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Evaluation of Renal Parenchymal Defects with ^{99m}Technetium Mercaptoacetyltriglycine Scintigraphy Using a Modified Grading and Scoring System: Comparison with ^{99m}Technetium Dimercaptosuccinic Acid

Teknesyum-99M Merkaptoasetiltriglisin Sintigrafisi ile Renal Parankimal Defektlerin Modifiye Gradeleme ve Skorlama Sistemi Kullanılarak Değerlendirilmesi: Teknesyum-99M Dimerkaptosüksinik Asit ile Karşılaştırma

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ORIGINAL INVESTIGATION
ÖZGÜN ARAŞTIRMA

ABSTRACT
ÖZET

Objective: The aim of this study was to evaluate whether cortical scars can be detected using the summed images of ^{99m}Technetium-mercaptoacetyltriglycine (^{99m}Tc-MAG3) renal dynamic scans, and to compare the results with 99mTechnetium-dimercaptosuccinic acid (^{99m}Tc-DMSA) scans.

Materials and Methods: We evaluated a total of 135 renal units from 68 patients (12 boys and 56 girls, with a mean age of 9 years old; range 3-16 years old) who had ^{99m}Tc-MAG-3 and ^{99m}Tc-DMSA scintigraphy within a period of two weeks. Differential renal function (DRF) values and parenchymal function parameters obtained from the two studies were compared with semiquantitative scoring and grading systems.

Results: The correlation between ^{99m}Tc-MAG-3 and ^{99m}Tc-DMSA cortical scintigraphy, according to the semiquantitative scoring and grading systems, was perfect (rk tau-b=0.833). The sensitivity, specificity, and accuracy of ^{99m}Tc-MAG-3 scintigraphy were 92.6%, 96.8%, and 95.5%, respectively. There was no significant difference between two methods in detecting renal scars (p>0.05).

Conclusion: Most parenchymal lesions detected on ^{99m}Tc-DMSA scans were also identified on ^{99m}Tc-MAG-3 parenchymal scans. By lowering the radiation exposure, ^{99m}-Tc MAG-3 scintigraphy can provide simultaneous information on renal perfusion, concentration, drainage, parencymal functions, and DRF without the need for additional imaging methods. The reliability of renal parenchyma evaluation was increased by using scoring and grading systems to compare the two methods.

Key words: ^{99m}Tc-MAG3, ^{99m}Tc-DMSA, scintigraphy, kidney cortex

Amaç: Bu çalışmada amaç, Teknesyum-99m Merkaptoasetiltriglisin (Tc^{-99m} MAG3) renal dinamik sintigrafinin toplanmış görüntüleri kullanılarak kortikal skarların tespit edilip edilemeyeceğini değerlendirmek ve sonuçların Tc^{-99m} Dimerkaptosüksinik asit (Tc^{-99m} DMSA) sintigrafisi ile karşılaştırılmasıdır.

Gereç ve Yöntemler: Tc^{-99m} MAG3 ve Tc^{-99m} DMSA sintigrafileri iki hafta içinde yapılmış 68 hastanın toplam 135 böbrek ünitesi (12 erkek ve 56 kız, ortalama yaş 9, yaş aralığı 3-16) değerlendirmeye alındı. Her iki çalışmadan elde edilen parankimal fonksiyon parametreleri semikantitatif skorlama ve gradeleme sistemleri ile karşılaştırıldı. Ayrıca her iki metodla hesaplanan diferansiyel renal fonksiyon (DRF) değerleri arasındaki ilişki değerlendirildi.

Bulgular: Semikantitatif skorlama ve gradeleme sistemlerine gore, Tc^{-99m} MAG3 ve Tc^{-99m} DMSA kortikal sintigrafileri arasındaki uyum mükemmeldi (rk tau b=0,833). Tc^{-99m} MAG3 sintigrafisinin sensitivite, spesifite ve doğruluğu sırasıyla %92,6, %96,8 ve %95,5 idi. Renal skarları belirleme açısından iki metod arasında anlamlı bir farklılık yoktu (p>0,05).

Sonuç: Tc^{-99m} DMSA sintigrafisinde belirlenen parankimal lezyonların çoğu Tc^{-99m} MAG3 sintigrafisinde de gösterildi. Düşük radyasyon maruziyeti ile Tc^{-99m} MAG3 sintigrafisi böbreğin perfüzyonu, konsantrasyonu, temizlenmesi, parankimal fonksiyonları ve DRF hakkında, ek bir görüntüleme metoduna gerek kalmaksızın benzer bilgiler sağlayabilir. İki metodun karşılaştırılmasında skorlama ve gradeleme sistemleri kullanılarak parankimal değerlendirmenin güvenilirliği artırılmıştır.

Anahtar kelimeler: Tc^{-99m} MAG3, Tc^{-99m} DMSA, sintigrafi, renal korteks

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Introduction

Vesicoureteral reflux (VUR) and repeated pyelonephritis result in renal scarring in early times of life which cause to subsequent development of hypertension, renal damage, or end-stage renal disease in a large number of patients in adulthood (1-3). These children are often referred for diagnostic imaging of the urinary tract and kidneys, with the thought that early detection of urologic abnormalities will prevent adverse outcomes (4). Although some radiologic imaging modalities like renal ultrasonography, contrast voiding cystourethrography, computed tomography, and magnetic resonance imaging are routinely performed in children with urinary tract infections, it is known that the sensitivities of these imaging modalities are low for the identification of renal paranchymal damage, especially scar tissue. However, radionuclide scans have been very useful to overcome the limitations of conventional imaging techniques. Properly performed, renal scintigraphy is a sensitive technique to detect, evaluate, and quantify numerous renal disorders. It also is possible to accurately quantify some parameters of renal function. Different renal tracers have been offered for renal imaging (5-7). There are three tracers which rely on tubular extraction: ^{123}I-Hippuran, ^{99m}Tc-MAG3, and ^{99m}Tc-EC (ethilencystein), one tracer dependent on glomerular filtration, ^{99m}Tc-DTPA (diethylentriamine pentaaceticacid), and two tracers dependent on cortical fixation, ^{99m}Tc-GH (glucoheptonate)

and ^{99m}Tc-DMSA (dimercaptosuccinic acid). ^{99m}Tecnetium-DMSA is the most appropriate tracer for imaging the renal cortex. DMSA is actively taken up into distal and proximal renal tubular cells, so that renal tubular cell function is reflected by its uptake and the uptake is herewith affected by both proximal tubular cell membrane transport and intrarenal blood flow (8). Approximately 90% of ^{99m}Tc-DMSA is bound to plasma proteins. Due to the tubular fixation of DMSA, 40-65% of the injected activity will be present in the cortex two hours after injection (9). So, ^{99m}Tecnetium-DMSA scintigraphy is deemed the imaging technique of choice to prove the presence of parenchymal damage due to acute-chronic pyelonephritis or renal parencymal abnormalities, to image functioning cortical mass, and to obtain information related to cortical scarring, relative renal size, and gross anatomy; it is also the most widely accepted procedure for the estimation of differential renal function (DRF) (10). Although it is the most reliable method in the evaluation of renal paranchyma, this agent delivers a slightly higher radiation dose in comparison with other renal agents due to tubular fixation of DMSA and a relatively longer processing time (11-13). In addition, excretion of this tracer from the kidneys may require a delay of 24 hours. Since an insignificant amount of DMSA is excreted in the urinary collecting system, DMSA studies do not provide data on ureteral emptying (14).

^{99m}Tc-MAG3, which is a proximal tubular secretion renal agent, is indicated to evaluate cortical tubular function and collecting system drainage, especially in obstructive uropathy, renovascular hypertension, and renal transplant abnormalities (15). In the first few minutes after injection, while the background activity is decreasing, MAG3 rapidly accumulates in the renal cortex because of its high extraction efficiency (40%-60% per pass). Therefore, the parenchymal phase, during the initial part of the study, reflects the distribution of functional parenchyma, allowing the detection of reversible or irreversible lesions. Furthermore, MAG3 provides information about the collecting system and urodynamics, and, in comparison with DMSA, delivers a much lower radiation dose and shorter procedural time (6, 16).

Thus, we investigated the detection efficacy of renal cortical scars by using the initial uptake phase of ^{99m}Tc-MAG3, as the initial part of the dynamic sequence involves the cortical uptake phase. Our study represents an attempt to systematically investigate the sensitivity and specificity of ^{99m}Tc-MAG3 cortical phase imaging, by comparing with ^{99m}Tc-DMSA, in the detection of renal parenchymal defects.

Materials and Methods

Our study was a prospective clinical trial that included consecutive patients followed up with a diagnosis of urinary tract infection or VUR in the Department of Pediatric Nephrology, Faculty of Medicine at Erciyes University Hospital. Institutional ethics approval was obtained (2008/17) for the study, and informed consent was obtained from the parents of children who participated.

Patients

We evaluated a total of 135 renal units from 68 patients (12 boys and 56 girls), with a mean age of 9 years (range 3-16 years) who had ^{99m}Tc-MAG-3 and ^{99m}Tc-DMSA scintigraphy. All consecutive patients had undergone dual renal imaging within an interval of two weeks. One patient had a single functioning kidney. All patients in the study had at least one episode of proven urinary tract infection with or without documented VUR.

Imaging Protocols

^{99m}Tc-DMSA scintigraphy was performed approximately three hours after the patients had been injected intravenously (IV) by a tracer dose activity of "adult dose (MBq) x body weight (kg)/70". Static images were obtained in supine posterior, left and right posterior oblique and anterior views (400 kcount/view) using a gamma camera equipped with a LEHR collimator in a 256x256 matrix. Using a special software program (Toshiba GMS software (V5.0) GPL), the perirenal regions of interest (ROIs) were drawn for both kidney uptake and body background. DRF and kidney to body background ratios were calculated quantitatively.

^{99m}Tc-MAG3 (2 MBq/kg) was injected IV during the patient lay in a supine position with sufficient hydration. Continues dynamic images were taken with the same gamma camera for 30 minutes. Dynamic images were recorded in a 64x64 matrix for 1 sec/64 frames and 15 sec/120 frames. Sedation was not used. Additionally, eight planar static images (256x256 matrix, 2 min/frame, between 0-2, 2-4, 4-6, 8-10, 10-12, 15-17, 20-22, 25-27 min) were recorded. If patients had renal pelvic and/or pelvicalyceal activity accumulation during the acquisition; the patients were injected with furosemide IV. The DRF was calculated from the slope of the background-subtracted renal curves. The first 2 min images of MAG3 (parenchymal phase) were compared with the DMSA images for the right and left kidneys separately.

Data Analysis

DMSA and MAG3 scans were analyzed separately by two nuclear medicine specialists. The manual regions of interest (ROIs) were created by tracing the kidney contours. ^{99m}Tc-labelled DMSA scans were considered normal if homogeneous uptake of the radioisotope was evident throughout the kidneys, if the renal size and contour was preserved with no cortical focal defects and with DRF over 45%. The presence of scarring, single or multiple focal defects; diffuse decreased uptake; kidney volume loss or no kidney were suggested by abnormal DMSA findings and DRF was also reduced in the cases of unilateral abnormalities by abnormal DMSA findings. The areas of decreased tracer uptake related to surface indentation or cortical thinning with loss of renal volume define as Renal scar. The first 2 min of the MAG3 scan were evaluated for paranchymal lesions.

Using a nine-point semiquantitave analysis of each kidney, only planar posterior images of the parenchymal phase of ^{99m}Tc-MAG3 scintigraphy and DMSA scintigraphy were evaluated. Each kidney was divided into thirds scored from 0 (normal uptake) to 3 (no uptake). Future more, the scintigrams were graded pursuant to the severity of the abnormality using a modified Goldraich system (17). Grade 0 is considered as normal or nearly normal (score 0-1); Grade 1 is considered as no more than two focal/relatively decreased activity sides and/or a single contour defect (score 2-3);

Grade 2 is considered as two or more contour defects, remnant areas of normal renal parenchyma and a normal sized kidney (score 4-5); Grade 3 is considered as reduction in the uptake of DMSA/MAG-3 throughout the whole kidney with or without multiple renal contour defects (score 6-7); and Grade 4 is considered as shrunken kidney or indistinct kidney margins (score 8-9).

For the evaluation of DRF, a paired t-test and Chi-Square test were used.

Results

A total of 68 patients, consisting of 135 renal units (kidney and ureter), were evaluated for the determination of paranchymal lesions.

Renal scars were shown in 41 (30%) renal units. A total of 41 of 135 (30%) renal units had scars on ^{99m}Tc-DMSA and ^{99m}Tc-MAG3 scintigraphy. A high correlation was found between two scintigraphic studies detecting renal parenchymal abnormalities (kappa analysis, k=0.895) (Table 1).

When ^{99m}Tc-DMSA scintigraphy was considered the reference teqnique, the sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of the ^{99m}Tc-MAG-3 cortical images for detecting renal lesions were calculated as 92.6%, 96.8%, 95.5%, 92.6%, and 96.8%, respectively.

A patient's parenchymal phase of ^{99m}Tc-MAG3 scintigraphy and ^{99m}Tc-DMSA scintigraphy are shown in Figure 1. There were no marked differences between the two images. The score of the left kidney was 7 and the distribution of parenchymal activity and outlines were interpreted as a global reduction in uptake throughout the whole kidney without contour defects. The score of the right kidney was 0 and the distribution of parenchymal activity and outlines were interpreted as normal.

One patient was excluded because he had only one functional kidney. As a result, a total of 134 renal units of 64 patients were evaluated for DRF. Ultimately, there were no statistically significant differences between ^{99m}Tc-DMSA and MAG-3 images in the DRF calculations (p>0.05) and there was a high correlation between the two methods (Pearson correlation test, r=0.986) (Table 2).

Table 3 shows the acceptable correlation in grading of DMSA and MAG3 scintigraphies, suggesting that the investigators agreed on the grades of kidneys with only one or two contradictions.

Our results show that both methods can be used equally for the calculation of differential kidney function. Most parenchymal lesions detected on ^{99m}Tc-DMSA scans were also identified on ^{99m}Tc-MAG-3 parenchymal scans. By lowering the radiation exposure, ^{99m}Tc-MAG-3 scintigraphy can provide simultaneous information on kidney perfusion, concentration, drainage, parenchyma, and differential renal function.

Another example of kidneys with good agreement between ^{99m}Tc-MAG3 scintigraphy and ^{99m}Tc-DMSA scintigraphy is given in Figure 2. The both tests showed lesions in the parenchyma and contour defects in two kidneys with excellent consistency.

Discussion

Valuable data on renal perfusion and the parenchymal and dynamic function of individual kidneys, as well as on urinary tract dynamics can be provided by Nuclear medicine procedures to clinicians. Different renal tracers have been offered for evaluating different renal functions. However, in the diagnostic techniques that use radiation, many factors such as reduced radiation dose, non-invasiveness, shorter take-up time, as well as more detailed information are considered.

A broad consensus has been reached that ^{99m}Tc-DMSA is the most appropriate tracer for renal cortical imaging (4, 8). ^{99m}Tc-DMSA

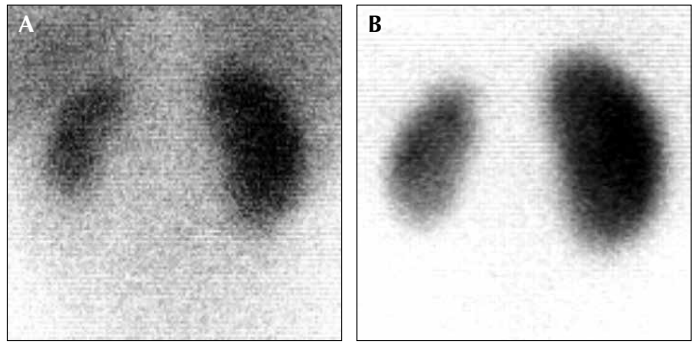

Figure 1. A 12-year-old girl with a history of grade III VUR in the left kidney had undergone 99mTc-MAG3 (A) and ^{99m}Tc-DMSA (B) scintigraphy within two weeks. According to the scoring system, it was evaluated that the left kidney had score of 7, whereas the right kidney had a score of 0

Table 1. The comparison of the ^{99m}Tc-MAG3 paranchymal phase and 99mTc-DMSA scintigraphies in the evaluation of scars

	^{99m}Tc-MAG-3		
^{99m}Tc-DMSA	Scar (-)	Scar (+)	Total
Scar (-)	91	3	94
Scar (+)	3	38	41
Total	94	41	135

Table 2. Demographic characteristics and the mean DRF values of left and right kidneys from ^{99m}Tc-MAG3 and 99mTc-DMSA scintigraphies

	Left kidney			Right kidney		
Procedure	n (M/F)	Range (%)	Mean±SD	n (B/G)	Range (%)	Mean±SD
^{99m}Tc- DMSA	67 (12/55)	2.7-98.6	48.04±16.87	67 (12/55)	1.4-97.3	51.96±16.87
^{99m}Tc- MAG3	67 (12/55)	3.3-98.7	48.43±16.93	67 (12/55)	1.3-96.7	51.57±16.93

M: boys, F: girls, SD: standard deviation

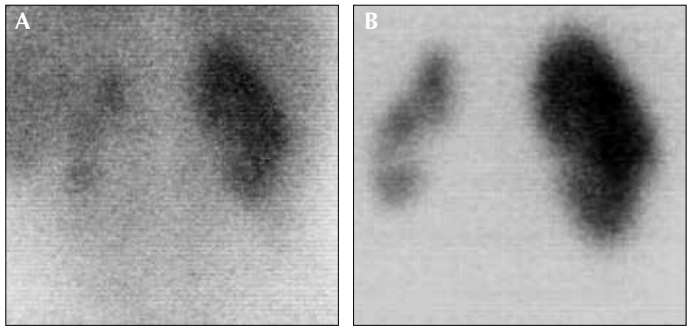

Figure 2. A six-year-old girl followed up with bilateral grade five VUR. 99mTc-MAG-3 (A) and ^{99m}Tc-DMSA (B) scintigraphies show the reduced sized of the left kidney in addition to multiple cortical scars and the normal size of the right kidney with cortical scarring in the middle region and lower pole. Structural damage to both kidneys was scored (score of 7 in the left kidney, score of 6 in the rigt kidney) and graded (grade III in both kidneys) by DMSA and MAG-3 scans

Table 3. Correlation between DMSA grades and MAG3 grades

	MAG3 Grade					
DMSA Grade	0	I	II	III	IV	Total
0	64	10	0	0	0	74
I	4	16	3	1	0	24
II	0	3	12	0	0	15
III	0	0	1	9	0	10
IV	0	0	0	1	11	12
Total	68	29	16	11	11	135

renal scanning is widely used in clinical practice, especially in the evaluation of APN, post-infection renal scarring and the calculation of DRF, but it does not provide any information about dynamic functions of the kidneys (8). After injection, a waiting period is needed for 40% of the dose to accumulate in the renal parenchyma and for the rest to be excreted in the urine (10). The optimal images should be taken in a period of 3 to 6 h after injection. This waiting period can sometimes cause a disturbance, especially in children.

Dynamic renal tracers can also provide simultaneous information on kidney parenchymal function, drainage and, split function, at the same time lowering the radiation exposure. The main goal of this investigation was to demonstrate that MAG3 scintigraphy as a dynamic agent can be used for the purpose of renal parenchymal evaluation as well as urinary tract dynamics without the need for DMSA scintigraphy (14, 15).

^{99m}Tc-DMSA images were acquired from the anterior, posterior, lateral, and oblique projections, and geometric mean and taking kidney depth into account by acquiring images both anteriorly and posteriorly were used to calculate DRF. Whilst images from the ^{99m}Tc-MAG3 investigations were acquired only in the posterior position. This situation yielded an advantage over DMSA regarding the evaluation of the renal paranchyma and the detection of cortical scars and DRF. However, it has been reported that even only posterior paranchymal images produced in the early phases of dynamic renal scans can provide some information about the renal cortex. Due to its high extraction efficiency, MAG3 provides high-resolution parenchymal images 1-4 min after injection and may be suitable for renal parenchymal (cortical) scintigraphy. Some investigators have evaluated the use of planar dynamic MAG3 scintigraphy for investigating the renal parenchyma in urinary tract infection patients (7, 15, 16).

In our case, for the estimation of DRF, there were no statistically significant differences between ^{99m}Tc-DMSA and ^{99m}Tc-MAG-3 images ($p>0.05$), and there was a high correlation between the two methods (Pearson correlation test, $r=0.986$). Radiopharmaceuticals designated as renal dynamic agents were used for cortical imaging because of their high tubular extraction feature.. They provide information concerning perfusion, differential function, drainage of upper outflow tracts, and indirect evidence of vesicoureteric reflux. These whole details above are useful in patients who require cortical investigation.

Although the DRF calculation provides an overall quantification of renal parenchymal uptake, it does not show changes in distinct renal parenchymal regions. During follow up, it does not show changes in a specific area of the kidney prior to detecting cortical defects. A contour defect with a corresponding photopenic area, or a cold area within the renal parenchyma with or without a contour defect can be determined by visual evaluation. However, the major problem with this kind of interpretation of scans is the absence of a recognized standard and the fact that it is observer-dependent. The extent of physician variability in the interpretation of renal parenchymal images has not been well-established. Different visual and quantitative evaluation methods have been used to assess the renal parenchyma so far. A grading system based on specifying the severity of renal abnormalities was used by Goldraich (17). Smokvina et al. (18) divided the renal parenchyma to three regions –the midzone, upper pole, and lower pole-as well as medial and lateral parts. In our study, renal parenchyma images were both graded and scored according to the severity of the abnormalities. So, this method provided more detail and more areas of possible abnormality in different parts of the kidney.

^{99m}Tc-mercaptoacetyltriglycine (MAG3) as a tubular tracer is usually preferred for the glomerular agent ^{99m}Tc-DTPA, especially in infants and young children and in patients with impaired renal function, due to its higher ratio of renal extraction (60%) and rapid plasma clearance (19). For all that, studies on the use of ^{99m}Tc-MAG3 to depict focal parenchymal abnormalities have been conflicted. Some investigators have reported that ^{99m}Tc-MAG3 is equivalent to ^{99m}Tc-DMSA in the estimation of differential renal functions and evaluation of the cortex (20, 21). Most of the investigators have used a 1-4 min summed image for reporting ^{99m}Tc-MAG3 scans. The early summed ^{99m}Tc-MAG3 images were found to have a sensitivity of 96% in revealing renal parenchymal defects; at the same time, the specificity was only found as 39% (8). This was due to the summed ^{99m}Tc-MAG3 images were quite noisy, giving a high false-positive rate (low specificity). This is because a small percentage of the injected dose of this agent accumulates in the hepatobiliary system,

thereby reducing its renal specificity at the same time, making the compound unattractive for various renal parameter measurements (16). Nonetheless, due to its high extraction efficiency, MAG3 provides high-resolution parenchymal images 1-4 min after injection and may be suitable for renal parenchymal (cortical) scintigraphy. Since space occupying lesions show as a non-specific finding of cold defects in different regions of kidney, they can present a problem on ^{99m}Tc-DMSA scan evaluation. In these cases, perfusion images of dynamic renal scans may be useful to differentiate vascularized from nonvascularized pathologies.

In our study, there was a high correlation between DMSA and MAG3 scans for detecting renal parenchymal abnormalities (kappa analysis, k=0.895). We utilized the first 2 min summed image to investigate the parenchymal defects. We determined an overall sensitivity of 92.6% and specificity of 96.8% of the ^{99m}Tc-MAG3 images for scar detection. Thus, the ^{99m}Tc-MAG3 scan was found to have good sensitivity and specificity to detect the renal cortical scars that is comparable with the ^{99m}Tc-DMSA scan.

It is proposed that patients should be administered the minimum activity consistent with achieving the intended clinical information. The greatest advantage of ^{99m}Tc-MAG3 is the low absorbed radiation dose (0.25 mGy/MBq, whole body dose) as compared with ^{99m}Tc-DMSA (1.60 mGy/MBq, whole body dose) (21). Hydration and diuretic-induced frequent bladder voiding provide further reductions in the radiation dose delivered to the bladder wall and the gonads. Another advantage of ^{99m}Tc-MAG3 is the short duration of the test, which requires no waiting period after injection. Immobilization is easier for this short period of time and sedation is rarely required.

It is important that some normal variants of the kidney should not be confused with parenchymal defects on DMSA images. The evaluation of this study was mostly based on visual interpretation of DMSA scans. Hydronephrosis is not a contraindication for DMSA scintigraphy, but constitutes a pitfall because of the reservoir effect of the dilated system. However, in dynamic scans, injection of furosemide contributes to emptying the normal drainage system and excludes truth obstruction, allows study of the renal parenchyma, and reduces radiation exposure to the urinary bladder by inducing frequent urination (9). Moreover, abnormalities in the accumulation and discharge of cortical activity of MAG3 have been determined in some renal parenchymal disorders. So, not only early images but also delayed images of dynamic scans can give some information about the renal parenchyma.

This study showed that all clear parenchymal lesions seen on DMSA were detected in the parenchymal phase MAG3 image. There were no statistically significant differences between estimated differential kidney function by DMSA and MAG3. This supports the idea of using a different approach to nuclear diagnostic procedures in the underlying field of indications. Replacing DMSA with MAG3 in the initial assessment of a patient would provide simultaneous information on kidney function, drainage, and split function, while at the same time lowering radiation exposure. The main studies were carried out to standardize the procedure, to avoid technical pitfalls, and to allow the comparison of results between institutions.

Conclusion

Lesions were well recognized on both MAG3 and DMSA in the lack of renal insufficiency although the target to non-target ratio was higher for DMSA. Both tests are not always necessary. Evaluation of the renal parenchyma in the early phase of the MAG3 scan is reliable and feasible in children and adults, considering the lower radiation burden, and provides diagnostic information of focal disease and quantitative data regarding renal function. These results support the idea of promoting MAG3 dynamic scintigraphy as an initial nuclear medicine procedure in the diagnosis of the majority of kidney diseases.

Conflict of Interest

No conflicts of interest were declared by the authors.

Authors' contributions: Conceived and designed the experiments or case: MK. Performed the experiments or case: ZE. Analyzed the data: ÜA, MK. Wrote the paper: ÜA, ZE. All authors read and approved the final manuscript.

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