^{99m}Tc-DMSA renal cortical quantitative SPECT/CT imaging in diabetic patients: feasibility and initial results

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Introduction
Diabetes mellitus is a common cause of chronic kidney disease. Radionuclide imaging of the kidneys using technetium-99m-labeled dimercaptosuccinic acid (^{99m}Tc-DMSA) is a well-established method for the evaluation of kidney parenchyma. We hypothesize that early preclinical detection of renal affection in diabetic patients can be done by quantitative single-photon emission computed tomography (SPECT) imaging using ^{99m}Tc-DMSA.

Patients and methods
In this study we included 29 patients: 13 diabetic and 16 volunteers as control. All must have within normal renal function. We excluded patients with known history of renal disease or abnormal renal function, patients with systemic diseases directly affect kidney function rather than diabetes. All patients included in our study were subjected to detailed clinical history, renal function, and quantitative ^{99m}Tc-DMSA renal imaging using SPECT/computed tomography techniques. About 5 mCi of ^{99m}Tc-DMSA were injected intravenously. Then imaging was acquired after 2–4 h in the supine position using a dual-head gamma camera with a low-energy all-purpose collimator. SPECT/computed tomography images are then taken. Data were reconstructed; then a 3D ball region of interest is drawn over each kidney to assess the counts of the kidney.

Results
There was a significant difference in the mean of the BMI-corrected counts divided by the injected dose ($P = 0.024$). The same results were obtained when the counts were summed and corrected according to the injected dose between the two groups ($P = 0.034$).

Conclusion
Quantitative SPECT ^{99m}Tc-DMSA imaging may have a role in the evaluation of renal functions in diabetics with no clinical evidence of renal affection.

Keywords:
diabetic patients, quantitative SPECT/CT, ^{99m}Tc-DMSA

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Background

The world prevalence of diabetes mellitus (DM) between adults (age 20–79 years) is 6.4%, affecting 285 million adults, in 2010, and is expected to increase to 7.7%, and 439 million adults by 2030 [1].

Chronic kidney disease (CKD) is defined as kidney damage or glomerular filtration rate (GFR) of less than 60 ml/min/1.73 m^2 for 3 months or more, whatever the cause. Kidney damage in many kidney diseases can be detected by the presence of albuminuria, defined as an albumin-to-creatinine ratio of more than 30 mg/g in two of the three spot urine specimens. Severity of the kidney disease is classified into five stages according to the level of GFR [2].

CKD is a worldwide public health problem. The number of patients enrolled with end-stage renal disease (ESRD) has increased from about 10 000 in 1973 to 661 648 in 2013 [3]. DM is a common cause of CKD; it is the most common cause of ESRD in the UK [4].

Assessment of GFR is essential for estimating the prognosis of CKD. The first widely used GFR estimating equations were developed in the 1970s to estimate creatinine clearance in adults from the serum creatinine level. Now, a number of new equations are developed for use with standardized serum creatinine levels and have gained worldwide acceptance for implementation into clinical practice as a 'first test' for assessing GFR in adults [5]. GFR can also be evaluated by renal radioisotope scan (diethylenetriamine pentaacetic acid study), whereas radionuclide imaging of the kidneys using technetium-99m-labeled dimercaptosuccinic

acid (^{99m}Tc-DMSA) is a well-established method for the evaluation of kidney parenchymal involvement [6]. Early detection of impaired renal function (tubular function) can be detected by ^{99m}Tc-DMSA. Rajić *et al*. [7] recommended the assessment of renal function in different stages of type 1 DM by radionuclide methods together with the determination of urinary albumin excretion rate to achieve a more reliable staging of diabetic kidney disease (DKD). The demonstration of glomerular hyperfiltration and tubular hyperfunction by radiopharmaceuticals contributes to the early detection of DKD, whereas the quantification of renal function allows the follow-up of progressive function loss later on in the course of the disease [7].

The aim of this prospective study was to evaluate the possible role of dimercaptosuccinic acid (DMSA) to detect renal affection in diabetic patients compared with nondiabetic cases.

Patients and methods

In this case–control study, we evaluated the renal uptake (right and left kidney count in single-photon emission computed tomography/computed tomography (SPECT/CT) images summed and corrected according to BMI and divided by the injected dose) in control and cases (Fig. 1).

We included known diabetic patients, all must have within normal renal function tests (urea and creatinine). We excluded patients with known history of renal disease or abnormal renal function, patients with systemic diseases directly affecting kidney function rather than diabetes, for example, systemic lupus, heart failure or liver cell failure, patients receiving drugs affecting kidney function like chemotherapy. Control cases are volunteers with no history of renal problem or any other disease known to affect kidney function and with normal renal function. After obtaining ethical approval from the ethics committee, all patients included in our study were subjected to detailed clinical history (including age, sex, if there is renal complaint or not, in control or diseased case, if diseased: duration of the disease, controlled or not, medication received, type 1 or type 2), renal function, and quantitative ^{99m}Tc-DMSA renal imaging using the SPECT/CT technique.

^{99m}Tc-DMSA was prepared using a commercially available DMSA kit. About 5 mCi (185 MBq) of ^{99m}Tc-DMSA was injected intravenously, then imaging of the patient was acquired after 2–4 h in the supine position using a dual-head gamma camera fitted with a low-energy all-purpose collimator, using a 20% energy window set at 140 KeV collimator. SPECT/CT images are taken: 120 projections, each for 25 s in a noncircular 360° arc and using a 128 × 128 matrix size, low-energy all-purpose collimator, matrix, zoom: 1. All precautions were taken to avoid movement. Quality control using phantom was done to determine the threshold of semiautomated processing.

SPECT/CT data were viewed and reconstructed using the flash 3D iterative algorithm (eight iterations, four subsets, Gaussian 8 mm filter) to generate transaxial, coronal, and sagittal cuts. The reconstruction was performed with attenuation correction (CT-based) using Osirix software (Image Processing software Osirix, Open source software; www.osirixviewer.com). After reconstruction, region of interest (3D ball) is drawn over each kidney in the sagittal view to assess the counts of the kidney according to the threshold obtained from phantom studies (40%). In our study, to optimally segment the kidneys, we first performed multiple phantom studies to obtain the optimum threshold for renal segmentation.

We compared the mean of the total count of control cases with the mean of the total count of patients using a *t*-test to know if the count in two groups show a significant difference or not. Commercially available software (SPSS for windows, Version 16.0, Chicago, SPSS Inc.) was used for the statistical analysis. A *P* values less than 0.05 was considered significant.

Results

Demographic data

It included 29 cases (13 diabetic patients and 16 controls). They were referred to the South Egypt Cancer Institute for functional quantitative renal radionuclide imaging using ^{99m}Tc-DMSA [Tables 1-3].

Right and left kidney parameters in controls

All paired values (right and left) showed a significant strong correlation of more than 80%. The right kidney SPECT total count and left kidney SPECT total were more than 93%.

Right and left parameters in the diabetic group

All paired values (right and left) showed moderate to strong correlation of more than 60%. Right kidney SPECT total count and left kidney SPECT total count in the diabetic group showed a strong correlation of more than 97%. No significant difference in renal parameters was seen between right and left kidneys, except one patient who had unilateral atrophic

kidney (differential function: left kidney 96.98% and right kidney 3.02%).

As the counts obtained from each kidney were found to correlate separately with the contralateral kidney, the counts from right and left kidneys were summed. Furthermore, to eliminate the effect of body size, the counts were corrected for BMI. Also, for more accurate results and to eliminate the factor of changing the dose, the counts were corrected also according to the injected dose.

After the counts were corrected according to BMI and the injected dose, there was a statistically significant difference in the mean of the BMI-corrected SPECT total counts between the two groups ($P = 0.024$).

The same results were obtained when we corrected the summed total counts according to the injected dose; there was a significant difference in the mean of the summed total counts divided by the injected dose between the two groups ($P = 0.034$).

Control of the disease

The effect of disease control on renal parameters could not be assessed in this group as all cases were uncontrolled (at presentation, random blood sugar was >180 mg/dl) except one case.

Duration of the disease

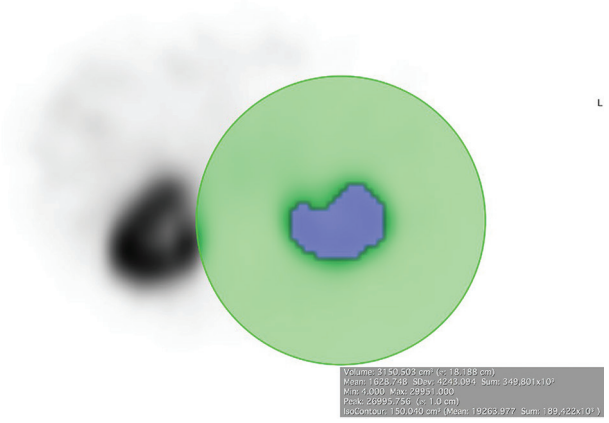
Duration of the disease has a significant impact on renal dysfunction. Cases with long duration of the disease (>10 years) have a percentage of uptake that ranged from 9.8 to 66%, whereas cases with short duration of the disease (<10 years) have a percentage of uptake that ranged from 74 to 99.7%. There is an inverse relationship between the duration of disease and percentage of uptake (Fig. 1 and Tables 1–3).

Discussion

The usual method to evaluate CKD is evaluation of GFR either by ^{99m}Tc-DMSA or by estimated GFR using serum creatinine level. In this study, we used ^{99m}Tc-DMSA to evaluate renal cortical function as a predictor to DKD instead of GFR evaluation by ^{99m}Tc-DMSA. Early changes in DKD include glomerular hyperfiltration, glomerular, and tubular epithelial hypertrophy [8].

Preclinical detection of impaired renal cortical function can be detected by ^{99m}Tc-DMSA. The challenge of quantifying DMSA counts from SPECT renal acquisitions is to accurately delineate the kidneys.

Figure 1



3D ball region of interest drawn on reconstructed kidneys.

Table 1 Distribution according to sex

Cases	Control	Patients
Total number	16	13
Men	8	8
Women	8	5

Table 2 Demographic data of control

	Median (range)	Mean±SD
Age	37 (22-69)	40±13.828
Weight	78.5 (48-107)	75.44±14.519
Height	165 (153-170)	164.88±4.66
BMI	28.155 (17.63-37.02)	27.8234±5.5636
Body surface area	1.83 (1.51-2.17)	1.818±0.1576

Table 3 Demographic data of diabetic patients

	Median (range)	Mean±SD
Patient age	50.5 (18-68)	47.67±16.571
Weight	79 (46-90)	77±11.939
Height	167 (152-177)	167.58±8.73
BMI	27.87 (19.91-33.06)	27.334±3.3443
Body surface area	1.91 (1.4-2.06)	1.8642±0.8108
Duration of diabetes mellitus	12 (0.5-22)	11.79±5.758

A previous study by Rajić and colleagues assessed the renal function in different stages of type 1 DM by radionuclide methods. In that study, 53 patients with DM were classified into four groups: normoalbuminuric (NA, 18 patients), microalbuminuric (12 patients), macroalbuminuric (13 patients), and chronic renal failure group (10 patients). Quantitation was done by the calculation of GFR and percentage of injected dose in planer DMSA. GFR was estimated by ^{99m}Tc-DMSA clearance rate, whereas tubular function was calculated by planner ^{99m}Tc-DMSA. In addition, ^{99m}Tc-DMSA clearance was correlated with the estimated GFR using the modified Modification of Diet in Renal Disease Study Group formula.

They found that ^{99m}Tc-DMSA clearance and ^{99m}Tc-DMSA fixation were significantly higher in

the normoalbuminuric group (P < 0.05 and <0.02, respectively), unchanged in the microalbuminuric group (P > 0.05, >0.05, respectively), and decreased in both macroalbuminuric (P < 0.0001, <0.00001, respectively) and chronic renal failure groups (P < 0.0001, <0.00001, respectively) [7].

Their study differs from our study in few aspects. First, they included patients with type I DM, whereas we included both. Second, the included patients already have clinical renal disease. Third, their method for quantifying DMSA uptake was different in that they calculated the counts of the kidney in posterior view only and in planner not SPECT, whereas we calculated the counts in SPECT after reconstruction.

Another study by Wu *et al*. [9] compared three groups of patients: 28 control women without type 2 DM and a history of urinary tract infections (UTIs), 25 male patients with type 2 DM but without a history of UTIs, and 103 female patients with type 2 DM using ^{99m}Tc-DMSA renal scan (planer only). The 103 women with type 2 DM were separated into three groups: 36 women without a history of UTIs, 34 patients with a history of cystitis only, and 33 with a history of pyelonephritis. They found that all the control women and male patients with type 2 DM without a history of UTIs had normal ^{99m}Tc-DMSA renal scan findings. However, 39.8% of women with type 2 DM had abnormal ^{99m}Tc-DMSA renal scan findings. They agreed with us that we should use ^{99m}Tc-DMSA renal scanning to investigate renal damage in patients with type 2 DM especially if they have a history of UTIs [9]. In that study, Wu *et al*. [9] performed only visual assessment of the kidneys, whereas in our study we also used quantitation.

A study by Yang *et al*. [10] measured the functional renal volume by ^{99m}Tc-DMSA SPECT in diabetic patients with or without proteinuria (15 diabetic patients and two patients with ESRD due to chronic glomerulonephritis) and control group (18 renal transplantation donors). In diabetic patients with creatinine clearance more than 30 ml/min and proteinuria, right and left renal volumes were greater than those of diabetic patients with normal renal function and without proteinuria, or renal transplantation donors (P < 0.05). That study recommended ^{99m}Tc-DMSA SPECT as a useful test for the measurement of functioning renal volume [10]. Their study focused on the measurement of functioning renal volume rather than counts as we did in our study. In addition, we did not measure urinary protein excretion in our study.

Quantitative ^{99m}Tc-DMSA could be used with other tools of investigations for the diagnosis of CKD in diabetic patients with no evidence of renal affection. Further studies may be needed to confirm or exclude these findings.

We recommend the use of quantitative ^{99m}Tc-DMSA in all diabetic patients and do follow-up quantitative ^{99m}Tc-DMSA to monitor the kidney function even without any renal complaints.

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Conflicts of interest
There are no conflicts of interest.

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