1 CKD. However, in an Asian study done by Kim et al[7] also reported that GFR by ^{99m}Tc-DTPA renal scan correlated significantly with MDRD-GFR in all CKD stages and all age groups ($p<0.001$). Another limitation of the MDRD formula lies in the day-to-day variations that are known to occur in serum creatinine (15.5%–19.6%). [8] We did not pay special attention to the calibration of serum creatinine measurements, which has been shown to be of critical importance in individuals with normal or near-normal serum creatinine values, and to influence the accuracy of MDRD equations. The accuracy of the creatinine based formula can be improved by calibrating serum creatinine measurement. MDRD equation is essentially rescaled serum creatinine levels with the same pitfalls as using the serum creatinine level itself, that is based on statistical models predicting averages, and our patient was not average. Ideally, a formula should be developed from a population that includes many individuals who vary widely with regards to GFR, age, race, ethnicity, body composition, health status, risk factors for CKD and types of CKD. Although an equation developed in one population is generally adopted for use in other populations, validation in the latter should ideally be performed.

Clinicians require a less expensive and less time consuming test than direct GFR measurement, and the result should be accurate and do not need to be precise as in clinical trials. Therefore, clinical judgment is always required with EGFR and the clinician has the advantage of being able to consider dietary history and physical examination factors not considered in these equations. In many studies, we found that camera based methods are not as accurate as plasma sample techniques, but their reproducibility appears to be good. Some unwanted factors and technical problems were sources of errors in assessing fractional renal uptake from the abbreviated Gate's method like protein binding, background subtraction, renal depth, age of the individuals and the shape of the kidneys. We cannot consider DTPA Gate's method as the gold standard because of varieties of sources of errors. The most important, in our opinion, was that the abbreviated Gate's method was derived from an empirical equation obtained using the measured creatinine clearance as reference GFR, to yield total and separate kidney clearance, because of the well-known pitfalls of CrCl, the Gate's method inherited inevitable shortcomings of CrCl. The Gate's method can be improved if a more proper reference GFR method is used instead of CrCl in prediction of total GFR.

Many studies have been conducted to test the accuracy of the abbreviated Gate's method in the estimation of GFR. John et al[9] compared the ^{99m}Tc-DTPA renal dynamic imaging method with ^{99m}Tc-DTPA plasma clearance as the reference GFR (RGFR), and found a significant difference between the abbreviated Gate's method and RGFR. Using inulin clearance as the reference standard, Natale et al[10] indicated that the Gate's method tended to overestimate GFR at low levels, and underestimate GFR at high levels of GFR. Kazuo Itoh et al[11] also found that Gates was proved to be inaccurate and less precise

than the CG for predicting the GFR. In addition, Gates tended to overestimate the GFR. The renal dynamic imaging method that measured GFR was far from satisfactory, and even less valuable than CrCl.[12] Serum Cr-based GFR equations take into account age, gender and race, and allow a more reliable GFR estimation compared with renal dynamic method.

Kazuo Itoh at al[11] studied found that the Gates' method in ^{99m}Tc-DTPA, renography is not suitable for the estimation of GFR in routine practice. The study done by Fleming et al[13] found that Gamma camera techniques provide rapid estimates of GFR, which are less accurate than those obtained by plasma clearance of labeled chelate. However Jeffrey et al[14] study found that the ^{99m}Tc-DTPA scintigraphic analysis method provided useful information with respect to differential (split) renal function. So the DTPA renogram using Gamma Camera will give not only the measured GFR but also it will help clinician to know the other valuable information like size and outline of kidney, relative function and excretory performance of the kidney.

CONCLUSION & RECOMMENDATIONS:

In our study the abbreviated MDRD method and radioisotope DTPA camera method performed in the estimation of total GFR estimation was not significantly different. So, it is suggested that GFR estimated by the current radioisotope DTPA camera and abbreviated MDRD method could be used as a marker for kidney function. For the renal transplantation, it is not important to know the GFR precisely; it is enough to know that which kidney is doing well. Even though the MDRD formula and Gamma camera method gives matching results about GFR, the Gamma Camera method gives several added information's and hence it is justified to be used in centers where the facility is available. I believe that the dynamic renal imaging method for estimation of GFR can be improved by using proper reference GFR, as well as more adequate background subtraction and soft-tissue attenuation correction.

Source of Funding: Nil.
Conflict of Interest: None.

References:

1. K/DOQI Clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. National Kidney Foundation, Am J Kidney Dis. 2002; 39 Suppl 1:S1-S2, 66.
2. Maton A, Hopkins J, McLaughlin CW, Johnson S, Warner Hart DL, Wright JD. Human Biology and Health. Englewood Cliffs, New Jersey, USA: Prentice Hall, 2011; 2(1): 100-07.
3. Froissart M, Rossert J, Jacquot C, et al. The predictive performance of the Modification of Diet in Renal Disease and Cockcroft-Gault equations for estimating renal function. J Am Soc Nephrol, 2005; 16:763-73.
4. Poggio ED, Wang X, Greene T, et al. Performance of the Modification of Diet in Renal Disease and Cockcroft-Gault equations in the estimation of GFR in health and in chronic kidney disease. J Am SocNephr (1. 2005;16:459-66.
5. Lin J, Knight EL, Hogan ML, Singh AK. A Comparison of Prediction Equations for Estimating Glomerular Filtration Rate in Adults without Kidney Disease. J Am Soc Nephrol 2003; 14: 2573-80.
6. Grassi G, Abdelkawy H, Barsotti M, Paleologo G, Tregnaghi C, Rizzo G et al. Living Kidney Transplantation: Evaluation of Renal Function and Morphology of Potential Donors, Transplantation Proceedings; 41 (4): 1121-24.
7. Perrone RD, Steinman TI, Beck GJ, Skibinski CI, Royal HD, Lawlor M et al. Utility of radio-isotopic filtration markers in chronic renal insufficiency: simultaneous comparison of 125I-iothalamate, 169Yb-DTPA, 99mTc-DTPA, and inulin, The Modification of Diet in Renal Disease Study, Am J

Kidney Dis, 1991; 17(6):724.

8. Bostom AG, Kronenberg F, Ritz: Predictive performance of renal function equations for patients with chronic kidney disease and normal serum creatinine levels. J Am Soc Nephrol 2002;13(8):2140-4.
9. John S, Peter W, James A, et al. Methods for measuring GFR with ^{99m}Tc-DTPA: an analysis of several common methods, J Nucl Med,2006; 31:1211–19.
10. Natale G, Pirtro A, Massimo C, et al. Measurement of glomerular Filtration Rate by the ^{99m}Tc-DTPA Renal dynamic imaging Is Less Precise than Measured and Predicted Creatinine Clearance, Nephron, 1999; 81:136–40.
11. Kazuo ITOH. Comparison of methods for determination of glomerular filtration rate:Tc-99m-DTPA renography, predicted creatinine clearance method and plasma sample method. Annals of Nuclear Med, 2003; 17(7):561–65.
12. Brenner I, Bertram AK. Kasiske:laboratory assessment of kidney disease, clearance, urinalysis and kidney biopsy. Brenner and Rector's, The Kidney, Elsevier, USA, 8th Ed: 724-734.
13. Fleming JS, Keast CS, Derek G. Wallerand Duncan Ackery. Measurement of glomerular filtration rate with ^{99m}Tc-DTPA: A comparison of gamma camera methods, Eur J of Nucl Med, 1976; 1:155-58.
14. Jeffrey JG, Morton KA, Whooten WW, Greenberg HE, Datz FL, Handy JE et al. Comparison of Methods for Calculating Glomerular Filtration Rate: Technetium-99m- DTPA Scintigraphic Analysis, Protein-Free and Whole-Plasma Clearance of Technetium-99m-DTPA and Iodine-125-Iothalamate Clearance, The J of Nuclear Med, 1990; 31(4):990.