Int J Biol Med Res. 2013; 4(2) : 3073- 3077

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International Journal of Biological & Medical Research

Journal homepage: www.biomedscidirect.com

Original Article

A study of glomerular filtration rate estimation by cockcroft-gault, mdrd and ckd-epi formula in comparison with dtpa renal scan – a comparative study among live related kidney donors in south india.

K.Senthamizh selvan[a], S.Karthikeyan[b] , G.Sundaramurthy[c]

ARTICLE INFO

Keywords:
GFR,
COCKCROFT-GAULT
MDRD
CKD-EPI
DTPA scan
CKD
Renal transplantation

ABSTRACT

BACKGROUND: Renal function assessment is the most important part of donor evaluation. The Glomerular Filtration Rate (GFR) is considered to be optimal test for overall assessment of renal function. We aimed to estimate GFR by prediction equations namely COCKCROFT-GAULT, MDRD and CKD-EPI, among live related kidney donors and to analyse how closely the GFR calculated by these equations correlate with that of DTPA renal scan. MATERIALS AND METHODS: A total of 50 individuals attending Nephrology OPD over a period of 6 months (April 2011- September 2011), for undergoing donor evaluation at the Department of Internal Medicine and the Department of Nephrology, Government Stanley Medical College and Hospital, Chennai, India, were included. They underwent basic investigations and GFR was estimated using prediction equations namely COCKCROFT-GAULT, MDRD and CKD-EPI. Then as a part of routine donor evaluation, they were subjected to DTPA renal scan. RESULTS: In our study on 50 potential donors, all the three prediction equations namely COCKCROFT-GAULT, MDRD and CKD-EPI were found to correlate with DTPA scan values, the correlation though weak, was statistically significant for MDRD and CKD-EPI, and statistically not significant for COCKCROFT-GAULT equation. However they underestimated GFR by 27.65%, 27.17% and 22.42% for COCKCROFT-GAULT, MDRD and CKD-EPI respectively when compared to DTPA renal scan. CONCLUSION: DTPA scan cannot be substituted by the GFR prediction equations in special situations like renal transplantation. Further studies are required to find newer ways of estimating GFR which can be applied in all clinical settings.

1. Introduction

CKD progresses into end stage renal disease (ESRD) inspite of our strategies to slow the progression of the disease. ESRD occurs when kidney function is not able to cope up with the bodys excretory load and hemodialysis, peritoneal dialysis, or kidney transplantation has to be substituted for native kidney function. Among them, kidney transplantation by far imparts a better quality of life in ESRD patients.

The shortage of donor organ is a global issue that restricts kidney transplantation. Hence patients and transplant surgeons are increasingly dependent on live kidney donors. Although kidney transplantation offers a favourable outcome for the recipient, it may be associated with some risk for the donor. To minimize the risks a strict pre-operative donor evaluation is essential.

Renal function assessment of the donor is the most important part of donor evaluation. Glomerular Filtration Rate(GFR) is considered to be optimal test for overall assessment of renal function. Serum creatinine is not considered appropriate for estimation of renal function due to its tubular secretion and also its variability with body mass, age, sex and race.

It is well known that GFR can be precisely measured by specific filtration markers such as Inulin, I125 Iothalamate, Cr 51 EDTA, Tc99-diethylene triamino penta acetic acid (DTPA). These standard methods cannot be used in daily clinical practice as they are expensive, time consuming and cumbersome and require specialized equipments and skills.

* Corresponding Author : **Dr.K.Senthamizh Selvan M.D.(gen med)**
Asst.Prof of Medicine,
Sri LakshmiNarayana Institute Of Medical Sciences
Pondicherry, India.
Mobile no-98423 20339
Email id-senthamizh2909@gmail.com

So a non invasive and accurate estimation of GFR is the need of the hour in Nephrology. Here comes the GFR prediction equations which are easy to apply, cost effective and less cumbersome. The new K/DOQI Guidelines also recommend estimating GFR by MDRD and COCKCROFT-GAULT equations[1]

This study was done to estimate GFR by COCKCROFT-GAULT formula, MDRD formula, CKD-EPI formula and DTPA renal scan among live related kidney donors in India.

2. Materials and Methods

This study was an observational study conducted in Department of Nephrology, Government Stanley Hospital, Chennai, India, during April 2011-September 2011. Sample size was 50 and sampling was done by simple random sampling. Normal individuals who were willing for kidney donation were included in the study. Those with age <20 and > 55 years, ABO incompatibility, history of hypertension and diabetes, newly detected hypertensives and diabetics, females with history of gestational diabetes and gestational hypertension and those with family history of renal disease were excluded from the study. After getting approval from the institutional ethical committee the study was started, all measures were taken to maintain a strict confidentiality about the personal details of the participants of the study. An informed consent was obtained from them. They were maintained on a regular diet, and were subjected to thorough history, clinical examination, biochemical investigations, screening ultrasonogram of the abdomen and finally DTPA renal scan.

Assessment panel includes-

- Measurement of body weight in kg
- Blood pressure
- Biochemical investigations:
- Urine : albumin,sugar,deposits
- Hemoglobin
- Blood grouping and typing
- Bleeding time and clotting time
- Random blood sugar
- Blood urea nitrogen
- Serum creatinine
- Screening ultrasonogram of the abdomen

Results were collected and analysed. Glomerular filtration rate was calculated by downloadable calculators.

COCKCROFT-GAULT FORMULA

$$eGFR = \frac{(140 - Age) \times Weight\ in\ kg)}{(Serum\ creatinine)(72)} \times (0.85\ if\ female)$$

MDRD FORMULA FOR e GFR :

$$186 \times (SCR)^{-1.154} \times (age)^{-0.203} \times (0.742\ if\ female) \times (1.210\ if\ African\ American)$$

CKD-EPI FORMULA FOR e GFR:

141 x min (SCr/k,1)a x max(SCr/k,1)-1.209 x 0.993age x [1.018 if female] x [1.159 if black]where 'SCr' is serum creatinine (mg/dL), 'k' is 0.7 for females and 0.9 for males, 'a' is -0.329 for females and -0.411 for males, 'min' indicates the minimum of SCr/k or 1, and 'max' indicates the maximum of SCr/k or 1.

Finally DTPA RENAL SCAN was taken. They were given 1 litre of water to drink one hour before the procedure, and Tc 99 labelled DTPA injection was given intravenously. After injection of the dye film was taken from zero minute to upto 30 minute. IV injection frusemide 20mg was given at 15th minute. After voiding urine an immediate post void film was taken. Four hours later another film was taken. No adverse reactions were observed during and after the procedure.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Software version 20. Correlation was made by calculating pearson co-relation coefficient, Student `t` test was used for comparison.`R` statistics were obtained by simple linear regression. This reflects the predictive ability of the model. p-value of 0.05 was considered statistically significant. The Blant and Altman method was used to determine concordance between DTPA scan with the prediction equations.

3. Results

Majority of our study group belongs to the age group of 41-50 years and almost three -forth of our study group was comprised of female population.

It was evident (Table:1) that the mean GFR calculated by DTPA scan was higher in males than in females and mean GFR was maximum in the age group of 31-40 years and mean GFR decreases as the age advance.

Table-1: Distribution Of Gfr (dtpa) In Various Age Groups

AGE GROUP(years)	SEX	GFR BY DTPA SCAN			
		MEAN	MEDIAN	SD	RANGE
>30	Male	107	107	-	-
	Female	99.8	101.5	7.9	21
31-40	Male	111.5	110	5.7	12
	Female	97.8	94	13.4	32.5
41-50	Male	105.7	105	13	26
	Female	98.8	99	12.5	41.8
>50	Male	98.6	100	14.2	31.6
	Female	91.9	92	9	27.6

The calculated GFR by various equation revealed that the mean GFR was higher in DTPA when compared to CKD-EPI, MDRD and C-G formula (Table:2)

Table: 2 GFR BY VARIOUS METHODS

METHOD	MEAN	MEDIAN	STD. DEVIATION	STD. ERROR OF MEAN
C-G	71.23	67.11	16.75	2.37
MDRD	71.82	69.63	16.75	2.37
CKD-EPI	76.50	73.50	17.84	2.5
DTPA SCAN	99.12	99.47	11.73	1.66

[C-G-cockcroft-gault]

After calculating the mean GFR, their difference from the DTPA scan was calculated. The difference in mean GFR was much lesser in case of CKD-EPI formula when compared to MDRD and COCKCROFT-GAULT. The median difference from DTPA and the mean percentage difference were lesser with CKD-EPI formula (Table:3).

Table:3 Comparison of difference in GFR from DTPA scan

METHOD	MEAN GFR	MEAN DIF DTPA	MEDIAN DIF. DTPA	STD DIF. DTPA	MEAN% DIF. DTPA
C-G	71.23	27.88	28.95	17.93	27.65
MDRD	71.82	27.30	28.45	17.27	27.17
CKD-EPI	76.50	22.62	23.5	18.09	22.42

Thus the prediction equations, Cockcroft-gault, MDRD and CKD-EPI underestimated GFR by 27.65%, 27.17% and 22.42% when compared to DTPA renal scan. COCKCROFT-GAULT formula predicted GFR with < 25% error in almost 40% of patients,25-40% error in 34% of patients and >40% error in 26% of patients. MDRD formula predicted GFR with <25% error in 44% of patients, 25-40% error in 36% of patients and >40 % error in 20% of patients. CKD-EPI formula predicted GFR with <25% error in 50% of patients,25-40% error in 36% of patients and >40% error in 14% of patients.

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The correlation with DTPA scan was statistically significant for MDRD and CKD-EPI and statistically not significant for Cockcroft-gault formula (Table: 4).

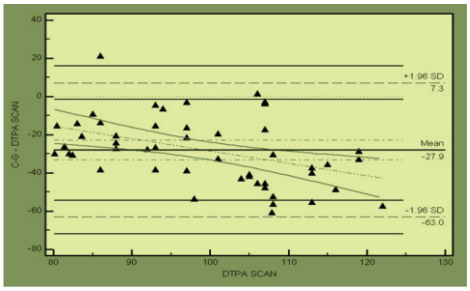
Table: 4 COMPARISON OF CO-EFFICIENT OF CORRELATION

FORMULA	COEFFICIENT OF CORRELATION	P-VALUE	SIGNIFICANCE
Cockcroft-Gault	0.246	0.085	Not significant
MDRD	0.305	0.031	Significant
CKD-EPI	0.307	0.030	Significant

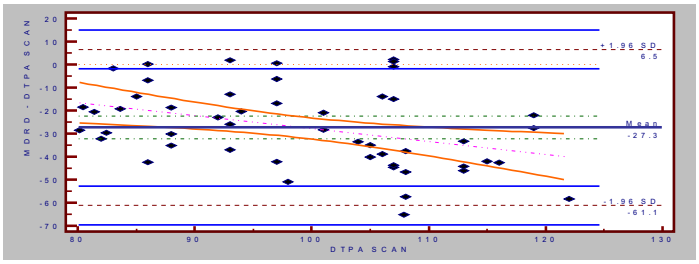
Bland and Altman method was used to establish concordance coefficient (Graph: 1, 2, 3).

It was obvious that majority of the plots were clustered around the mean line with a confidence interval of 95%, however these equations tend to underestimate GFR at all the levels with a mean difference of 27.9ml/min, 27.3ml/min and 22.6ml/min for Cockcroft-Gault, MDRD, and CKD-EPI respectively.

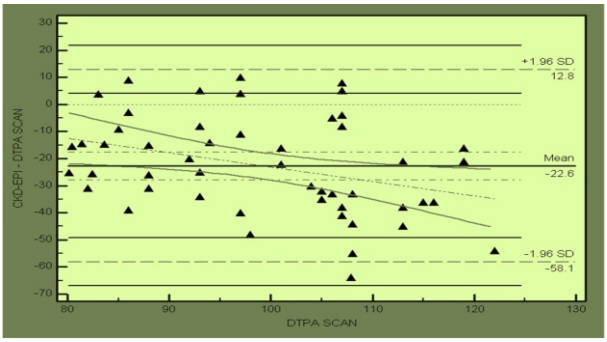
Graph:1 CONCORDANCE ANALYSIS OF C-G AND DTPA SCAN



Graph: 2 CONCORDANCE ANALYSIS OF MDRD AND DTPA SCAN



Graph: 3 concordance analysis of CKD-EPI AND DTPA SCAN



Discussion

Chronic kidney disease is a global (CKD) problem, gaining importance day by day. CKD burden increases due to increased prevalence of hypertension, diabetes Mellitus, cardiovascular diseases and increased longevity. There are studies, which show that the prevalence of early CKD is much greater than the prevalence of late CKD [4]. Hence early detection of CKD and initiation of treatment measures to halt its progression is the need of the hour.

The concept of using serum creatinine as a marker of GFR is not validated in most of the clinical settings .Since a 50 % fall in GFR is necessary for the creatinine level to rise, it is high likely that early cases of CKD may be missed. GFR can be estimated using prediction equations, again these equations employing serum creatinine depends on the calibration and variability of the method used[5]. However the new K/DOQI guidelines recommend use of prediction equations in estimating GFR [1].

In our study mean GFR estimated by Cockcroft-gault, MDRD and CKD-EPI formula were 71.23, 71.82 and 76.50; likewise the mean difference from DTPA scan were 27.86, 27.30 and 22.62 respectively. Thus it is obvious the prediction equations significantly underestimate the GFR. However there was a fair amount of correlation of these prediction equations with the DTPA scan values, where CKD-EPI correlating better among the three.

Cockcroft-Gault formula does not correct for race of the individuals, also our study group comprised predominantly of elderly females. The serum creatinine not being calibrated with standard measurements, could be another reason for underperformance of the Cockcroft-Gault.

MDRD formula was devised, based on the creatinine clearance of the CKD population. Our study group being normal individuals, might contribute for underperformance of the MDRD. There were studies where MDRD underestimated GFR upto 29% [6]. Again errors in caliberating serum creatinine might be a potential reason for underperformance of the MDRD[7].

Regarding the CKD-EPI formula, which was introduced recently has not been validated in different clinical studies. Although limited references state that CKD-EPI performs better than MDRD [2],[3].

In our study CKD-EPI also underestimates GFR, with a mean of 76.50 ml/min where mean GFR measured by DTPA was 99.12 ml/min. The possible causes could be the predominant study population being elderly females, none of them being African-American, and errors in serum creatinine estimation. It requires creatinine estimation by isotope dilution mass spectrometry, which again could be a setback in our study.

There were many studies reported in the literature, comparing the predicting equations namely Cockcroft-Gault and MDRD. In the Levey et al study[8], 1628 CKD patients were included and the mean GFR was 48.6. The creatinine clearance estimated by 24 hour urine creatinine clearance and the Cockcroft-Gault overestimated GFR BY 16% but MDRD performed better in them. In the Lewis et al [9] study 1703 African –American patients with CKD were included, where the mean GFR was 56.8. Here Cockcroft-Gault underestimated GFR and MDRD estimated GFR accurately, the study population being the CKD patients MDRD performed better in these studies. In Bertolus et al study [10], 22 potential donors with creatinine clearance <80ml/min were included, and showed both the equations performed poorly and it suggested to index serum creatinine by height rather than body surface area .

In the Bostom et al study [11], 109 CKD patients were included, showed MDRD was a much precise equation, but considering the multiple possibilities of error the equation had to be used with caution. Measurement of GFR using markers like Inulin, DTPA, Iohexol and Iothalamate is practically difficult in developing countries because of their limited availability and the cost involved. MDRD may be used to estimate GFR in patients with early CKD.

In the Vervootet al [12] study, 46 healthy adults and 46 type 1 diabetics without proteinuria were included which showed that the MDRD equation performed poorly in the diabetics. In the Kingdon et al [13] study, 26 patients with scleroderma were included and they found that the MDRD equation employing demographic and serum variables performed excellently in those patients .In the Poggio et al study [17], MDRD equation overestimated GFR in CKD patients and both MDRD and Cockcroft-Gault equations underestimated GFR in patients with normal kidney function.

Although all these studies have employed Cockcroft-gault and MDRD equations none employed CKD-EPI. Only few studies were reported, which employed CKD-EPI equation. A research article from France[14] , states that prediction equations (MDRD, CKD-EPI) created discrepancy in epidemiological assessment of CKD prevalence.

A study in Australia in 2010 [15] showed, the prevalence of CKD in the Australian population aged more than 25 years, using MDRD was 13.4% , the prevalence was 11.5% using CKD-EPI , this was because 266 individuals in the study belonged to the CKD group. According to MDRD equation they were reclassified as not having CKD by the CKD-EPI ,due to better estimation of GFR .

Another study in Netherland [16], stated that both MDRD and CKD-EPI were able to predict with higher accuracy when compared

to other equations. Lin et al study[18], the MDRD equation underestimated GFR, and the Cockcroft-Gault equation consistently overestimated measured GFR in people with normal kidney function. In potential kidney donors, prediction equations may not be sufficient for estimating GFR and radioisotope studies like DTPA SCAN may be needed for a better assessment of GFR.

In a Chinese study of comparing the prediction equations in potential live kidney donors [20] all the prediction equations performed poorly and considering the importance of the kidney transplantation more accurate methods of GFR calculation needs to be devised.

Another study from Thailand [21] included 60 healthy adults, and found that the prediction equations were suboptimal, and suggested newer methods for employing prediction equations among various ethnic groups.

Winding up, in our study on 50 potential donors, the prediction equations namely Cockcroft-gault, MDRD and CKD-EPI underestimated GFR by 27.65%, 27.17% and 22.42% respectively when compared to DTPA renal scan. These equations were able to predict GFR with <25% error in 40%, 44% and 50% of the study group for Cockcroft-Gault , MDRD, and DTPA scan respectively.

However all these 3 equations were found to correlate with DTPA scan values, the correlation was statistically significant for MDRD and CKD-EPI, and statistically not significant for Cockcroft-Gault equation. The possible reasons could be lack of standardization in calibration of serum creatinine, study population predominantly being females, smaller sample size, absence of African –Americans in the study.

MDRD and Cockcroft-Gault was devised in the CKD setting and not in the normal population whereas our study group belonged to normal and healthy adults. These prediction equations were not validated in our population and our clinical setting. DTPA scan gives split GFR of each kidney, renal tubular function, details about renal blood supply, renal tubular obstruction or damage. DTPA scan cannot be substituted by the prediction equations in special situations like renal transplantation. However extensive research work are under process , which may bring out newer, more accurate, less invasive and cheaper ways of estimating GFR which is applicable in all the clinical settings.

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