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Evaluation of the glomerular filtration rate by using the modified gates method (*in vivo* study) and the modification of diet in renal disease method (*in vitro* study) for patients with renal diseases

Osiris W.Guirguis[1]*, Rania M.Abdel Halim[2], Adel M.K.Meselhy[3]

[1]Biophysics Department, Faculty of Science, Cairo University, Giza, (EGYPT)

[2]Fahd Center, Faculty of Medicine, Cairo University, Giza, (EGYPT)

[3]Physics Department, Faculty of Science, Helwan University, Cairo, (EGYPT)

E-mail: osiris_wgr@yahoo.com

ABSTRACT

The purpose of the study was to compare the estimation of glomerular filtration rate (GFR) from ^{99m}Tc-DTPA renography with that estimated from "Modification of Diet in Renal Disease" (MDRD) equation and studying the effect of different parameters on the evaluation of the glomerular filtration rate of patients with renal diseases such as radioactive ^{99m}Tc-DTPA for patients, time of counting of radioactive syringe and distance between syringe and detector of gamma camera. ^{99m}Tc-DTPA renography was performed on 158 patients with a wide range of renal function. The GFR was determined by two methods: gamma camera uptake method modified Gates (*in vivo* method); and Modification of Diet in Renal Disease method (MDRD) (*in vitro* method). Different radioactivities of 3, 6, 9, 12, 15 and 18 mCi of ^{99m}Tc-DTPA are being counted within 60 seconds and at distance 30 cm from gamma camera detector. The radioactivity of 12 mCi is being counted in different times in the range from 10 to 30 seconds and at different distances from 10 to 40 cm. The obtained results show that maximum count per pixel was approximately the same in all images except for 3 mCi sample image, suggesting saturation of the pixels in high activities. In conclusion the Gates correlates with MDRD equation, and also, the ^{99m}Tc-DTPA renography will become more accurate in measurement of GFR, if the parameters are corrected.

KEYWORDS

Glomerular filtration rate;
Renography;
Modification in diet in renal disease equation;
^{99m}Tc-DTPA.

INTRODUCTION

Chronic kidney disease, a major public health problem whose prevalence is constantly increasing worldwide, is traditionally diagnosed and is monitored by assessment of glomerular filtration rate (GFR)[1,2]. In accordance with the Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines, estimates of glomerular filtration rate (GFR) are the best overall indices of the level of renal function[3]. Glomerular filtration rate provides an excellent measure of the filtering capacity of the kidneys. It can be used as an index of functioning renal mass; and changes in GFR which can delineate progression of kidney disease. The level of GFR being

Regular Paper

a strong predictor of the time to onset of kidney failure and the risk of complications of chronic kidney disease (CKD) such as cardiovascular disease, hypertension, anemia, malnutrition, bone disease, neuropathy, decreased quality of life and death[3,4]. The determination of serum creatinine is the most widely used and commonly accepted measure of renal function in clinical medicine. Regardless of its widespread use, the accuracy of estimating GFR on the basis of the serum creatinine concentration only is limited, because it is affected by several factors, including body mass, gender, and age. In an attempt to circumvent these limitations, a variety of formulas have been developed, which also take into account age, sex, and body size in their calculation. Among these formulas, the Modification of Diet in Renal Disease equations (MDRD) are widespread, since they are supposed to compensate for the major drawbacks of serum creatinine determination and adequately correlate with GFR measured by the reference method[1]. Rapid and accurate estimation of the glomerular filtration rate (GFR) is required for many major clinical decisions in patients with chronic nephropathies. Direct GFR measurement is time-consuming and expensive, frequently requires urine collection and isotope use, and is routinely available in only a few medical centers[5]. Due to limitation of references methods, it is recommended to estimate glomerular filtration rate (GFR) by serum creatinine–based equations[6]. Therefore, simple and accurate determination of the GFR is still a challenge clinically[7]. Estimation of the glomerular filtration rate (GFR) is required in the assessment of patients with chronic kidney disease (CKD) in order to provide information regarding the functional status of the kidneys. Current guidelines advocate the use of prediction equations, such as the Modification of Diet in Renal Disease (MDRD) study-derived equations, over clearance of endogenous creatinine (Ccr) in achieving this aim[8]. The gamma camera uptake method with ^{99m}Tc- DTPA is simple and less time consuming for the determination of the glomerular filtration rate (GFR)[9]. In ^{99m}Tc-DTPA renography, the glomerular filtration rate (GFR) is calculated without blood or urine sampling[10]. The gamma camera method has been stated as less accurate than the plasma clearance method of radionuclides[9,13] and is more complex than the well counter used for the plasma clearance method and factors such as field uniformly, linearity and spatial resolution which can affect the image quantification. In the present study, it was found that there are other factors may affect on GFR measurements.

The purpose of the study was to compare the estimation of glomerular filtration (GFR) from ^{99m}Tc-DTPA renography with that estimated from "Modification of Diet in Renal Disease" (MDRD) equation and studying the effect of different parameters on the evaluation of the glomerular filtration rate of patients with renal diseases such as radioactive ^{99m}Tc-DTPA for patients, time of counting of radioactive syringe and distance between syringe and detector of gamma camera. The GFR was determined by two methods: first, gamma camera uptake method modified Gates (*in vivo* method); and second, Modification of Diet in Renal Disease method (MDRD) (*in vitro* method). Different radioactivities of 3, 6, 9, 12, 15 and 18 mCi of ^{99m}Tc-DTPA are being counted within 60 seconds and at distance 30 cm from gamma camera detector. The radioactivity of 12 mCi is being counted in different times in the range from 10 to 30 seconds and at different distances from 10 to 40 cm.

SUBJECTS AND METHODS

Patients

In the present work 158 subjects (100 males and 58 females) ranging in age from 18 to 76 years (mean ± SD, 45 ± 14.4). The 158 patients suspected of having different renal diseases were referred to Nuclear Medicine Department of King Fahd Unit, Cairo University Hospitals, Egypt. The patients were referred for evaluation of renal function and pathophysiology in routine practice. They were given a wide variety of clinical diagnosis including chronic renal failure, hydronephrosis, reduced renal function in an unknown cause and healthy persons for donation. The present study was done during the period of January 2009 to May 2010.

Calculation of GFR by MDRD equation

For measuring serum creatinine, it was withdrawn 3 ml sample of blood from patients. The serum creatinine was done on Auto Analyzer Model Hitachi 912 (Japan) and using the simplified MDRD equation[14]:

$$\text{eGFR (ml/min/1.73 m}^2\text{)} = 186.3 \times [\text{serum creatinine (mg/dl)}]^{-1.154} \times [\text{age (years)}]^{-0.203} \times [0.742 \text{ (female) or } 1.210 \text{ (black)}] \quad (1)$$

The simplified MDRD equation allows the classification renal function with acceptable precision and requires only minimal information about the patient. It has therefore been included as the primary GFR marker in the Practice Guide- lines for Chronic Kidney Disease, published in 2002 by the Kidney Disease Outcomes Quality Initiative of the National Kidney Foundation (K/DOQI) and the more recent KDIGO guidelines[3,4].

Calculation of GFR by gates method

^{99m}Tc-DTPA was prepared in Radioisotope Laboratories in King Fahd Unit, Cairo University Hospitals (Egypt) using a commercially available freeze-dried kit. The dose was ranged from 3.5 to 6.4 mCi and was administered to 158 patients with different renal disease and healthy persons. Prior to the administration, the pre-injection syringe with straight needle was counted by two different devices: Dose Calibrator (ATOMLAB 100); and Gamma Camera (Siemen, Orbit, Single head), which was attached to a Low-Energy General-Purpose Parallel-Hole Collimator. The patient was hydrated with 300-500 ml of water, 30 minutes prior to the examination. The patient lay down on a bed in the supine position and the image will acquired a posterior except one patient with ectopic kidney lay down on a bed in the prone position. ^{99m}Tc-DTPA was given through a butterfly needle into vein and was followed by infusion of 20 ml of normal saline then 2 ml lasix. Frames of 128 ×128 matrix were recorded with an online-computer, initially at one second for one minute and then at 10 seconds for 20 minutes. The post-injection syringe with a straight needle which was detached before the injection was again counted by a gamma camera in the same way as pre-injection. Region of interest (ROI) over each kidney was assigned manually on the frame added from 1 to 3 minutes following injection. The semilunar background ROI around each kidney was defined. The background corrected time-activity curve was generated, and the renal uptake of individual kidney for 1 minute from 2 to 3 minutes after the injection was calculated. The GFR (GFR Gates) was automatically estimated by a commercially available computer (Oddesey Pegasis Labratorias, Adac) according to the Gates' algorithm.

Pre-injected syringe count as a parameter affecting GFR calculation

^{99m}Tc-DTPA was prepared by Different radioactivities of doses 3, 6, 9, 12, 15 and 18 mCi of ^{99m}Tc-DTPA are being counted within 60 seconds and in a distance of 30 cm from gamma camera detector. Also, activity of 12 mCi is being counted in different times in the range 10-30 seconds and at different distances in the range 10-40 cm. Each of these counts is repeated three times. Applying a same region of interest (ROI), the rate of total and the maximum count in each pixel is being achieved for each of this image. The object of this method is to obtain the best amount of descriptive radioactive ^{99m}Tc-DTPA for patient, the distance between syringe and detector and time of counting of pre-syringe, post-syringe and time of scan as a parameters affecting GFR calculation.

Statistical methods

Statistical analysis of the results were performed by using the Analysis of Variance (ANOVA) to determine the effect of radioactive doses, time of counting and distance between the detector of gamma camera and the syringe and their interaction on glomerular filtration rate (GFR), means at significance level of 0.05. Correlation and regression analyses were also estimated to compute the correlation coefficient (R) for the GFR that measured by Gate's method and GFR that calculated by MDRD equation. All statistics and illustrations (scatter plots) were carried out using Statistical Analysis Systems[15] program Ver. 9.1, SAS Institute in Corporation Cary, NC 27513 USA.

RESULTS

Patient characteristics

One hundred and fifty eight (158) patients (100 males and 58 females) with varying levels of kidney function were investigated in the present study. The patients are referred for evaluation of renal function in routine practice. They are given a wide variety of clinical diagnosis including 43 chronic renal failure, 71 reduced renal function and 44 healthy persons that come to the center for donation. Table 1 illustrates the age of patient in years, the radioactive dose in mCi, the weight in kg, the height in cm and the serum creatinine of each patient in mg/dl. The mean age of the patients was 45 ± 14.4 years and the serum creatinine (Scr) ranged from 0.4 to 8.4 mg/dl with a mean of 1.64 ±1.48 mg/dl and also presented in TABLE 1.

Regular Paper

Glomerular filtration rate

The correlation between GFRs measured by the modified Gates (*in vivo* method) in ml/min/1.73 m^2 and the GFRs determined by Modification of Diet in Renal Disease equation (MDRD) (*in vitro* method) in ml/min/1.73 m^2 for 158 patients are shown in Figure 1. From the figure, it is clear that, a linear correlation between modified Gates' and MDRD–predicted GFR is detected and the regression equation was $y = 1.212 x + 19.15$ ($R = 0.71$, $p < 0.0001$). This means that the *in vivo* method correlates with that of the *in vitro* method. The means of GFR *in vivo* and GFR *in vitro* are also illustrated in TABLE 1.

TABLE 1: Clinical parameters for 158 patients with different renal diseases

Parameter	Mean ± SD
Radioactive dose, mCi	5.03 ± 0.57
Age, years	45.00 ± 14.40
Weight, kg	74.50 ± 18.14
Height, cm	163.59 ± 10.03
Serum creatinine, mg/dl	1.64 ± 1.48
Mean GFR *in vivo*, ml/min/1.73 m^2	59.90 ± 29.90
Mean GFR *in vitro*, ml/min/1.73 m^2	91.81 ± 50.95

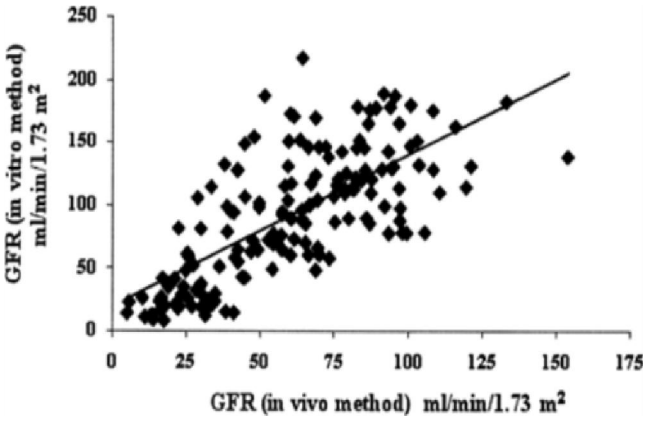

Figure 1: Scatter plot of GFRs determined by the modified Gates (*in vivo* method) against that by the Modification of Diet in Renal Disease equation (MDRD) (*in vitro* method) for 158 patients before studying the parameters that affecting on GFR *in vivo*

The difference in GFRs measured by the modified Gates' (*in vivo* method) and the GFRs determined by Modification of Diet in Renal Disease equation (MDRD) (*in vitro* method) against the mean GFR of the two methods before studying the different parameters in ml/min/1.73m^2 for 158 patients are shown in Figure 2. The difference in the mean GFR (mean GFR_{MDRD} – mean GFR_{gates}) was 31.91±36.4 ml/min/1.73 m^2. This indicates that MDRD results were much higher than that obtained with modified gates. Indeed, in most subjects (in 133 out 158) the MDRD was higher than modified gates. In these individuals, the MDRD-gates difference had positive values.

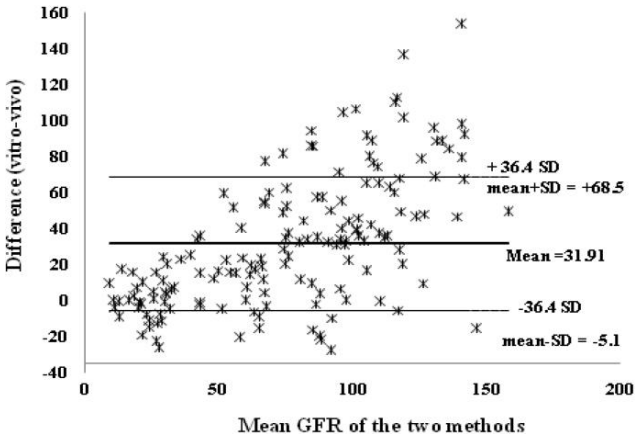

Figure 2: Plots showing the difference in GFRs by the MDRD equation method (*in vitro* method) and the modified Gates' method (*in vivo* method) against the mean GFR of the two methods for 158 patients

Factors affecting on measurement of GFR by scintigraphy

The gamma camera method has been stated as less accurate than the plasma clearance method of radionuclides[9,11,12,13]. The gamma camera is more complex than the well counter used for the plasma clearance method and factors such as field uniformly, linearity and spatial resolution can affect the image quantification. In the present study, it was found that there are other factors may affect on GFR measurement like radioactive dose, time of counting of radioactive pre-syringe and post-syringe and the distance between the detectors of gamma camera and syringe.

Different radioactivities (3, 6, 9, 12, 15 and 18 mCi) of ^{99m}Tc- DTPA which are being counted within 60, 30, 20 and 10 seconds and at distance of 30 cm from the detector of gamma camera and the results are tabulated in TABLE 2. In this way each of these counts are repeated three times. Applying the same region of interest (ROI), the rate of total and the maximum count in each pixel are being achieved for each of these images. The object of this method is to obtain the best amount of descriptive radioactive ^{99m}Tc-DTPA for patient, the distance between syringe and detector and time of counting of pre-syringe, post-syringe and time of scan as a parameters affecting GFR calculation. Table 2 also shows the analyses of results of the different radioac-

Regular Paper

tivities of ^{99m}Tc- DTPA which are being counted within different times. These results were done by Statistical

TABLE 2: Shows the maximum count and mean pixel count in line for different doses at different times at 30 cm. The means procedure for radioactivities of ^{99m}Tc- DTPA at 10, 20, 30 and 60 seconds are also indicated

Time (seconds) Dose	60		30		20		10	
	Max. count	Pixel count in line	Max. count	Pixel count in line	Max. count	Pixel count in line	Max. count	Pixel count in line
18 mCi	22527	7327.54	10992	5222.26	7285	3402.81	3511	1580.95
	21522	7534.73	10922	4786.76	7150	3041.44	3381	1488.72
	21498	7573.23	10802	5059.72	7136	2826.08	3170	1506.00
Mean max.	21849.00		10905.33		7190.17		3354.00	
± SD	587.2878340		96.0902354		82.4474580		172.0959035	
± SE	339.0707891		55.4777233		47.6010621		99.3596162	
Mean pixel	7478.50		5022.91		3090.11		1525.22	
±SD	132.1448209		220.0706944		291.4291507		49.0280087	
±SE	76.2938479		127.0578747		168.2566986		28.3063340	
15 mCi	14251	4928.33	7085	2285.14	4762	1892.27	2411	773.115
	13954	5333.73	7114	2338.65	4662	1709.32	2302	794.88
	13875	4800.22	6964	2202.38	4609	1653.03	2368	835.73
Mean max.	7054.3300000		7054.3300000		4677.6700000		2360.3300000	
± SD	79.5633919		79.5633919		77.6938436		54.9029447	
± SE	45.9359457		45.9359457		44.8565615		31.6982299	
Mean pixel	5020.7600000		2275.3900000		1751.5400000		801.2416667	
±SD	278.5062094		68.6562095		125.0833350		31.7885618	
±SE	160.7956350		39.6386810		72.2168971		18.3531347	
12 mCi	13187	6150.74	6435	2981.22	4405	2204.65	2131	1092.72
	13278	6875.98	6538	3371.54	4413	1980.53	2108	1124.52
	13186	6236.02	6607	3303.75	4385	2011.28	2143	1097.97
Mean max.	13217.00		6526.67		4400.67		2127.33	
± SD	52.8299158		86.5582655		14.4942517		17.7857621	
± SE	30.5013661		49.9744379		8.3682601		10.2686145	
Mean pixel	6420.91		3218.84		2065.49		1105.07	
±SD	396.3993226		208.5548638		121.4957433		17.0475071	
±SE	228.8612556		120.4092068		70.1456001		9.8423828	
9 mCi	12089	5601.75	6077	3290.38	4048	2077.82	1969	1091.36
	12295	5957.93	6088	3097.98	4081	2090.22	2002	1110.40
	11876	5841.84	6102	3126.8	3984	2022.22	2041	1168.22
Mean max.	12086.67		6089.00		4037.67		2004.00	
± SD	209.5097452		12.5299641		49.3186915		36.0416426	
± SE	120.9605078		7.2341781		28.4741598		20.8086520	
Mean pixel	5800.51		3171.72		2063.42		1123.33	
±SD	181.6518137		103.7679854		36.2149141		40.0273523	
±SE	104.8767236		59.9104743		20.9086904		23.1098026	
6 mCi	7122	3840.00	3538	1890.05	2426	1397.03	1188	644.75
	7121	4271.88	3554	1958.66	2423	1400.35	1232	678.82
	7108	4001.46	3532	2067.56	2322	1402.54	1186	685.99
Mean max.	7117.0000000		3541.1700000		2390.3300000		1202.0000000	
± SD	7.8102497		11.4491630		59.1974099		26.0000000	
± SE	4.5092498		6.6101773		34.1776405		15.0111070	
Mean pixel	4037.7800000		1972.0900000		1399.9700000		669.8533333	
± SD	218.2187902		89.5138185		2.7742446		22.0337294	
± SE	125.9886773		51.6808272		1.6017109		12.7211796	

Regular Paper

Time (seconds) Dose	60		30		20		10	
	Max. count	Pixel count in line	Max. count	Pixel count in line	Max. count	Pixel count in line	Max. count	Pixel count in line
3 mCi	3294	1740.36	1616	897.47	1074	609.45	564	302.16
	3326	1996.55	1637	974.78	1102	648.31	552	286.39
	3321	1909.50	1663	932.01	1067	621.18	587	325.22
Mean max.	3313.3300000		1638.5000000		1081.0000000		567.6666667	
± SD	17.3949226		23.2862620		18.5202592		17.7857621	
± SE	10.0429633		13.4443297		10.6926766		10.2686145	
Mean max.	1882.1400000		934.7533333		626.3133333		304.5900000	
± SD	130.2685420		38.7279412		19.9320905		19.5287199	
± SE	75.2105778		22.3595873		11.5077978		11.2749117	

Analyses Systems[15].

DISCUSSION

Estimation of the glomerular filtration rate (GFR) is required in the assessment of patients with chronic kidney disease (CKD) in order to provide information regarding the functional status of the kidneys. Current guidelines advocate the use of prediction equations, such as the Cockcroft –Gault (CG) formula and the Modification of Diet in Renal Disease (MDRD) study-derived equations, over clearance of endogenous creatinine (Ccr) in achieving this aim[8]. Renal scintigraphy is a valuable way to assess the three sequential phases of renal function. The first phase constitutes the rapid dynamic imaging that is done during the first minute after tracer injection which evaluates perfusion. The second phase is the period in which the nephrons extract the tracer from the blood and excrete it by glomerular filtration and /or tubular secretion. The third phase is the period during which the tracer drains through the pelvicalyceal system. Time-activity curves generated using a region of interest over the kidney reflects these sequential changes in renal function. Each such curve is called a renogram. Radionuclide renograms based on these three stages of renal function provide a method for quantitatively evaluating kidney function[16].

The Gates correlated well with the plasma sample method. The significant correlation of the renal uptake of ^{99m}Tc-DTPA against the 24-hours creatinine clearance has promoted this method for clinical application in routine practice[17]. However; the Gates was proved to be inaccurate and less precise than the CG for predicting the GFR. In addition, the Gates tended to overestimate the GFR. These results were consistent with previous reports[11,18]. It has debated whether the Gates' method is accurate for predicting the GFR[19]. Several sources of errors in the estimation of GFR by scintigraphy are recognized: background correction, decay statistics, attenuation correction, and estimation of arterial plasma activity, volume measurements and radiopharmaceutical quality[20]. Review of the obtained results from different activities within 60 seconds showed that the total count is increased from 3 up to 15 mCi while increased sharply at 18 mCi. This means that the gamma camera will be paralyzed in high activity. So, descriptive amount of activity should be less than 15 mCi in order to prevent the paralysis of the device. Review of the maximum mean count in pixel in the images that mentioned showed that except the amount of 3 mCi, in which the maximum mean count in each pixel was equal to 3313. In activities more than 9 mCi up to 18 mCi, the maximum mean count in pixel of all images was equal to 21849. This may be indicated that saturation of pixel in activities of 9 to 18 mCi. As it can be proved here in this event, increase in the total count is appropriate to the increase in activity. But, this is not a one to one ratio. In order to decrease the saturation of pixel, the time of counting should be decreased. Counting within different times of 12 mCi and at a distance of 30 cm showed that the maximum counts/pixel in 10 and 20 seconds are less than saturation limit. But, in images of 30 and 60 seconds indicate again face to the phenomenon of saturation. So, the time of counting should be mentioned less than 20 seconds to prevent the saturation of pixels. Moreover, the count performed of activity 12 mCi in different distances showed that saturation of pixels will happen in distance at 10 cm, but at distances of 20 to 40 cm the saturation phenomenon is not existed. By increasing the distance from 20 to 40 cm, remarkable count decrease will be happened i.e., the count will decrease proportion to the inverse square.

Lack of count will be justified with increase of distance in these pictures and with increase field of view of collimator holes. In accordance with the obtained results in these events, the amount of activity 12 mCi, as an optional amount for computing of GFR, is mentioned with coincident scan and is being counted at distance of 30 cm from collimator with 10 seconds. Then, the dose mentioned above and routine scan of kidney [with matrix of 128 × 128] is done for 32 minutes.

Finally, the injected syringe and also the place of injection for 30 seconds and at a distance of 30 cm are being imaged. The optional matrix for image of syringe; pre-, post-, and place of injection was in 256 × 256. So this present study showed that computation of GFR coincident with performance of scan the kidney will be possible.

CONCLUSIONS

In conclusion, by studying the different parameters (radioactive ^{99m}Tc-DTPA for patient, time of counting of radioactive syringe and distance between syringe and detector of gamma camera), it was found that the ^{99m}Tc-DTPA renography will become more accurate in measurement of GFR, if these parameters are corrected. The present study showed that computation of GFR, coincident with performance of scan of the kidney, will be possible to use this technique, if the following points are offered:

1. Amount of descriptive radioactive ^{99m}Tc-DTPA for patient is from 10 to 15 mCi.
2. Time of counting the syringe should put in consideration at distances in the range from 20 to 40 cm (where time of counting is inversely proportional to the distance between the syringe and detector).
3. After injection, the scan will be done in two stages (the first stage: 60 images for 1 second and the second stage: 180 images for 10 seconds).
4. The distance between syringe and detector should be considered in the range 20–40 cm.
5. When the scan of kidney finished, counting of syringe after injection and counting of the place of injection will be performed within 30 seconds.
6. Optimal matrix for image of syringe (pre and post) and place of injection is 256 × 256 and for scan 128 × 128.
7. Using a formula offered by Gates, the computation of GFR is done.
8. Although, in this study, in the case of the radioactive doses of 3, 6, 9, 12, 15 and 18 mCi, the distance and time of counting is a presented limit, but each part should use a specified number in limits mentioned above so that the obtained results be repetitive.

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