



Estimated Glomerular Filtration Rate (eGFR) in Healthy Kidney Donors

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ABSTRACT

Introduction: *This study was done to determine the range of Glomerular filtration rate (GFR) in healthy kidney donors, from Kerala.*

Materials and Methods: *This retrospective study was done by including all consecutive voluntary kidney donors, who underwent donor nephrectomy at Amrita Institute of Medical Sciences, Kochi, Kerala from 2001 to 2011. The GFR was assessed by 99mTc-diethylenetriamine pentaacetic acid (DTPA) renogram (GC Gates method) as part of protocol during preoperative evaluation. The GFR by DTPA method was compared to values obtained by four variable MDRD formula and Cockcroft-Gault formula (CGF).*

Results: *The mean age of the study population was 45.32 years (Range - 18 to 64 years) with 71.7 % being females. The majority of the donors were parents (54.78%) followed by siblings (33.04%) and spouses (12.17%). The eGFR in a healthy kidney donor ranged was 56 to 117 ml/min by 99mTc DTPA; GC Gates method. The mean eGFR were 82.89 (SD:22.46), 85.25 (SD:16.90), and 84.56 (SD:11.60) ml/min by CGF, MDRD and DTPA respectively. There was positive correlation in eGFR between methods used in the study. In donors with DTPA GFR ranging from 80-100 ml/min; there was no significant difference in mean eGFR between methods.*

Conclusions: *The mean eGFR of a kidney donor from India, was 84.56 (\pm 11.60) ml/min, which is lower than the normal value of western population. In donors with DTPA GFR < 80 ml/min; MDRD and CGF methods overestimated GFR. In donors with DTPA GFR >100 ml/min; the CGF, MDRD methods underestimated the GFR.*

Introduction

Glomerular filtration rate (GFR) is defined as the volume of plasma that can be completely cleared of a particular substance by the kidneys in unit time. The exogenous (Inulin, Iohexol, Chromium-51-Ethylene Diamine Tetraacetic Acid (EDTA), Technetium-99m labelled Diethylene Triamine Penta Acetic acid (DTPA) or I-125 (labelled Iothalamate) and endogenous markers (Blood Urea, Creatinine, Cystatin C) are used for estimation of GFR. Estimations by using exogenous markers is expensive and often available only at referral or research centres. GFR estimation by Inulin infusion is considered as gold standard, but it is cumbersome, expensive and is only used research centres. Endogenous markers are most commonly used, because they are available in most of the centres, and can be repeated multiple times, whenever in doubt, as they are relatively inexpensive.

Live donor evaluation forms central part of any renal transplant program, because without them transplant centre cannot function effectively, as cadaver/brain dead organ donation is still rare India, except in few states. All the live kidney donors undergo evaluation as per protocol prior to donor nephrectomy and renal transplantation to their near and dear ones. We have limited data

regarding normal eGFR ranges in Indian population.^[1-13] This study was done to determine reference range of eGFR in healthy kidney donors from Kerala.

Aims and objectives

1. To determine the reference range of GFR in healthy kidney donors from Kerala.
2. To compare of GFR values obtained by DTPA, Cockcroft and Gault equation and MDRD (4 variable) equations.

Materials and Methods

This was an observational study done in Nephrology unit of Amrita Institute of Medical Sciences & Research Centre, Kochi, Kerala. All voluntary kidney donors who underwent donor nephrectomy from 2001 to 2012 at were included in the study. The donor evaluations were done as per our protocol. Creatinine levels were estimated by using Jaffe kinetic method. The normal ranges for serum creatinine level in our laboratory were 0.6-1.2 and 0.8 to 1.4 mg/dl for females and males respectively. The GFR was estimated by Cockcroft and Gault formula (CGF) and modification of diet in renal disease (MDRD)(4 variable) equation. The mGFR was estimated by DTPA by using Gamma camera by Gates method.

Estimation of GFR by CGF and MDRD equation

eGFR equation	Males	Females	
CGF	$\{(140-\text{age}) \times \text{weight}\} / \{72 \times \text{Cr}\}$	X 0.85	
MDRD	$186 \times (\text{Cr})^{-1.154} \times (\text{age})^{-0.203}$	X 0.742	X 1.212 if Black
Cr =serum creatinine concentration in mg/dl, age in years			

Estimation of GFR by ^{99m}Tc DTPA:

The subjects were given 1 litre of water to drink one hour before the procedure, and Tc 99 labelled DTPA injection was given intravenously, followed by gamma camera imaging from zero minute to 30 minutes. After voiding urine an immediate post void imaging was done, followed by a delayed film at 4 hours. The GFR was estimated, using Gates method. In the Gates method, the GFR was automatically calculated by

the software in Infinia Hawkeye (GE) gamma camera. A region of interest (ROI) was drawn manually for each kidney from 2 to 3 min summed images. The infrarenal background ROI was assigned.

Firstly, fractionated uptake (FU) of each kidney was assessed according to the equation.

$FU = (\text{renal count}/e-\mu y)/\text{total injected dose counts} \times 100$, where the renal count was background

subtracted and the dose counts were expressed in counts per minute (cpm).

The renal count was calculated from the renal uptake between 2 and 3 min in the renogram; μ = attenuation coefficient of Tc-99m (0.153) and y = kidney depth (cm), which was calculated as described in Tonnesen's formula.

The GFR, in ml/min, was calculated as: $9.75621 \times FU - 6.19843$.

Statistical Analysis: Mean \pm standard deviation (SD) were used for summarizing the data. For continuous variables, mean values were compared using oneway ANOVA. The difference in mean values of eGFR gender and age groups were tested by independent sample t test. Pair-wise comparison of the mean difference in eGFR was performed using the paired t-test. The confidence interval (CI) of 95% and a $P < 0.05$ (2 tailed) was used for statistical significance. All statistical analyses were performed with SPSS version 17.0 and Analyse-it $\text{\textcircled{R}}$ 16 for Windows.

Results

Baseline characteristics of donors

A total of 230 voluntary kidney donors, aged from 18-64 years (Mean: 45.32, SD:10.01) were included in the study (Table 1). Majority of the donors were females (165; 71.74%) with M: F ratio of 2.54:1 (Table 2). The parents (126; 54.78%) constituted for majority of the kidney donors in the study followed by siblings (76; 33.04%) and spouses (28; 12.17%) (Table 2). The mean height, weight, BSA and BMI of the donors were 129 cm (SD:8.87), 59.65Kg (SD:10.63), 1.59m² (SD:0.16) and 24.97 (SD:3.96) respectively (Table 1). The serum creatinine level ranged from 0.7 to 1.40 (mean:0.99) mg/dl in males and 0.5 to 1.3 (mean:0.82) mg/dl in females.

The eGFR and its methods for estimation

The range, mean and SD of eGFR of all subjects in study is summarized in Table 1. The mean eGFR were 82.89 (SD:22.46), 85.25 (SD:16.90), and 84.56 (SD:11.60) ml/min by CGF, MDRD and DTPA respectively (Table 3). The SD

of eGFR was least with DTPA indicating that narrower range of values with this method of estimation, in comparison to MDRD or CGF.

There was significant (p value < 0.001) positive correlation in eGFR between methods used in the study (Table 3). The correlation was strongest between CGF & MDRD (Pearson's R of 0.706), followed by DTPA & MDRD (Pearson's R of 0.341), and DTPA & CGF (Pearson's R of 0.332) (Table 4). There was no significant difference in mean eGFR by DTPA to that by MDRD and CGF method; however, the difference in eGFR was significant between MDRD and CGF methods. The coefficient of variation or relative variability of mean eGFR between methods used in the study were 6.5%, 8.9% and 19.4% between DTPA & MDRD, DTPA & CGF and MDRD and CGF respectively. The bias in eGFR among methods used for its estimation was -0.11%, -4.53% and -4.41% between DTPA & MDRD, DTPA & CGF and MDRD and CGF respectively with CI of 95% (Bland Altman method) (Figures 4,5 and 6).

The subjects were categorised into three categories based on eGFR by DTPA (< 80 , 81-100 & > 100 ml/min) to compare the mean eGFR by paired t test between CGF, MDRD and DTPA methods. The mean, SD, standard error of mean and subjects number in each category are summarised in table 4.

In donors with DTPA GFR eGFR < 80 ml/min ($n=89$); the mean eGFR were 74.09, 78.84 and 72.94 ml/min by CGF, MDRD and DTPA respectively (Table 3). There was positive correlation (Pearson's R) between methods. There was positive correlation in eGFR between methods used in the study. The correlation between MDRD and CGF methods was stronger (Pearson's R 0.706) in comparison that between DTPA with MDRD (Pearson's R 0.341) or DTPA with CGF (Pearson's R 0.332) methods (Table 4). The mean eGFR by DTPA was lower than mean eGFR by MDRD ($p < 0.001$) and CGF ($p = 0.604$) methods (Table 4).

In donors with DTPA GFR ranging from 80-100 ml/min ($n=120$); the mean eGFR were 87.69,

88.99 and 89.52 ml/min by CGF, MDRD and DTPA respectively (Table 3). There was positive correlation between methods (Table 4). There was no significant difference ($p > 0.05$) in mean eGFR by between methods used for its estimation in eGFR (Table 4).

In donors with DTPA GFR > 100 ml/min ($n = 21$); the mean eGFR were 92.81, 91.08 and 105.43 ml/min by CGF, MDRD and DTPA respectively (Table 3). There was positive correlation (Pearson's R) between methods. However, the correlation between eGFR by DTPA with MDRD (Pearson's R: 0.143) and CGF (0.173) methods was weak (Table 4). The mean eGFR by DTPA was higher than mean eGFR by MDRD ($p = 0.002$) and CGF ($p = 0.011$) methods (Table 4).

GFR and relation with age

The donors were grouped in to 3 for analysis; 18-39, 40-49, 50-64 years, comprising of 56, 91 and 83 donors respectively. The range, mean and SD of eGFR in each group is summarized in table 5. There was no significant difference in serum creatinine levels between the groups, however, the eGFR showed a statistically significant ($p < 0.001$) negative trend with age, by all 3 methods (Table 5 and figure 1,2,3). The Pearson correlation of

eGFR with age was -0.532, -0.413 and -0.394 for CGF, MDRD and DTPA methods respectively.

GFR and its relation with gender

The mean eGFR was higher in males than females by all 3 methods. The difference in eGFR between males and females was statistically significant by MDRD equation ($p = 0.002$), however, it was insignificant by DTPA ($p = 0.407$) or CGF methods ($p = 0.486$) (Table 6).

Effect of donor comorbidities on eGFR

There were 13 with obesity (BMI > 30 kg/m²), 16 subjects with stage 1 primary hypertension (BP controlled to $< 130/80$, with single drug), 7 with dyslipidemia and 3 with IGT. They explained regarding the future risks associated with kidney donation. However, they underwent donor nephrectomy, as they were parents donating to their children.

The CGF overestimated the eGFR in obese individuals and difference was statistically significant. Obesity did not have any significant effect on eGFR by MDRD and DTPA methods (Table 7). The presence of well controlled stage I primary hypertension (table 8), IGT or dyslipidemia did not have any statistically significant effect ($p > 0.05$) on eGFR by all 3 methods

Table 1: Age, Weight, BMI, and GFR in Healthy Kidney Donors

	Minimum	Maximum	Mean	Std. Deviation
Age	18	69	45.33	10.01
Weight	39.00	97.00	59.65	10.63
Serum creatinine (mg/dl)	0.50	1.40	0.87	0.15
BMI (kg/m ²)	16.00	38.00	24.57	3.96
eGFR by CGF	34.57	177.50	82.90	22.46
eGFR by MDRD	44.56	148.76	85.25	16.90
eGFR by 99mTcDTPA	56.00	117.00	84.56	11.60

Table 2: Gender and relationship of donor to recipient

Parameter		Males	Females	Total (Percentage)
Donor and recipient relationship	Parents	26	100	126 (54.78)
	Siblings	35	41	76 (33.04)
	Spouse	3	25	28 (12.17)
	Total	65	165	230

Table 3: The eGFR categorised by DTPA range & its relation of to CGF and MDRD method

Method		Mean	N	Std. Deviation	Std. Error Mean
All subjects					
eGFR	CGF	82.90	230	22.46	1.48
	MDRD	85.25	230	16.90	1.11
	DTPA	84.56	230	11.60	0.76
DTPA GFR upto 80 ml/min					
eGFR	CGF	74.09	89	21.00	2.23
	MDRD	78.84	89	13.48	1.43
	DTPA	72.94	89	5.55	0.59
DTPA GFR 81-100 ml/min					
eGFR	CGF	87.69	120	21.90	1.99
	MDRD	88.99	120	17.59	1.60
	DTPA	89.52	120	5.37	0.49
DTPA GFR > 100 ml/min					
eGFR	CGF	92.81	21	19.81	4.32
	MDRD	91.08	21	18.11	3.95
	DTPA	105.43	21	5.45	1.19

Table 4: Correlation between methods for eGFR

GFR Method	Pearson's R	Paired t test (p-value)
All subjects		
CGF and MDRD	0.706	0.026
DTPA and MDRD	0.341	0.533
DTPA and CGF	0.332	0.245
DTPA GFR upto 80 ml/min		
CGF and MDRD	0.610	0.008
DTPA and MDRD	0.143	< 0.001
DTPA and CGF	0.173	0.604
DTPA GFR 81 - 100 ml/min		
CGF and MDRD	0.714	0.361
DTPA and MDRD	0.230	0.737
DTPA and CGF	0.126	0.363
DTPA GFR > 100 ml/min		
CGF and MDRD	0.704	0.594
DTPA and MDRD	0.172	0.002
DTPA and CGF	0.206	0.011

Table 5: Serum Creatinine, GFR according to age groups

Parameter	Number of donors	Minimum	Maximum	Mean	Standard deviation
Age 18-39 years					
sr. creatinine	56	0.5	1.2	0.87	0.15
GFR-CG		53.52	156.86	96.49	21.65
GFR - MDRD		52.93	148.76	94.61	19.85
GFR -DTPA		71	117	90.55	11.32
Age 40-49 years					
sr. creatinine	91	0.6	1.2	0.83	0.13
GFR-CG		48.27	177.50	86.67	21.84
GFR - MDRD		52.36	130.21	86.09	14.79
GFR -DTPA		56	111	84.95	10.92
Age 50-69 years					
sr. creatinine	83	0.6	1.4	0.90	0.17
GFR-CG		34.57	112.45	69.59	15.79
GFR - MDRD		44.56	118.85	78.02	13.41
GFR -DTPA		60	102	80.08	10.70

Table 6: Mean eGFR and its variation with Gender

eGFR	Gender	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum	ANOVA test p value
						Lower Bound	Upper Bound			
CGF	Male	65	84.54	19.12	2.37	79.81	89.28	50.63	128.21	0.486
	Female	165	82.25	23.66	1.84	78.61	85.89	34.57	177.50	
	Total	230	82.90	22.46	1.48	79.98	85.82	34.57	177.50	
MDRD	Male	65	90.74	16.93	2.10	86.55	94.93	56.34	130.99	0.002
	Female	165	83.09	16.44	1.28	80.56	85.62	44.56	148.76	
	Total	230	85.25	16.90	1.11	83.06	87.45	44.56	148.76	
DTPA	Male	65	85.57	12.73	1.579	82.41	88.72	60	117	0.407
	Female	165	84.16	11.14	0.868	82.44	85.87	56	112	
	Total	230	84.56	11.60	0.765	83.05	86.06	56	117	

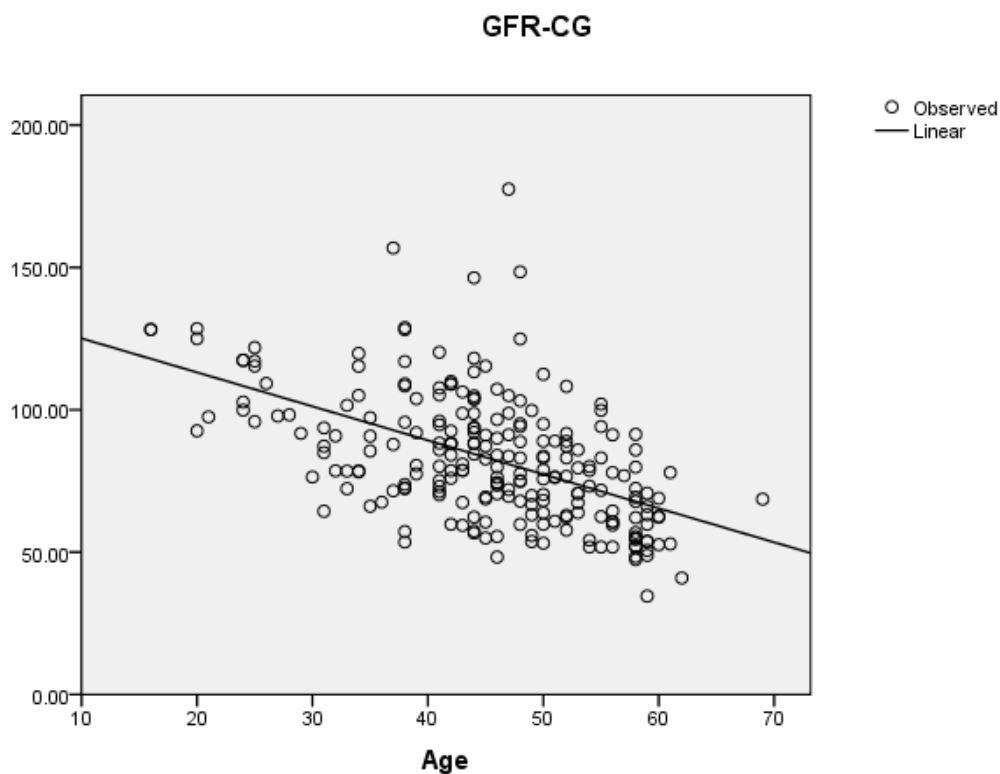
Table 7: Mean eGFR and variation with obesity

GFR	Weight	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum	ANOVA test p value
						Lower Bound	Upper Bound			
CGF	Non obese	217	81.57	21.30	1.45	78.71	84.42	34.57	156.86	<0.001
	Obese	13	105.03	29.79	8.26	87.03	123.04	78.21	177.50	
	Total	230	82.89	22.46	1.48	79.97	85.81	34.57	177.50	
MDRD	Non obese	217	85.55	16.83	1.14	83.30	87.81	44.56	148.76	0.27
	Obese	13	80.25	17.90	4.97	69.43	91.07	54.66	113.89	
	Total	230	85.25	16.90	1.11	83.06	87.45	44.56	148.76	
DTPA	Non obese	217	84.72	11.55	0.78	8.1	86.27	56	117	0.37
	Obese	13	81.77	12.57	3.48	74.17	89.37	61	101	
	Total	230	84.56	11.60	0.76	83.05	86.06	56	117	

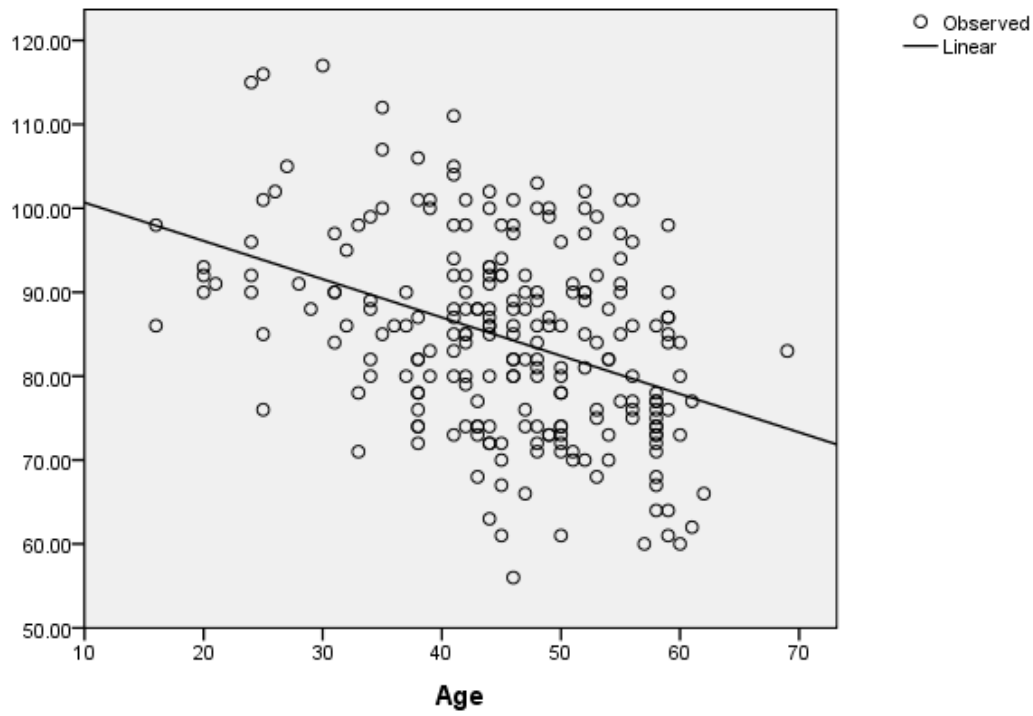
Table 8: Mean eGFR and its variation in presence of hypertension

eGFR method	HTN	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum	ANOVA test p value
						Lower Bound	Upper Bound			
CGF	NO	214	82.69	22.88	1.56	79.60	85.77	34.57	177.50	0.610
	YES	16	85.66	15.85	3.96	77.21	94.11	54.25	113.33	
	Total	230	82.89	22.45	1.48	79.97	85.81	34.57	177.50	
MDRD	NO	214	85.57	17.30	1.18	83.24	87.90	44.56	148.76	0.294
	YES	16	80.97	9.46	2.36	75.92	86.01	67.06	97.53	
	Total	230	85.25	16.90	1.11	83.05	87.45	44.56	148.76	
DTPA	NO	214	84.59	11.747	0.80	83.01	86.18	56	117	0.860
	YES	16	84.06	9.788	2.44	78.85	89.28	61	101	
	Total	230	84.56	11.604	0.76	83.05	86.06	56	117	

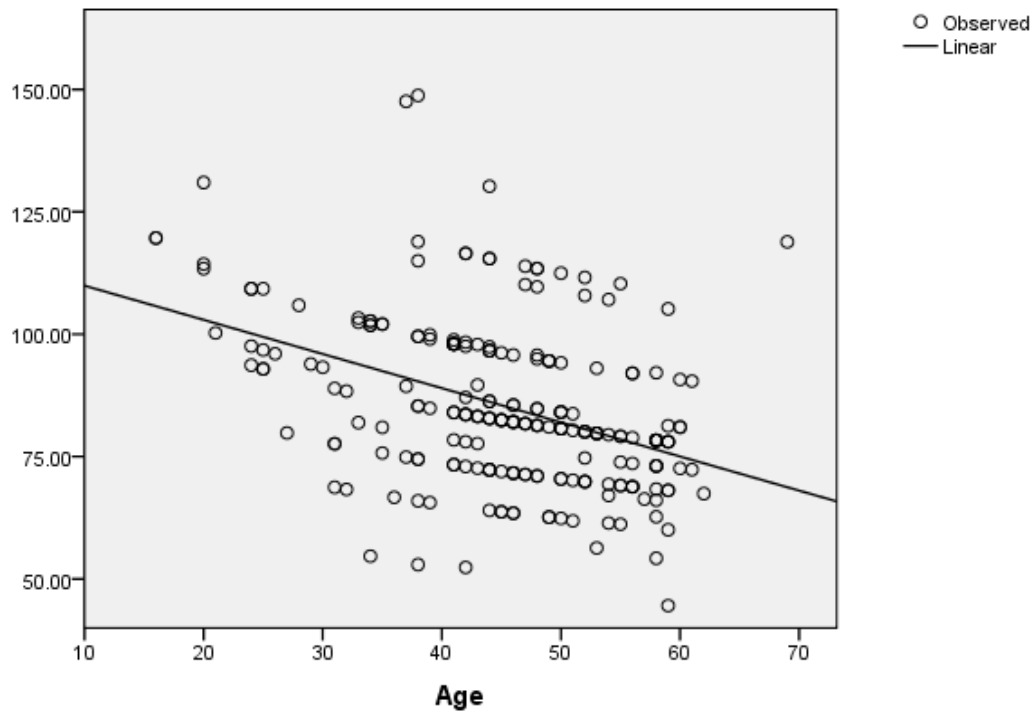
Figures 1,2,3: Scatter plots showing the trend of eGFR with age



GFR - TcDTPA



GFR - MDRD



Discussion

This study was conducted to find out the range of GFR among healthy kidney donors and evaluate the correlations among methods used for its measurement prior to donor nephrectomy. The GFR was estimated using CG formula and 4 variable MDRD equation and this was compared to GFR obtained by DTPA renogram by GC Gates method. The individual kidney GFR by DTPA and renal vascular anatomy by CT angiography was used to decide regarding the donor nephrectomy.

Our study subjects included 230 voluntary kidney donors, aged from 18-64 years (Mean:45.32); majority (71.74%) being females with M: F ratio of 2.54:1. The mean serum creatinine level was 0.99 and 0.82 mg/dl in males and females respectively. The donor profile in terms of age, female predominance in our study is with earlier reports from India. ^[1,2,4,5,7,9,10]

The eGFR by DTPA method (Gates method) ranged from 56-117 ml/min, with mean and standard deviation of 84.56 ml/min and 11.60 respectively. The range and mean eGFR in our study is consistent with other India studies which reported the mean eGFR (Gates method) of 61 to 119.34 ml/min. ^[1-10] The GFR in healthy Indian is lower than western population with different studies reporting the mean eGFR from 119 to 130 ml/min. ^[11,12] The mean eGFR in South Korean was reported as 77.1 ml/min with SD of 16.3, which is similar to mean eGFR from Indian studies. ^[13] The bias between methods for eGFR estimation was least between MDRD and DTPA.

The mean eGFR were 82.89 (SD:22.46), 85.25 (SD:16.90), and 84.56 (SD:11.60) ml/min by CGF, MDRD and DTPA respectively; the SD of eGFR was least with DTPA indicating that narrower range of values with this method of estimation, in comparison to MDRD or CGF. The findings of our study population correlates with an earlier report in which the mean eGFRs were; 82.19 ± 18.28 , 95.57 ± 22.35 and 83.42 ± 13.4 by CGF, MDRD and DTPA methods respectively. ^[5]

The Pearson's correlation between MDRD and CGF (0.706) methods was stronger followed by that between DTPA with MDRD (0.341) and DTPA with CGF (0.332) methods. A similar correlation strength (0.372) between DTPA and MDRD methods was demonstrated in an earlier report. ^[9] Hence DTPA cannot be substituted by CGF or MDRD for estimation of GFR due to weaker correlation, and ability of assess relative kidney function by DTPA method and not by other two.

In the donors with DTPA eGFR < 80 ml/min; the mean eGFR (ml/min) were 74.09, 78.84 and 72.94 by CGF, MDRD and DTPA respectively. Both MDRD and CGF overestimated eGFR in comparison to DTPA method. In donors with DTPA eGFR ranging from 80-100 ml/min; the mean eGFR (ml/min) were 87.69, 88.99 and 89.52 by CGF, MDRD and DTPA respectively. There was positive correlation between methods; there was no significant difference in mean eGFR by between methods used for its estimation in eGFR; i.e. all methods fared equally if the GFR is in above range. In donors with DTPA eGFR > 100 ml/min; the mean eGFR (ml/min) were 92.81, 91.08 and 105.43 by CGF, MDRD and DTPA respectively. Both MDRD and CGF methods underestimated eGFR by in comparison to that by DTPA method. A similar variation of eGFR by DTPA with that from MDRD and CKD-EPI methods was demonstrated in earlier study using limits for analysis as > 90 and < 90 ml, in Korean population. ^[13]

There was no significant difference in serum creatinine levels between the age groups; however, the eGFR showed a reducing trend with age, by all 3 methods, consistent with other studies. ^[1, 6] The mean eGFR was higher in males than females by all 3 methods; however, the difference was eGFR was significant only in MDRD method. The insignificant difference in GFR by DTPA between males and females was also demonstrated in an earlier study. ^[4, 9]

^{9]} Statistically significant difference in MDRD

GFR, between males and females, is consistent with the finding of an earlier study.^[9]

Donors with DTPA GFR < 80 ml/min or comorbidities (grade 1 hypertension, IGT, obesity, dyslipidemias) were considered as marginal donors, they were selected for donation if there are no alternative donors after explaining regarding the risk associated with surgery.^{[14, 15,}

^{16]}The CGF overestimated the eGFR in obese individuals and difference was statistically significant. Obesity did not have any significant effect on eGFR by MDRD and DTPA methods. The presence of well controlled stage I primary hypertension, IGT or dyslipidemia did not have any statistically significant effect on eGFR by all 3 methods.

There only few studies assessing the long term effects after kidney donation in India, which showed minimal increase in proteinuria and blood pressure, after mean follow-up period of 63 months, our study group also needs long term follow-up.^[2]

Conclusions

Our study included healthy related donors, aged from 18-64 years (Mean:45.32); majority (71.74%) being females with M: F ratio of 2.54:1. The mean serum creatinine level was 0.99 and 0.82 mg/dl in males and females respectively.

The range of eGFR (ml/min) was 56-117 (Mean:84.56, SD:11.60) by DTPA, Gates method. There was positive correlation in eGFR between methods used in the study; however, correlation of eGFR by DTPA method with MDRD and CGF across all ranges was weak; i.e. the DTPA GFR method cannot be substituted by either MDRD or CGF. The DTPA method also gives us the individual kidney GFR or relative renal function, which will aid us deciding the selecting the side of nephrectomy.

In donors with DTPA GFR ranging from 80-100 ml/min; there was no significant difference in mean eGFR between methods used for its estimation. In the donors with DTPA GFR < 80 ml/min; MDRD and CGF methods overestimated

GFR. In donors with DTPA GFR >100 ml/min; the CGF, MDRD methods underestimated the GFR.

The eGFR showed a reducing trend with age, by all 3 methods. The mean eGFR was higher in males than females by all 3 methods; however, the difference was significant only in MDRD method. The CGF overestimated the eGFR in obese individuals. The presence of well controlled stage I primary hypertension, IGT or dyslipidemia did not have any statistically significant effect on eGFR by all 3 methods.

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