GFR ESTIMATION USING 99mTc DTPA GATES METHOD FOR ASSESSMENT OF EARLY DIABETIC NEPHROPATHY – A COMPARISON WITH 24-HOUR CREATININE CLEARANCE

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ABSTRACT

Objective: To correlate Gates glomerular filtration rate (GGFR) using technetium-99m diethylene triaminepentacetic acid (99mTc DTPA) with 24-hour creatinine clearance (CRCL) and to establish relationship with duration of diabetes in patients with early diabetic nephropathy.

Study Design: A cross-sectional comparative study carried out in Nuclear Medical Centre from Aug 2009 to Jan 2010 at Armed Forces Institute of Pathology (AFIP), Rawalpindi, Pakistan.

Patients and Methods: A total of eighty three subjects were enrolled, who were divided into three groups; group 1 comprised 31 normotensive diabetics, group 2 had 37 hypertensive diabetics while group 3 had 15 normal subjects. The DTPA GFR and creatinine clearance in healthy subjects as well as diabetic patients were compared using the unpaired student's t-test. The linear association between GFR, creatinine clearance and disease duration was expressed by Pearson's correlation coefficient 'r' along with their significance levels.

Results: Gates GFR showed hyperfiltration in normotensive diabetics (96.6 ± 3.3 ml/min/1.73 m^2), significantly (p<0.05) higher than controls (85.5 ± 5 ml/min/1.73 m^2), whereas hypertensive diabetics had a significantly lower (p<0.05) Gates GFR (76.8 ± 3.7) than that of controls. Significant degree of correlation existed between GGFR and CRCL in hypertensive diabetics (p<0.05, r=0.716) and controls (r=0.546). Gates GFR also showed good correlation with duration of diabetes in both diabetic groups as compared to that of CRCL. GGFR also correlated well with duration of hypertension 0.37 (0.31-0.43) as compared to CRCL 0.155 (0.15-0.16) in all groups.

Conclusions: The 99mTc-DTPA clearance correlates significantly with 24-hour creatinine clearance as well as with disease duration and can provide a simple and convenient index of kidney function in patients of early diabetic nephropathy.

Keywords: Creatinine clearance, Diabetic nephropathy, Gates GFR.

INTRODUCTION

Diabetes mellitus is the leading cause of end-stage renal disease (ESRD) being responsible for approximately 43% of new cases of ESRD in the world every year. According to world health organization (WHO) estimate, Pakistan (16.2% in men and 11.7% in women[1] will unceremoniously rise to the fourth place in the year 2025 having 14.5 million diabetic persons at that time[2]. Because of high prevalence of diabetes in Pakistan, regular surveillance for diabetes complications goes a long way in detection, prevention and treatment of ESRD. One of the major complications of diabetes mellitus is diabetic nephropathy, which is an important cause of morbidity and mortality and is now among the most common causes of end stage renal disease (ESRD) in the developed countries[3]. Approximately 25% to 40% of patients with type 1 diabetes mellitus ultimately develop diabetic nephropathy (DN), which progresses through about five predictable stages[4]. An estimated 5% to 15% of type 2 DM cases also progress through the five stages of diabetic nephropathy (DN) but the timeline is not as clear.

Serum urea and creatinine can remain within normal range despite the loss of over 50% of renal function. Measurement of effective renal plasma flow (ERPF) with the help of para-aminohippuric acid (PAH) or radio pharmaceuticals like MAG3 etc is another method. However gold-standard is an isotopic

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GFR measurement with the help of inulin or radiopharmaceuticals i.e. dynamic renography.

The glomerular filtration rate (GFR) is considered as the best measure of absolute renal function. The normal corrected GFR is 80-120 mL/min/1.73 m^2. The corrected GFR is approximately 8% lower in women than in men[5]. After age 20-30 yrs, the GFR declines at the rate of 1ml/min/1.73m^2/year[6]. The creatinine clearance has been widely used as only alternative to inulin clearance in routine practice. It compares the level of creatinine in urine with the creatinine level in the blood, usually based on assessments of a 24-hour urine sample and a blood sample drawn at the end of the 24-hour period[7]. However, logistic problems involved in estimation of GFR from serum creatinine and creatinine clearance are inaccurate urine collection and volume measurement, interference in creatinine measurement due to non-creatinine chromogens and tubular secretion of creatinine (inhibited by cimetidine). For these reasons, diagnostic modalities like radionuclide methods need to be addressed in their full strength, to detect and manage the resulting complications beforehand. Radionuclide methods provide information of both the renal function and morphology. Gates method is specific gamma camera based method for GFR estimation[8]. The fractional renal uptake of intravenously administered 99mTc DTPA within 2 to 3 minutes following radiotracer arrival in the kidneys, is proportional to the glomerular filtration rate (GFR).

Objectives of our study were to correlate Gates GFR with 24-hour creatinine clearance and to establish relationship between Gates GFR and duration of diabetes with and without hypertension in Pakistani population.

PATIENTS AND METHODS

This cross-sectional comparative study was carried out in Nuclear Medical Centre at Armed Forces Institute of Pathology, Rawalpindi after approval of protocol by its ethical committee. A written informed consent was obtained from all the patients and healthy volunteers. Each subject underwent 24-hour creatinine clearance after instructions on how to collect a 24- hour urine sample. All diagnosed diabetic patients, 20-60 years of age with good glycemic control i.e. glycosylated Hb<7% were included in the study except pregnant and lactating diabetic females, diabetic nephropathy patients who were diagnosed hypertensive before the diagnosis of diabetes, patients with abnormal serum creatinine levels and post-nephrectomy patients. Potential kidney donors with no previous history of any systemic illness and a completely normal 99mTc DTPA renal scan were taken as controls.

A total of 90 subjects were enrolled, out of which 83 were included in the studies who were divided into three groups; group 1 comprised 31 normotensive diabetic patients, group 2 included 37 diabetics with hypertension while group 3 had 15 normal control subjects. Male to female ratio was 1: 2.

Technetium-99m DTPA was freshly formulated using a commercially available freeze-dried stannous DTPA kit (produced by IPD, PINSTECH, Islamabad). Each subject was well hydrated with 300-500 ml of fluids an hour prior to the study. Just before the start of study, patients were asked to empty their bladder[9]. About 7.0 mCi of 99mTc DTPA was administered intravenously while keeping the patient in supine position. Dynamic study was acquired in posterior projection such that the field of view included both kidneys and bladder[10] using Single Head Siemens ECAM Gamma Camera system interfaced with windows based power PC 8. After injection, data was acquired at 1 sec/frame for 60 seconds and then 30 seconds/frame for 30 minutes. Intravenous furosemide (Lasix®) was given in dose of 0.5 mg/kg body weight at 15 minutes post injection of radiopharmaceutical in case of obstruction[11].

Renograms were generated for each study by drawing regions of interests around each kidney manually and semi lunar regions of

interests were drawn inferolaterally for background (Figure-1).

The Gates Itoh software program automatically calculated the total and individual kidney GFR on the basis of manually entered data along with the pre and post injection syringe counts, patients' age, sex and renograms. Normalization of GFR was done by the inbuilt software with the help of body surface area (BSA-kg/m^2) calculated on the basis of height and weight of the patient.

Statistical Package for Social Sciences (SPSS) version 10.0 was used to perform the statistical analyses. To compare the renal function measurements between different groups, we used a t-test. For descriptive purposes, mean renal function was calculated. The mean, standard deviation (SD) and standard error of mean (S.E.M) were calculated for the parameters like age, duration of DM, duration of hypertension, creatinine clearance and GFR. Clearance values in healthy subjects and patients were compared using analysis at variance (ANOVA), $p < 0.05$ was considered statistically significant. Pearson's correlation coefficient was used to express the linear association between the Gates GFR and creatinine clearances.

RESULTS

A total of 83 subjects were included in the study with a mean age of 44.4 ± 8.97 years. Whole population was normally distributed. Male to female ratio was 1 : 2. GFR assessment was done by using 99mTc DTPA followed by 24- hour creatinine clearance estimation (CRCL). Mean GFR and CRCL along with their standard error of means (S.E.M) have been given in the table-1 for each group, 24-hour creatinine clearance was compared with Gates GFR in different groups. Both of these techniques in different patient groups were compared and correlated with that of controls.

Table-1: Group wise distribution of creatinine clearance (CRCL) and gates glomerular filtration rate (GFR) in terms of mean.

Group	No (n)	CRCL (ml/min/1.73 m^2)	GFR (ml/min/1.73 m^2)
1	31	82.0 ± 6 NS	96.6 ± 3.3*
2	37	60.5 ± 4.7 NS	76.8 ± 3.7 NS
3	15	77.2 ± 5	85.5 ± 5

± Standard Error of Mean (S.E.M), * Significant, NS Insignificant

Table-2: Correlation of creatinine clearance (GFR) and glomecular filteration rate (CRCL) with disease duration between the study groups.

Parameters	1	2	3
GFR versus CRCL; R-value	0.032	0.716	0.546
GFR versus Dur of DM; R-value	0.669 NS	0.883 NS	***
CRCL ± versus Dur of DM; R-value	0.404 NS	0.201 NS	***
GFR versus Dur of HTN; R-value	***	0.431	***
CRCL ± versus Dur of HTN; R-value	***	0.166	***

* Significant, Dur: Duration, DM: Diabetes mellitus, HTN: Hypertension, NS: Insignificant

Group 1: Patients of this group had mean ± S.E.M GFR of 96.6 ± 3.3 ml/min/1.73 m^2. GFR was significantly increased in this group ($p < 0.05$) as compared to controls. Gates GFR exhibits high degree of correlation (r = 0.669) with duration of diabetes in normotensive diabetics while moderate degree of correlation between CRCL and duration of diabetes (r = 0.404) was observed.

Group 2: Significant difference was observed among CRCL and GFR ($p < 0.05$) in this group with high degree of correlation (r = 0.716) when compared among themselves and when compared with group 3. Gates GFR showed a

very high degree of correlation (r = 0.883) with duration of diabetes in hypertensive diabetics while slight positive correlation among CRCL and duration of diabetes (r = 0.201) was noted. Gates GFR showed moderate correlation (r = 0.431) with duration of hypertension while 24-hr CRCL showed slight degree of correlation (r = 0.166).

Group 3: In this group CRCL and GFR correlated well (r = 0.546) with a significant difference between the two ($p < 0.05$)(Table-2).

DISCUSSION

Twenty four hour creatinine clearance (CRCL) is the commonly employed technique for assessment of kidney function. However 99mTc DTPA renal scan is also available along with other radionuclide techniques like 99mTc MAG3 and DMSA scintigraphy. We estimated Gates GFR using 99mTc DTPA in 68 patients of early diabetic nephropathy with and without hypertension and 15 potential kidney donors as controls. We compared and correlated Gates GFR results with 24-hour creatinine clearance. Along with renal function assessment, correlation of GFR and CRCL with duration of diabetes was also measured. There are numerous studies in which 99mTc DTPA, 99mTc DMSA and 99mTc MAG3 scintigraphy had been used to assess renal functions. However, use of Gates GFR using 99mTc DTPA to evaluate renal function in early diabetic nephropathy remains to be explored in Pakistani population. Hence, we used gamma camera based Gates method for renal function assessment to compare and correlate it with some of the commonly used techniques.

We found out that normotensive diabetics had significantly higher Gates GFR and CRCL as compared to controls as they are in the early stages of diabetic nephropathy i.e. stage 1 and 2, in which kidneys are usually enlarged in size with hyperfiltration. Increased GFR has also been found to be a predictor of diabetic nephropathy risk in some studies[13] but not in others. Gates GFR correlated well with the duration of diabetes in normotensive group (r = 0.669) as well as hypertensive one as compared to the CRCL (r = 0.404) thus taking into account the changes in

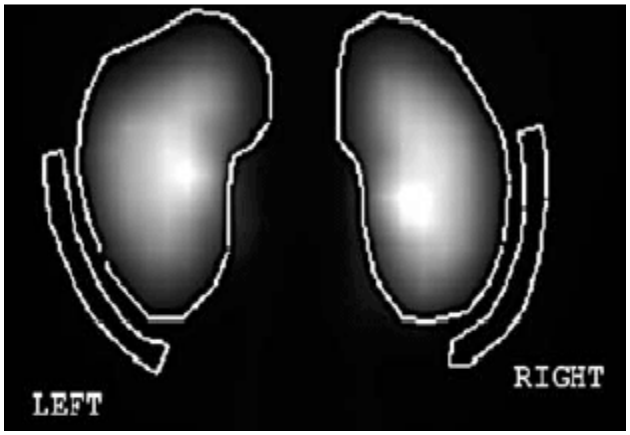

Figure-1: Renogram showing generation of region of interests (ROI) around each kidney.

diabetic nephropathy with increasing duration of diabetes mellitus. The finding is in accordance with that of studies that confirmed the role of increased duration of diabetes in the development of microalbuminuria in type II diabetics[14].

In hypertensive diabetics, mean CRCL and GFR levels were 60.5 and 76.8 significantly different from each other ($p < 0.05$) and when compared with controls ($p < 0.05$). This significant difference from the controls is likely because of advanced diabetic renal disease. GFR and CRCL correlate really well in this group with a correlation coefficient of 0.685. So, GFR and CRCL are equally effective to pick the prevailing abnormalities. Gates in this group correlates moderately (r = 0.468) with duration of diabetes and hypertension (r = 0.312). CRCL correlates poorly with both duration of diabetes and hypertension (r = 0.025, r = 0.150, respectively). Possible explanations for these observations are that creatinine clearance level may not be a perfect measure of GFR like other methods of its estimation from CG and MDRD formulas. Because of collection errors, large variation for the same renal functional status, cumbersome nature and imprecision of the test 24 hours creatinine clearance is not in practice any more in developed countries and has been replaced by

other much precise and easier methods like estimated CRCL or isotopic GFR techniques.

CONCLUSION

Our study has shown that Gates GFR correlates well with CRCL apart from a superior edge by virtue of its ability to provide visual information regarding perfusion, cortical uptake, tubular tracer transit, clearance of activity from the kidneys and quantitative individual renal function measurement. This method in our study has also proved its validity in relation to the disease duration.

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