Influence of Different Diuretic Renography Protocols using ^{99m}Tc-DTPA on the Split Renal Function and Equivocal Renograms in Adult Patients with Suspected Unilateral Obstructive Uropathy

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Abstract:

Background and Purpose: To assess the influence of three different diuretic renography (DR) protocols using ^{99m}Tc-DTPA on the calculation of split renal function (SRF) compared to ^{99m}Tc-DMSA cortical scintigraphy and the frequency of equivocal renograms in adult patients with suspected unilateral obstructive uropathy.

Methods: This prospective study enrolled patients with suspected unilateral obstructive uropathy, patients were divided into three groups based on the timing of furosemide administration: 15 minutes before (F-15, n=40), concurrently with (F+0, n=40), and 15 minutes after (F+15, n=42) ^{99m}Tc-DTPA injection. All patients underwent ^{99m}Tc-DMSA scintigraphy. Visual and quantitative analyses of DRs were conducted to compare SRFs obtained using ^{99m}Tc-DTPA with those calculated by ^{99m}Tc-DMSA and to identify the number of equivocal renograms in each group.

Results: The study included 82 patients (45 males and 37 females, with a mean age of 40±12 years). A significant correlation between SRFs acquired with ^{99m}Tc-DTPA and ^{99m}Tc-DMSA was observed in all protocols. When comparing the mean difference in the computed SRF between both approaches in the three protocols, a significant difference was detected between the F-0 and F+15 protocols (p=0.030). Moreover, the difference was greater in the F-15/F+0 protocols compared to the F+15 protocol on Bland–Altman analysis. The number of equivocal curves was significantly lower in the F-15 than the F+0 protocol (p=0.049), yet without significant difference when compared to F+15 (p=0.154).

Conclusion: ^{99m}Tc-DTPA dynamic scintigraphy is a simple, non- invasive and reliable tool for evaluating SRF. The F+15 protocol is suggested as a single study to evaluate SRF as well as to confirm or rule out obstruction in patients with suspected obstructive uropathy.

Keywords: ^{99m}Tc-DTPA, Diuretic renography, Obstructive uropathy, Split renal function, Equivocal renograms

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Background:

Urine outflow obstruction may result in obstructive uropathy, which is a serious public health concern since it can cause renal parenchymal damage in the majority of cases [1]. Suspicion of urine outflow obstruction is frequently based on clinical findings or the incidental discovery of upper urinary tract dilatation [2]. Nevertheless, in some patients, the dilated upper urinary tract may be a sequence to an anatomical stenosis or obstruction to the urinary outward flow. In other cases, it could be just a simple dilatation with no underlying stenosis/obstruction [3].

The duration of the obstruction may have an impact on the restoration of renal function following

intervention [4]. A diagnostic test capable of accurately distinguishing between obstructive and non-obstructive uropathies is thus required for deciding a definitive management [5].

Diuresis renography (DR) is a simple, noninvasive, repeatable, and widely available imaging tool that provides information on both urodynamics and renal function in a single procedure. It is relied on the increased endogenous rate of urine flow after diuretic administration [6]. The interpretation of DR is based on the renal function and tracer washout from the collecting system [7]. Tracer washout is classically described using the T1/2, which is defined as the time taken for the renal radioactivity to decline to 50 % of its peak value. A T1/2 of less than 10 minutes rules out obstruction, whereas a T1/2 of more than 20 minutes indicates renal obstruction. T1/2 values between 10 and 20 minutes, on the other hand, are considered as equivocal results which create an ambiguity in patient management [8]. Selected radiopharmaceutical and the time interval between its administration and diuretic injection affect the T1/2 calculation [9]. That is why the choice of DR protocol that yields more conclusive results is eventually necessary [8].

Indeed, there is no consensus on the timing of diuretic administration in DR. The timing of diuretic administration includes different protocols; F−15, F+0, F+2, F+5, F+10, F+20, and F+30; interpreting diuretic administration 15 minutes before radiotracer injection, simultaneous injection of diuretic and radiotracer, and diuretic administration 2, 5, 10, 20, and 30 minutes after radiotracer injection, respectively [10].

When compared to the F-15, the F+20 protocol yielded more equivocal results and was deemed less specific [11]. On the other hand, F+0 protocol was associated with fewer disrupted studies due to impeding urination, so it was thought to be more practicable than the F-15 protocol [12].

Renal function quantification is well known to be one of the primary goals of renal nuclear imaging [13]. Split renal function (SRF) or relative renal function (RRF) represents the relative contribution of each kidney to the total renal function; it measures the ability of tracer extraction by each kidney; SRF in the range of 45-55 % is considered normal [14]. SRF is useful in the assessment and management of a variety of renal disorders. Renal scintigraphy can estimate SRF using different radionuclides, including ^{99m}Tc-dimercaptosuccinic acid (^{99m}Tc-DMSA), ^{99m}Tc-diethylenetriaminepentaacetate (^{99m}Tc-DTPA) and ^{99m}Tc-mercaptoacetyltriglycine (^{99m}Tc-MAG3) [15]. However, some discrepancies in the estimated SRF using these radiotracers are noted, which are primarily related to the distinct biological characteristics of used pharmaceuticals [16].

^{99m}Tc-DMSA is actively handled by the proximal renal tubular cells; approximately 40-65% of the injected dose binds to the proximal renal tubules within 2 hours of injection, allowing excellent imaging of the renal cortex [17]. ^{99m}Tc-DTPA is entirely filtered by the glomerulus and is neither secreted nor reabsorbed by the renal tubules, it can be used to calculate the glomerular filtration rate (GFR) and SRF [18].

^{99m}Tc-DMSA renal cortical scintigraphy was proclaimed to be the gold standard for SRF assessment [19], [20], [21].

Many prior studies with conflicting results compared SRF estimation with ^{99m}Tc-DMSA renal cortical scintigraphy and ^{99m}Tc-DTPA dynamic renal scintigraphy in various age groups. Some articles emphasized that ^{99m}Tc-DTPA is as reliable as ^{99m}Tc-DMSA in the calculation of SRF [15], [22], [23], [24]. Other articles, conversely, concluded that ^{99m}Tc-DTPA is not as accurate as ^{99m}Tc-DMSA in SRF computation [25], [26]. Moreover, all of these studies' analyses were based solely on a single DR protocol.

Accordingly, the current study aimed to compare ^{99m}Tc-DTPA-based SRF with standard ^{99m}Tc-DMSA-derived SRF in adult patients with suspicion of unilateral obstructive uropathy, as well as to clarify of the impact of three different DR (F-15, F+0 and F +15) techniques on the SRF calculation and on the frequency of equivocal renograms.

Patients and Methods:

Our institution's ethical committee approved this prospective, comparative study. It included 82 adult patients (≥18 years) with suspected unilateral obstructive uropathy who were referred to our department for routine renal scintigraphy. Pediatric patients, as well as those with severely compromised renal function of the target kidney (GFR <20 ml/min), only functioning one kidney, renal anomalies such as malrotation, renal ectopia or solitary kidneys were excluded. Forty patients were submitted to both F+0 and F-15 DR protocols within a one-week interval, while the remaining 42 patients underwent F+15 DR. ^{99m}Tc-DMSA renal cortical scintigraphy was performed for all patients. Serum creatinine and blood urea were also measured for all patients at the time of the study. Informed consent was obtained from patients underwent F+0/F-15 diuresis protocols for approval to do both techniques. Patients were assigned into three groups based on diuretic administration timing: F-15 (n=40), F+0 (n=40), and F+15 (n=42).

Imaging protocol

Imaging was done using a hybrid SPECT/CT dual-head gamma cameras [(Symbia T; Siemens Healthcare, Erlangen, Germany for the F-15/F0 groups) and (Symbia Intevo; Siemens Healthcare, Erlangen, Germany for the F+15 group)] equipped with low energy all-purpose parallel hole collimators, set at 140 KeV, with a 15% energy window. Data was acquired using a matrix size of 64x64 for dynamic acquisition and 256x256 for static acquisition.

^{99m}Tc-DTPA diuretic scintigraphy

All patients were encouraged to drink 300–500 ml of water 20–30 minutes prior to tracer injection. They were asked to void just before starting the study. A bolus of approximately 185-222 MBq (5-6 mCi)

^{99m}Tc-DTPA was injected intravenously while the patient in the supine position with kidneys, ureters, and bladder in the field of view. The dose of furosemide was 40 mg injected intravenously as a slow bolus. Images were acquired posteriorly at 1 second/frame for 1 minute (perfusion phase) followed by 15 second/frame for 4 minutes (uptake phase), and finally1 minute/frame for 15-25 minutes (clearance phase).

Furosemide was administered concurrently with the injection of ^{99m}Tc-DTPA in the F+0 DR. In the F-15, furosemide was given 15 minutes before ^{99m}Tc-DTPA injection. The acquisition time in both procedures was 20 minutes. In the F+15 protocol (our department's routine protocol), furosemide was administered 15 minutes after the injection of ^{99m}Tc-DTPA and the study was maintained for another 15 minutes after diuretic administration, the total acquisition time was 30 minutes.

Following acquisition, regions of interest (ROIs) were drawn for both kidneys and background on a composite image (2-3 minutes following injection) in the posterior views to generate time/activity (renogram) curves. T1/2 values were calculated from the curves and SRF was obtained. Visual analysis of renograms and dynamic images, as well as careful reviewing of the drainage T1/2 in each group was carried out before reporting as patent drainage, obstructed drainage or equivocal.

^{99m}Tc-DMSA static scintigraphy

Static images were acquired in the supine position 2–4 h following an intravenous injection of 185-222 MBq (5-6 mCi) ^{99m}Tc-DMSA for 500 k counts in both anterior and posterior views. ROIs were drawn over both kidneys in the anterior and posterior projections. SRF was calculated using the geometric mean of the anterior and posterior counts. Both ^{99m}Tc-DMSA and ^{99m}Tc-DTA scans were conducted 7-10 days apart.

The data was analyzed by two experienced nuclear medicine physicians.

Statistical analysis

IBM SPSS software version 27 was used in data analysis. Qualitative data were described using number and percentage and compared using Chi square test or Fisher's exact test. Quantitative data were described using median, range, mean, and standard deviation, and then compared using Mann Whitney test or independent t-test when comparing between two groups. Kruskal–Wallis test or ANOVA test was used to compare more than two groups. The Spearman rho correlation coefficient test was used to assess the relationship between various variables. Agreement of results was conducted using Cohen's kappa coefficient. Bland–Altman analysis was performed to calculate the limits of agreement. In all analyses, a p-value of ≤ 0.05 was considered statistically significant.

Results:

Table 1 summarizes the demographic data of studied patients. The study enrolled 82 patients, with a mean age of 40±12 years. Forty-five patients (54.9%) were males and 37 (45.1%) were females. Fifty-nine (72%) patients had manifestations of obstructive uropathy, while 23 (28%) were incidentally discovered to have dilated upper urinary tract. Forty patients underwent both F+0 and F-15 ^{99m}Tc-DTPA diuresis protocols, whereas 42 patients underwent F+15 diuresis protocol. There was no significant statistical difference between the two groups in terms of age (mean= 37±8 and 42±14 years, respectively), sex (17 and 20 female patients; 23 and 22 male patients, respectively), levels of serum creatinine (mean= 1±0.23 and 0.97±0.38, respectively) and blood urea (mean= 31.75±7.53 and 33.09±6.78, respectively), as displayed in Table 2. There was no statistically significant difference in the estimated SRF of the diseased kidney between F-15, F+0, and F+15 groups using ^{99m}Tc-DTPA (p=0.766), nor between F-15/F+0 and F+15 groups using ^{99m}Tc-DMSA (p=0.357), Table 3.

A highly significant strong positive correlation was found between SRFs of the diseased kidney obtained with ^{99m}Tc-DMSA and ^{99m}Tc-DTPA in F-15, F+0 and F+15 protocols (r=0.898, 0.916, and 0.950, respectively) ($p<0.001$), as demonstrated in Fig.1.

When we evaluated the difference in the target kidney SRF assessed by both ^{99m}Tc-DMSA and ^{99m}Tc-DTPA between applied protocols, we observed no statistically significant difference between F-15 and F+0 (p=0.637) or F-15 and F+15 (p=0.126). A significant difference was only found between F+0 and F+15 (p=0.030), Fig.2.

Further analysis using Bland-Altman plots to identify the limit of agreement (LOA) between both modalities in the calculation of SRFs for the diseased kidney among the three protocols revealed that the mean differences were 1.57 (LOA: -16.05–14.48), 2.20 (LOA: -15.36–13.17), and 0.66 (LOA: -13.44–12.74) for F-15, F+0 and F+15 protocols, respectively, indicating a greater difference in SRF between ^{99m}Tc-DTPA and ^{99m}Tc-DMSA in the F-15, F+0 protocols compared to the F+15 protocol, Fig .3.

There was a non-significant correlation between the calculated difference in SRF of the diseased kidney obtained by both ^{99m}Tc-DMSA and ^{99m}Tc-DTPA and the other investigated parameters in the three protocols, including age, gender, serum creatinine, blood urea and ^{99m}Tc-DTPA-based SRF. However, a substantial positive correlation between the SRF difference and ^{99m}Tc-DMSA-based SRF was noted in all protocols (r=0.388, p=0.013), (r=0.423, p=0.006), (r=0.306, p=0.049), respectively, Table 4.

The current study included 122 renograms: F-15 (n=40), F+0 (n=40) and F+15 (n=42). The number of equivocal results was significantly lower in F-15 (5/40) than F+0 (12/40), with no significant difference observed between F-15 and F+15 (8/42) or F+0 and F+15, Fig 4. F-15 clarified 7/12 equivocal renograms in F+0 as obstructed (4/7), and non-obstructed (3/7). Fig. 5 illustrates a representative example in this regard.

Table 1: Demographic and clinical data of all studied patients

Variables		All patients (n = 82)	
Age (years)			
Mean ± SD		40±12	
Median (IQR)		39 (32 – 50)	
Serum creatinine (mg/dl)			
Mean ± SD		0.99 ±0.31	
Blood urea (mg/dl)			
Mean ± SD		32.44 ±7.14	
		N	**%**
Sex	Male	45	54.9
	Female	37	45.1
Presentation	Symptomatic	59	72
	Incidentally discovered	23	28

IQR: Inter quartile range SD: Standard deviation

Table 2: Comparison between studied patients in (F+0/F-15) and F+15 groups in terms of demographic and laboratory data

Variables		**F+0/F-15 (n = 40)**		**F+15 (n = 42)**		***p-value***
Age (years)						
Mean± SD		37± 8		42± 14		0.065
Median (IQR)		36 (32-40)		43 (33-54)		
		N	**%**	**N**	**%**	
Sex	**Male**	23	57.5%	22	52.4%	0.506
	Female	17	42.5%	20	47.6%	
Serum creatinine (mg/dl)						
Mean ± SD		1 ±0.23		0.97 ±0.38		0.290
Blood urea (mg/dl)						
Mean ± SD		31.75 ±7.53		33.09 ±6.78		0.449

SD: Standard deviation, IQR: Inter quartile range

Table 3: Comparison between SRF_{DTPA} and SRF_{DMSA} of the diseased kidney in studied protocols

Variables	**Protocols**			***p-value***
	F-15 (n=40)	**F+0 (n=40)**	**F+15 (n=42)**	
^{99m}Tc-DTPA-SRF of the diseased kidney (%)				
Mean ± SD	48.73 ±14.12	49.36 ±13.95	51.15 ±18.41	0.766
Median (IQR)	51.25 (41.10-57.00)	50.35 (45.40-55.30)	51.25 (42.20-58.40)	
^{99m}Tc-DMSA-SRF of the diseased kidney (%)				
Mean ± SD	47.16 ±16.38		50.38 ±20.02	0.357
Median (IQR)	50.58 (43.24-55.00)		50.50 (44.00-60.00)	

IQR, inter quartile range; SD, standard deviation; SRF, split renal function; ^{99m}Tc-DTPA, technetium-^{99m} diethylene triamine pentaacetic acid; ^{99m}Tc-DMSA, $^{technetium\text{-}99m}$ dimercaptosuccinic acid

Table 4: Correlation between the difference in SRF_{DTPA} and SRF_{DMSA} of the diseased kidney and the other investigated parameters in studied protocols

Parameters		Difference in SRF (%) between DMSA and DTPA		
		F-15	F0	F+15
Age	r value	-0.111	-0.082	-0.196
	p value	0.495	0.614	0.213
Gender (male)	r value	0.113	0.006	0.081
	p value	0.489	0.973	0.612
Serum creatinine	r value	-0.249	-0.096	0.067
	p value	0.121	0.554	0.675
Blood urea	r value	-0.158	-0.060	0.065
	p value	0.331	0.715	0.682
DTPA -SRF of the diseased kidney (%)	r value	0.016	0.066	0.019
	p value	0.924	0.686	0.906
DMSA-SRF of the diseased kidney (%)	r value	0.388	0.423	0.306
	p value	0.013*	0.006*	0.049*

SRF, split renal function; ^{99m}Tc-DTPA, technetium-99m diethylene triamine pentaacetic acid; ^{99m}Tc-DMSA, technetium-^{99m} dimercaptosuccinic acid

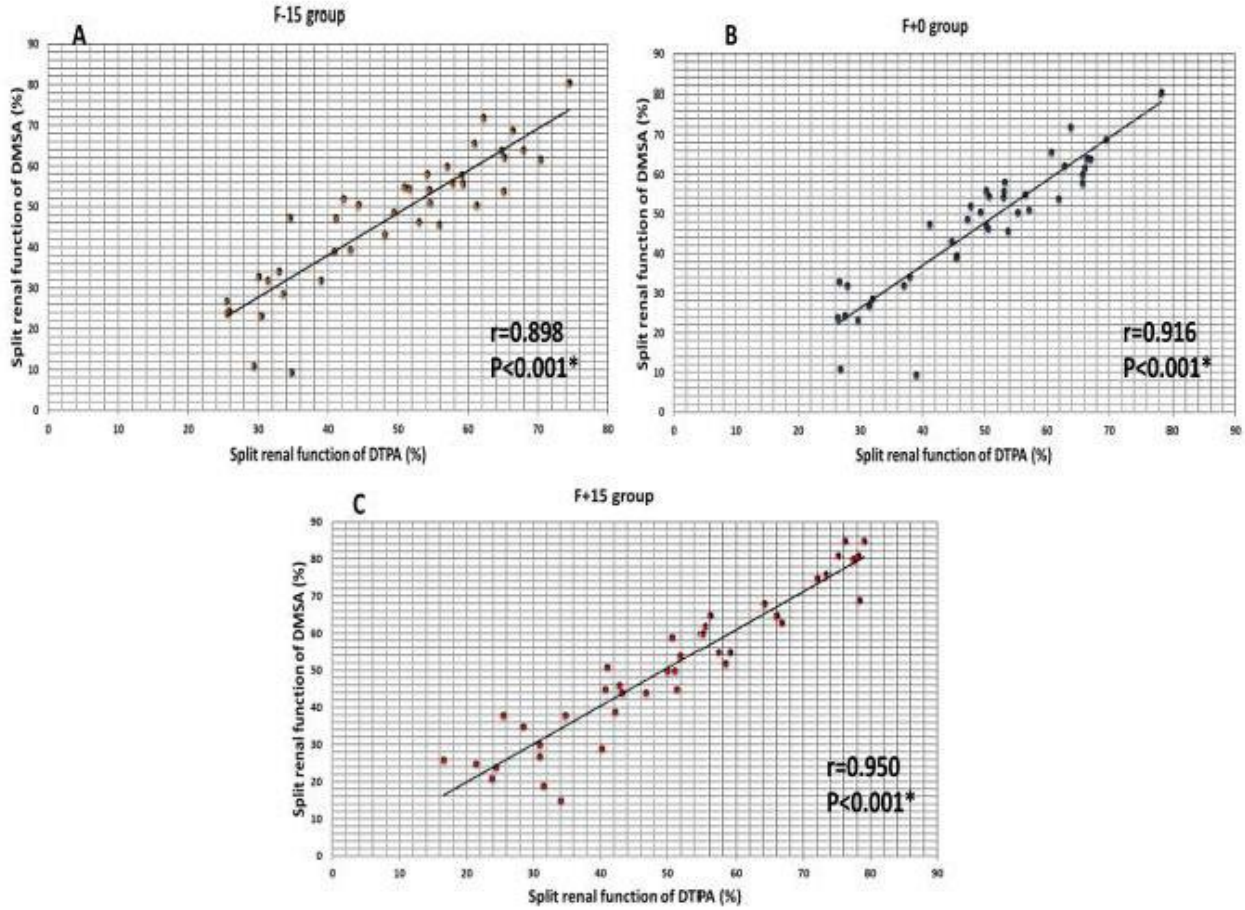

Fig. (1): Correlation between SRF_{DMSA} and SRF_{DTPA} of the diseased kidney in studied protocols

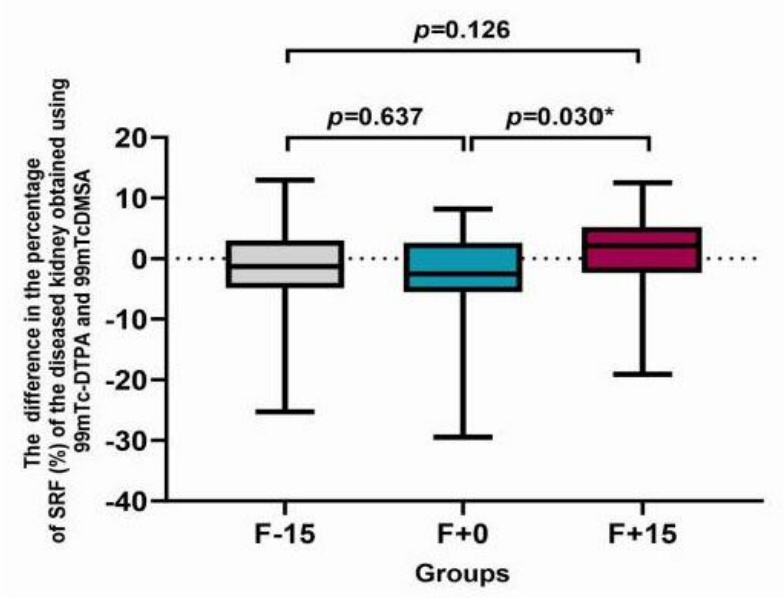

Fig. (2): Comparison between the differences in SRF of the diseased kidney obtained by ^{99m}TcDMSA and ^{99m}TcDTPA in studied protocols

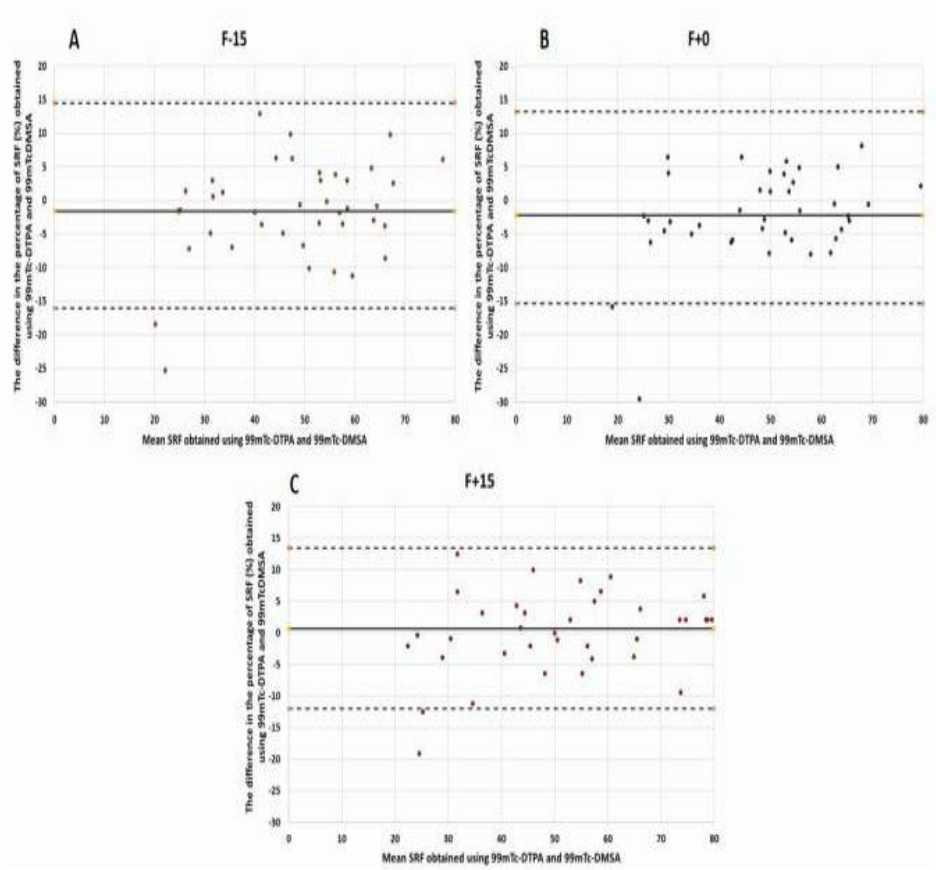

Fig. (3): Bland-Altman-Plots of SRF_{DMSA} and SRF_{DTPA} of the diseased kidney in studied protocols

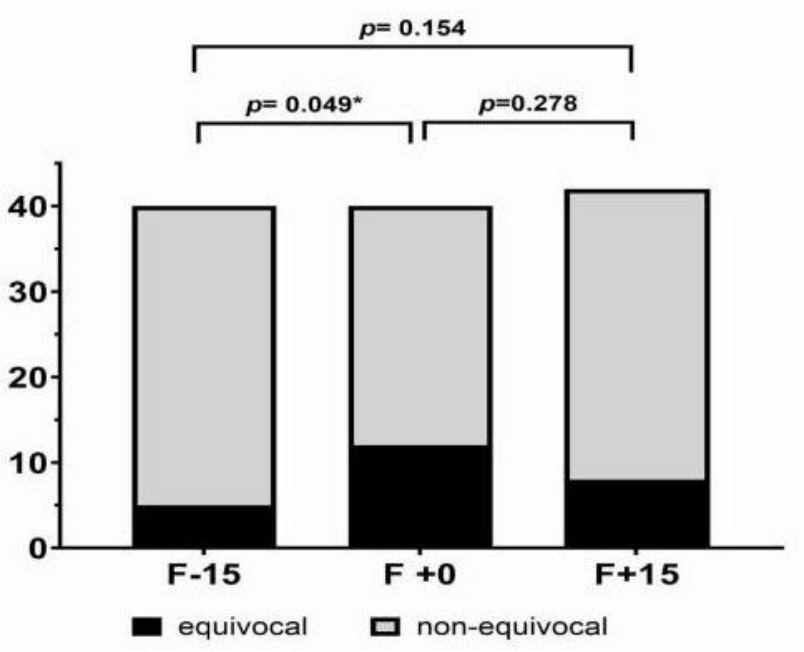

Fig. (4): Comparison of equivocal findings in studied protocols
P1, difference between F-15 and F+15 protocols; P2, difference between F-15 and F+0 protocols, P3: difference between F+0 and F+15 protocols

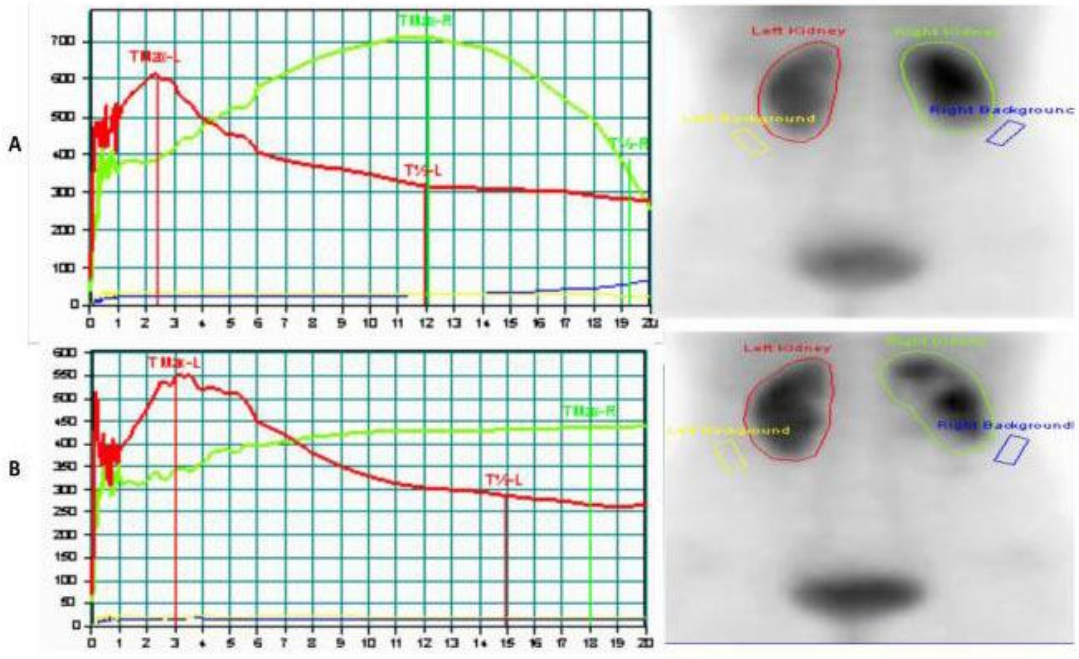

Fig. (5): F+0 (A) and F-15 (B) renogram curves of the same patient, the green line representing the right kidney and the red line representing the left kidney. The top image depicts an equivocal curve in the F+0 protocol (T1/2=19.3), whereas the bottom image demonstrates a rising up curve in the F-15 protocol (T1/2>20), indicating an obstructed right kidney.

Discussion:

There is a considerable variation in the interpretation of DR, which is primarily due to the different protocols used by nuclear medicine departments, as well as other factors such as inadequate patient preparation and diminished renal function, which can result in equivocal findings, particularly in the diagnosis of obstructive uropathy [27]. Furthermore, various factors were proposed in the literature as having a potential impact on the reproducibility of SRF calculation. These factors are associated with patient and renal characteristics such as renal immaturity and severely impaired renal function [28].

For these reasons, in our prospective work, we investigated the effect of time variation of furosemide injection on the calculation of SRF using ^{99m}Tc-DTPA dynamic scintigraphy, relying on SRF estimated with ^{99m}Tc-DMSA cortical scintigraphy as a gold standard, as well as on the interpretation of DR in terms of equivocal renograms after excluding pediatric patients and patients with poorly functioning kidneys, in an attempt to establish a standard protocol for DR.

Taking into consideration that the diuretic effect of furosemide begins within 1-2 minutes and reaches its peak within 15-18 minutes after intravenous injection [29], the current study included two groups of patients: F+0/F-15 and F+15, both are comparable in age, gender, and renal function (serum creatinine and blood urea). We compared these three DR protocols in adults with suspected unilateral obstructive uropathy.

To date, there are no reports discussed the influence of three different DR protocols on the calculation of SRF using ^{99m}Tc-DTPA compared with that using ^{99m}Tc-DMSA. In the three (F-15, F+0 and F+15) protocols, we found a highly significant positive correlation between standard ^{99m}Tc-DMSA-based SRFs and those calculated with ^{99m}Tc-DTPA for the diseased kidney.

Momin and his colleagues concluded that the evaluation of RRFs using ^{99m}Tc-DMSA and ^{99m}Tc-DTPA in a wide age range is nearly identical [24]. Çelik et al. retrospectively compared the RRFs measured with ^{99m}Tc-DTPA and ^{99m}Tc-DMSA in children and reported a good correlation between the two methods ($r=0.963$, $P<0.001$) [23].

These findings support those of Yalcin et al., who retrospectively compared SRFs given by ^{99m}Tc-DTPA and ^{99m}Tc-DMSA in only adult patients and demonstrated a good correlation between SRFs calculated with both modalities ($r=0.937$, $p<0.001$). The study's authors concluded that ^{99m}Tc-DTPA dynamic renal imaging could be employed instead of ^{99m}Tc-DMSA cortical renal imaging in the evaluation of SRF, especially when renogram curves and GFR measurements are necessary [22].

In contrast, Domingues et al. reported that ^{99m}Tc-DTPA is not as reliable as ^{99m}Tc-DMSA, the gold standard for estimating SRF [26]. The inclusion of patients with significant renal impairment in their study could explain the inconsistent results.

When we compared the difference in the calculated SRF of the affected kidney obtained with ^{99m}Tc-DTPA and ^{99m}Tc-DMAS in the evaluated protocols, we noted that this difference was statistically evident in the F+0 compared to the F+15 protocol ($p=0.030$). These results can be considered in line with those of Kandeel et al., who prospectively investigated the influence of F+0 versus F+10 DR using ^{99m}Tc-DTPA on the calculation of SRF of the diseased kidney compared to that based on ^{99m}Tc-DMSA scintigraphy and reported a high statistically significant discrepancy in the SRF measured with both ^{99m}Tc-DTPA and ^{99m}Tc-DMSA between both groups in favor of F+10 ($P<0.001$), the authors hypothesized that the difference was due to the time effect of furosemide injection [30]. We assume that administering furosemide at the F+10th and F+15th minutes following ^{99m}Tc-DTPA injection eliminates the diuretic influence on the SRF calculation, which is computed within the first 2-3 minutes after tracer injection.

In all three protocols, we noted a significant positive correlation between the difference in SRF obtained by ^{99m}Tc-DMSA and ^{99m}Tc-DTPA and the estimated SRF with ^{99m}Tc-DMSA for the diseased kidney, denoting that this difference increases with increasing SRF of the diseased kidney. Kandeel et al., on the other hand, found no significant correlation between the difference in SRF using both modalities and the ^{99m}Tc-DMSA-based SRF in both F+0 and F+10 protocols [30]. Different characteristics of the recruited cohorts in their study [broad age range (2.5 months–80 years) and wide ranging SRFs (3–58%)] could explain this disagreement.

Regarding the effect of diuretic injection timing on the frequency of equivocal findings, multiple studies reported that the F+20 protocol yielded equivocal findings in at least 15% of patients, whereas the F-15 protocol could decrease the number of such results [31],[32]. We found that the frequency of the equivocal responses was significantly less in F-15 (12.5%) compared to F+0 (30%) protocol. Furthermore, we observed that the F+15 protocol resulted in less equivocal results than the F+0, yet with no statistically significant difference.

Similar to our results, Adeyoju et al. stated that the F−15 is superior to the F+0 protocol in terms of minimizing equivocal results; (3%) versus (17%), respectively. However; in contrast to ours, they reported identical equivocal findings when comparing F+0 and F+20 protocols. Different radiotracer (^{99m}Tc MAG) and patient position (sitting position) in their work may have contributed to these disparities [33].

The lower frequency of equivocal results with the F-15 protocol is mostly attributable to the coincidence of the study timing with the maximum diuretic effect of furosemide [34].

In conclusion, our findings demonstrate a highly substantial correlation between ^{99m}Tc-DTPA dynamic and ^{99m}Tc-DMSA static renal scintigraphy in assessing SRF in all three DR protocols: F-15, F+0, and F+15. When the mean difference between SRF_{DMSA} and SRF_{DTPA} in the three procedures was compared, the

F+15 revealed the smallest difference. F-15, on the other hand, is better than F+0 protocol in reducing the number of equivocal renograms and yielding more conclusive results, yet with no significant difference when compared to F+15. As a result, the F+15 protocol is suggested as a single test for evaluating SRF and discriminating between obstructive and non-obstructive uropathy.

List of Abbreviations:

^{99m}Tc-DMSA	^{99m}Tc-dimercaptosuccinic acid
^{99m}Tc-DTPA	^{99m}Tc-diethylenetriaminepentaacetate
^{99m}Tc-MAG3	^{99m}Tcmercaptoacetyltriglycine
ANOVA	Analysis of variance
DR	Diuresis renography
GFR	glomerular filtration rate
IQR	Inter quartile range
LOA	Limit of agreement
MBq	Megabecquerel
mCi	Milicurie
ROIs	Regions of interest
RRF	Relative renal function
SD	Standard deviation
SPSS	Statistical Package for the Social Sciences
SRF	Split renal function

Competing interests

There are no conflicts of interest, according to the authors.

Authors' contributions:

Conception and design: NMM, WGF, MAM, TMI, WAD

Acquisition of data: WGF and NMM

Analysis and interpretation of data: WGF and NMM

Drafting of the manuscript: WGF and NMM

All authors participated in the revision of the manuscript.

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