

# Alteration of $^{99m}\text{Tc}$ -DMSA biodistribution in glomerulonephritis

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## Abstract

**BACKGROUND:** The aim of this study was to assess the relation between  $^{99m}\text{Tc}$ -DMSA biodistribution and its reliability as a marker of renal function in patients with glomerular kidney diseases. **MATERIAL AND METHODS:** Sixty-seven patients involved in this study were classified into two groups according to  $^{99m}\text{Tc}$ -DTPA clearance and serum creatinine values: the 1<sup>st</sup> group consisted of 42 patients without renal failure while the 2<sup>nd</sup> group included 25 patients with renal failure.  $^{99m}\text{Tc}$ -DMSA biodistribution was determined by measuring kidney, blood and urine activity at 2 h and 4 h.

**RESULTS:** The results, compared with those of 23 healthy volunteers, indicated the quantitative alteration of  $^{99m}\text{Tc}$ -DMSA distribution in both glomerulonephritis patient groups. In reference to the control mean values of 2 h and 4 h, in patients without renal failure, kidney activity was found decreased to 52% and 57%, while the blood activity increase of 37% and 44% was recorded together with the urine activity increase of 38% and 23%. In patients with renal failure the alterations of renal and blood activity were more remarkable, but the urine loss was found to be unchanged.

**CONCLUSIONS:** It is suggested that these biodistribution changes originate mainly from tubular impairment. However, in glomerulonephritis patients, altered glomerular filtration might considerably affect biodistribution of this radiopharmaceutical and limits its suitability for precise quantitative estimation of renal function.

**Key words:**  $^{99m}\text{Tc}$ -DMSA, kidney activity, blood activity, urine activity, glomerulonephritis

## Introduction

Renal handling of  $^{99m}\text{Tc}$ -DMSA depends basically on its physical and chemical properties.  $^{99m}\text{Tc}$ -DMSA binds to plasma proteins to a high degree [1] and disappears from the blood at a very slow rate. It is mostly cleared from the circulation by tubular cell uptake [2], and only a smaller non-bound fraction is filtered through glomeruli [3]. Other organs, such as the liver and muscles, also take up this agent [4].

Physical and chemical alterations of the radiopharmaceutical, as well as those of the body medium, may cause disturbances in  $^{99m}\text{Tc}$ -DMSA biological behaviour [5–7]. Impairment of renal function, particularly tubular disorders, also affects  $^{99m}\text{Tc}$ -DMSA distribution. Human and experimental tubular diseases are accompanied by a decrease of  $^{99m}\text{Tc}$ -DMSA renal uptake and an increase of the urinary loss of the tracer [8, 9]. However, reduced  $^{99m}\text{Tc}$ -DMSA renal uptake was also revealed in human glomerulonephritis [10] and rats with glomerular damage induced by puromycin aminonucleoside [11].

This study aimed to establish the link between  $^{99m}\text{Tc}$ -DMSA biodistribution and its reliability as an indicator of renal function in patients with glomerular kidney diseases.

## Material and methods

### Subjects

Biodistribution studies were performed in 67 patients with glomerulonephritis and 23 healthy volunteers of both sexes. Each study participant signed an informed consent form explaining the investigative nature of the study, its risks and its merits.

Patients were classified into two groups according to  $^{99m}\text{Tc}$ -DTPA clearance values and serum creatinine levels: 1<sup>st</sup> group (GN) — 42 patients without renal failure ( $^{99m}\text{Tc}$ -DTPA clearance over 50 ml/min/1.73 m<sup>2</sup> and serum creatinine values up to 120 μmol/l); 2<sup>nd</sup> group (GN-CRF) — 25 patients with renal failure ( $^{99m}\text{Tc}$ -DTPA clearance below 50 ml/min/1.73 m<sup>2</sup> and serum creatinine above 120 μmol/l). Among the glomerulonephritis patients, 36 were with primary glomerulonephritis and 31 with overt diabetic nephropathy. Renal biopsy revealed IgA nephropathy in 14 out of the total 36 patients with primary glomerulonephritis, mesangioproliferative glomerulonephritis in 8, membranous glomerulonephritis in 6, focal segmental glomerulosclerosis in 6 and membranoproliferative glomerulonephritis in 2 patients. Patients with oedema or urinary stasis were excluded from the study because of interfer-

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**Table 1. Patients' data**

Group	N	Age (years)	Gender		S Creatinine [ $\mu\text{mol/l}$ ]	$^{99\text{m}}\text{Tc-DTPA}$ clearance [ml/min/1.73 m <sup>2</sup> ]
			female	male		
Control	23	41.1 $\pm$ 8.7	14	9	64.0 $\pm$ 8.3	122 $\pm$ 7
GN	42	44.8 $\pm$ 12.4	25	17	93.4 $\pm$ 15.2 <sup>a</sup>	84.6 $\pm$ 16.7 <sup>a</sup>
GN-CRF	25	50.4 $\pm$ 11.1 <sup>b</sup>	14	11	194 $\pm$ 77 <sup>a,c</sup>	33.0 $\pm$ 12.0 <sup>a,c</sup>

GN — glomerulonephritis patients with normal creatinine, GN-CRF — glomerulonephritis patients with high creatinine, vs. control: <sup>a</sup>P < 0.0001, <sup>b</sup>P < 0.005; vs. GN: <sup>c</sup>P < 0.0001

ence of these disturbances with radiopharmaceutical distribution. Patients' data are presented in Table 1.

### Biodistribution studies

In each subject blood, kidney and urine activity of  $^{99\text{m}}\text{Tc-DMSA}$  are measured to determine its biodistribution.

**Preparation of patients.** All patients were hydrated orally with water 10 ml/kgBW 30 minutes prior to radiotracer injection and with an additional intake of the same amount 30 minutes later to provide an adequate urine volume. Patients were asked to urinate before the beginning of the study.

**Radiopharmaceuticals.** The aqueous solution of 2 ml DMSA (Vinča, Yugoslavia) was labelled with 600 MBq of Tc-99m-sodium-pertechnetate in the volume of 3 ml. One kit of the radiopharmaceutical was employed for 4 patients within two hours after reconstitution. The properties of  $^{99\text{m}}\text{Tc-DMSA}$  preparations determined by the manufacturer were: kidneys/liver ratio of 14.5 (median) and plasma protein bound fraction of 72.7  $\pm$  6.8% (mean  $\pm$  SD). The former parameter was obtained by measuring whole organ activity in a well counter after rats were sacrificed, while the latter was determined by perchloric acid method [1]. Radiopharmaceuticals used in this study,  $^{99\text{m}}\text{Tc-DMSA}$  and  $^{99\text{m}}\text{Tc-DTPA}$  (Vinča, Yugoslavia), were found to contain less than 1% of free  $^{99\text{m}}\text{Tc-pertechnetate}$  by thin layer chromatography (manufacturers' data). They were applied intravenously in a dose of 1.85 MBq/kgBW.

**Measurement of  $^{99\text{m}}\text{Tc-DMSA}$  activity.** Renal scintigraphies were performed with computerised gamma camera ("Siemens"), equipped with low energy parallel hole collimator. Well detector ("Beckman") was used to count blood and urine specimens of 1 ml. Activity of the dose administered was measured both by well counter and gamma camera. The net administered counts were calculated by subtracting postinjection from preinjection syringe counts. All measurements were carried out within one minute and corrected for radionuclide decay. Individual values of blood, kidney and urine activity were expressed as a percentage of the dose applied.

**Blood activity.** Whole blood activity was calculated by multiplying 1 ml blood sample counts with blood volume determined

from normogram [12]. Elimination rate of  $^{99\text{m}}\text{Tc-DMSA}$  from the blood was estimated by half time (T 1/2) calculated using slope/intercept method with two blood samples taken at 2 h and 4 h.

**Urine activity.** Activity of 1 ml urine sample was multiplied with total urine volume obtained as a sum of the voided and residual urine volume. The latter was calculated from pre- and post-voiding bladder counts and voided urine volume [13].

**Renal activity.** Fraction of  $^{99\text{m}}\text{Tc-DMSA}$  taken up by the kidneys was evaluated from scintigrams made up to 4 h. Dynamic imaging with 20 s frames was performed for 30 min in 64  $\times$  64 matrix to determine 1, 5, 10, 15, 20, 25 and 30 min renal uptake. Static images were obtained at 2 h and 4 h in 128  $\times$  128 matrix.

Renal activity was corrected for background counts, soft tissue absorption and radionuclide decay. For background correction, regions of interest were placed around lateral parts of lower kidney poles. Background counts normalised to kidney surface were subtracted from total renal counts to obtain true renal activity. It was corrected for soft tissue absorption using renal depth and the linear absorption coefficient. Kidney depth was determined on lateral images as a distance from the middle point of the renal bipolar diameter to the oppositely placed "hot" point marked with radiation source on patient's back skin [14]. The linear absorption coefficient (for LEAP collimator) of 0.129 cm<sup>-1</sup> was calculated by using water phantom. Renal counts were also corrected for radionuclide decay for each studied time period.

**Determination of  $^{99\text{m}}\text{Tc-DTPA}$  clearance.**  $^{99\text{m}}\text{Tc-DTPA}$  clearance was measured from the one compartment system using a single sample technique. Volume of distribution was determined from blood specimens drawn 3 h after radiopharmaceutical injection. Its high correlation with clearance values obtained using multiple blood samples ( $y = -0.0128x^2 + 3.077x - 30.3$ ) was applied to calculate individual clearance values of patients studied. The error of estimated glomerular filtration rate was found to be only 7.8 ml/min [15].

**Statistical analysis.** Group values were presented as mean  $\pm$  SD and Student's t-test was used to demonstrate group value differences for all parameters studied, except  $^{99\text{m}}\text{Tc-DMSA}$  blood T 1/2 values, when median and Mann-Whitney's U test were applied.

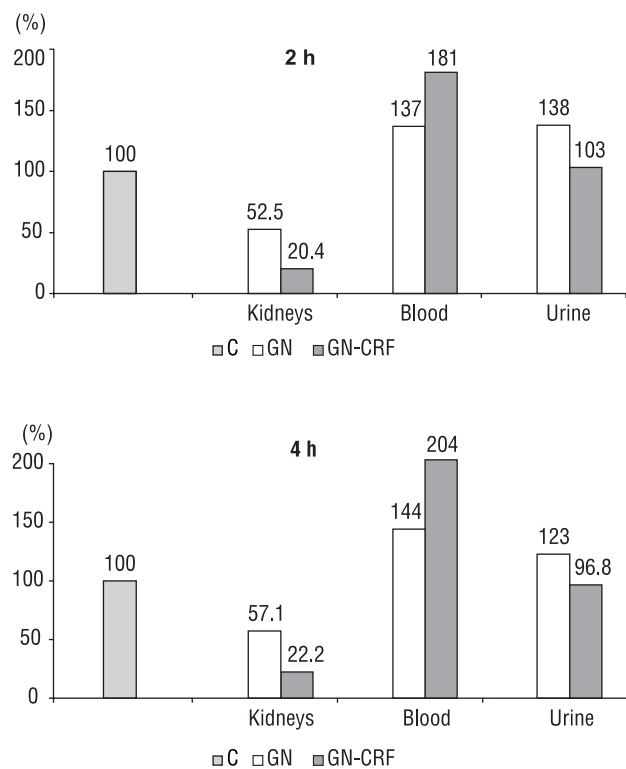
## Results

Values of  $^{99\text{m}}\text{Tc-DMSA}$  blood, kidney and urine activity measured in glomerulonephritis patients 2 h and 4 h after application are presented in Table 2. In the control group, the highest activity was found in the kidneys at both periods. The greatest share of the agent in GN patients was in the blood at 2 h, but in the kidneys at 4 h, while in GN-CRF group it was in the blood at both time intervals.

**Table 2.  $^{99\text{m}}\text{Tc-DMSA}$  distribution at 2 h and 4 h in patients with glomerulonephritis**

Group	Kidneys (%)		Blood (%)		Urine (%)	
	2 h	4 h	2 h	4 h	2 h	4 h
Control	44.2 $\pm$ 5.0	50.4 $\pm$ 5.6	26.7 $\pm$ 4.9	18.0 $\pm$ 3.6	12.2 $\pm$ 4.0	19.0 $\pm$ 4.6
GN	23.2 $\pm$ 5.9 <sup>a</sup>	28.8 $\pm$ 7.7 <sup>a</sup>	36.7 $\pm$ 6.6 <sup>a</sup>	25.9 $\pm$ 6.7 <sup>a</sup>	16.8 $\pm$ 6.2 <sup>b</sup>	23.4 $\pm$ 6.0 <sup>b</sup>
GN-CRF	9.0 $\pm$ 3.5 <sup>a,c</sup>	11.2 $\pm$ 3.9 <sup>a,c</sup>	48.4 $\pm$ 9.9 <sup>a,c</sup>	36.7 $\pm$ 8.8 <sup>a,c</sup>	12.6 $\pm$ 4.3 <sup>d</sup>	18.4 $\pm$ 4.5 <sup>d</sup>

vs. control: <sup>a</sup>P < 0.0001, <sup>b</sup>P < 0.001; vs. GN: <sup>c</sup>P < 0.0001, <sup>d</sup>P < 0.005



**Figure 1.** The percentage of renal, blood and urine activity alterations in patients with glomerulonephritis related to control mean values (expressed as 100%): at 2 h (upper panel) and at 4 h (lower panel); C — control, GN — patients with glomerulonephritis and normal serum creatinine, GN-CRF — patients with glomerulonephritis and high serum creatinine.

In patients studied, alteration of renal, blood and urine activity related to control mean values (expressed as 100%) is displayed in Figure 1. As can be seen, renal and blood activity were more remarkably changed in GN-CRF group, while urine activity was altered significantly only in GN group.

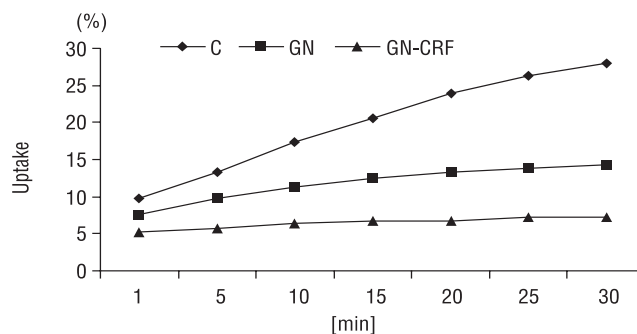
The analysis of changes in 2–4 h period indicated the increase of renal and urine activity and the decrease of the blood activity in all groups studied. Although absolute values of renal uptake were lowered, the percentage of increase from 2 h to 4 h was found to be more rapid in both patients' groups than in control.

Early renal uptake of  $^{99m}\text{Tc}$ -DMSA within the period of 1–30 min was lowered considerably in both patient groups (Fig. 2). In the control group uptake was  $9.9 \pm 1.8\%$  at 1 min and  $28.0 \pm 2.9\%$  at 30 min. The significant decrease to  $7.58 \pm 2.48\%$  ( $P < 0.001$ ) in GN group and to  $5.15 \pm 2.12\%$  ( $P < 0.0001$ ) in GN-CRF group appeared already after one minute. Significantly lower uptake remained up to 30 min, when the greatest difference was noted, since uptake values in patient groups were  $14.34 \pm 3.52\%$  ( $P < 0.0001$ ) and  $7.22 \pm 3.72\%$  ( $P < 0.0001$ ), respectively.

Half time of  $^{99m}\text{Tc}$ -DMSA blood disappearance was significantly prolonged only in GN-CRF group (Table 3).

## Discussion

The present study of the healthy subjects 2 h following injection showed somewhat less than one half of applied activity in the



**Figure 2.**  $^{99m}\text{Tc}$ -DMSA renal uptake from 1 to 30 min in patients with glomerulonephritis; C — control, GN — patients with glomerulonephritis and normal serum creatinine, GN-CRF — patients with glomerulonephritis and high serum creatinine.

**Table 3. Half-time of  $^{99m}\text{Tc}$ -DMSA blood disappearance activity in patients with glomerulonephritis**

Group	T $\frac{1}{2}$		
	Minimum	Median	Maximum
Control	100	208	266
GN	112	213	392
GN-CRF	202	330 <sup>a, b</sup>	673

vs. control: <sup>a</sup>P < 0.0001; vs. GN: <sup>b</sup>P < 0.0001

kidneys, approximately one quarter in the blood, and about 10% excreted by the urine. The corresponding 4 h values were nearly one half for renal activity, while blood and urine activity were each about 20%. These results are in agreement with those obtained in other  $^{99m}\text{Tc}$ -DMSA distribution studies [4].

In both glomerulonephritis groups quantitatively altered biological behaviour of  $^{99m}\text{Tc}$ -DMSA was observed. Renal uptake was decreased, while blood activity increased. Urinary elimination during 4 h was found to be increased in patients without renal failure, but unchanged in those with insufficiency. Previous radionuclide investigations in patients with glomerular diseases [10] and experimental glomerulonephritis [11] showed also the decrease of  $^{99m}\text{Tc}$ -DMSA renal uptake.

The most important cause of altered DMSA distribution is obviously the impairment of tubular function. Tubular disorder was shown by the decrease of renal uptake, which was more remarkable in patients with renal failure. Higher percentage of renal activity increase from 2 to 4 h in glomerulonephritis patients related to healthy subjects could be due to delayed plateau achievement over normal time [14].

Although glomerular damage develops primarily, many reviews have suggested tubular injury as a prominent pattern in glomerular kidney disease [16]. The results of the present study show tubular dysfunction even in patients without renal failure. The damage of tubules is triggered by glomerular injury. Many substances produced by damaged glomeruli, such as cytokines and growth factors, play an important role in the mechanisms of tubular impairment [17]. Other important factors leading to tubular injury are ischaemia due to obliteration of peritubular capillaries and interstitial fibrosis [16, 18], as well as the action of toxic substances and immunocomplexes deposited at this level [17].

The direct consequence of the impaired tubular extraction of  $^{99m}\text{Tc}$ -DMSA is its retention in the blood. In the current study, the presence of prolonged half time was recorded only in the group with renal failure. Although the use of inadequate time periods for blood sampling (due to multiexponential blood activity fall) cannot be excluded, the intensified glomerular passage coupled with greater transfer into the organs other than kidneys should be taken into account for the lack of blood clearance alteration in patients without renal failure. On the other hand, in patients with renal insufficiency a huge reduction of tubular uptake results in slower blood clearance, in spite of elevated uptake by other organs. Such uptake was found to be normally encountered in liver and muscles, each 5% [19] and to have a decreasing tendency within 24 h period.

The increase of  $^{99m}\text{Tc}$ -DMSA urinary loss, apart from tubulopathies [8, 9], was reported to occur in lupus glomerulonephritis [20]. In our glomerulonephritis patients without renal insufficiency higher urinary elimination of  $^{99m}\text{Tc}$ -DMSA could have a different origin. The availability of greater blood amount of  $^{99m}\text{Tc}$ -DMSA for glomerular filtration may contribute to higher urinary excretion. However, the analysis of ultrathin sections of renal biopsies taken from kidneys with glomerular diseases showed glomerular lesions that lead to the reduction of blood flow and filtration surface area [21, 22]. Therefore, another factor that should be considered for the accelerated urinary elimination of this tracer is the filtration of  $^{99m}\text{Tc}$ -DMSA fraction that is bound to plasma proteins. Such an assumption is supported by electrophoretic detection of globulin fraction in the urine of glomerulonephritic patients involved in the current study (data not presented), as well as in other investigations [23, 24]. Augmented glomerular filter permeability in glomerulonephritis patients is induced by structural and charge alterations of glomeruli that result in the loss of molecule size selectivity [25]. Assuming that radiopharmaceutical reabsorption from tubular lumen occurs normally [2], the suppression of this pathway in glomerulonephritis patients could also be speculated as a factor increasing the urine activity. However, this mechanism has to be taken into account cautiously, since micropuncture and microperfusion studies of isolated rat nephron showed filtered amount of  $^{99m}\text{Tc}$ -DMSA completely excreted into the urine [26]. The lack of the increase of  $^{99m}\text{Tc}$ -DMSA urinary activity in patients with renal failure occurs probably due to advanced glomeruli loss associated with the intensive removal of the radiopharmaceutical by other organs.

In this issue quantitative alteration of  $^{99m}\text{Tc}$ -DMSA biodistribution in glomerulonephritis patients was found to be dependent on multifactorial affection. Although, the main factor altering radiopharmaceutical renal handling appears to be tubular impairment, nonselective glomerular filtration of protein bound  $^{99m}\text{Tc}$ -DMSA and its intensified transfer to other organs should also be considered to have an additional role in  $^{99m}\text{Tc}$ -DMSA biodistribution patterns in glomerulonephritis patients. The finding of higher urinary loss limits the suitability of  $^{99m}\text{Tc}$ -DMSA for quantitative estimation of renal function in patients with glomerulonephritis.

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