Diagnostic Tools for Sensitive Estimation of Renal Function & Early Detection of Lupus Nephritis

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ABSTRACT

Introduction: Systemic Lupus Erythematous (SLE) is a systemic autoimmune disease where the immune system mistakenly attacks the body cells and tissues, resulting in a state of chronic inflammation and tissue damage. SLE is characterized by unpredictable course, with periods of flares alternating with remissions. It can affect any part or body tissues, including heart, joints, skin, lungs, liver, nervous system, blood vessels, but still the kidney affection is one of the most commonly involved visceral organs in SLE. Although only approximately 50% of patients with SLE develop clinically evident renal disease, biopsy studies demonstrate some degree of renal involvement in most patients. Acute or chronic renal impairment may develop with lupus nephritis leading to acute or end stage renal disease. Early recognition and management of these cases can reduce the percentage of development of end stage renal disease among these patients to less than 5% of cases. Nephron is the functioning unit of the kidney, whose function is always effected as an early response to inflammation; this function can be evaluated through the estimation of the glomerular filtration rate (secretory function) as well as its excretory function. So searching for a more sensitive and specific indicator for early detection of disease flare or activity depends on the estimation of the nephron function.

Aims of the study: The aims of the study are: to evaluate the most sensitive and accurate diagnostic tool to assess glomerular function and glomerular filtration rate (GFR) in lupus nephritis patients, in relation to clinical manifestations and laboratory indices, as a trial for early detection of lupus nephritis, to investigate whether dynamic renal 99mTechnetium Diethylene Triamine Penta Acetic Acid (99mTc-DTPA) Glomerular Filtration Rate (GFR) is a more sensitive indicator of the degree of renal involvement in lupus nephritis patients than laboratory measurement of serum creatinine level and creatinine clearance (CrCl) through estimated Glomerular Filtration Rate (eGFR) formulae, and to assess renal morphology by static renal 99mTechnetium Di-Mercapto Succinic Acid (99mTc-DMSA), as well as split function of both kidneys in view of renal ultrasonography (U/S).

Patients & Methods: Twenty-eight patients with biopsy-proven lupus nephritis selected according to WHO classification for renal staging. The disease activity was recorded using Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) to detect active disease requiring increased treatment for activity. Immunological profiles, including ANA, anti-dsDNA, complement levels (C3, C4) were assessed. Kidney function tests, including serum creatinine, blood urea nitrogen (BUN), creatinine clearance (CrCl), glomerular filtration rate (GFR) using Cockcroft–Gault (CG),the 4-variable abbreviated Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration Formula (CKD-EPI) method, urinalysis with microscopy, 24 hours urinary proteins, as well as total serum proteins and serum albumin were measured. Dynamic 99mTechnetium labeled with Diehtylene Triamine Penta Acetic Acid (99mTc-DTPA) radioisotope renal scan was done for all patients as a part of assessment of renal GFR in all patients in the study group. Another static study was done using 99mTechnetium Di-Mercapto Succinic Acid (99mTc DMSA) to assess the morphological status as well as the split function of both kidneys in view of renal ultrasonography.

Results: This study was carried out on 28 patients: 9 males (32.1%) and 19 females (67.9%).Their age ranged from (16 - 44 years) with a mean age (23.57± 9.57 years). Their height ranged from (147 - 169cm) with a mean height (155.14±7.97) and weight ranged from (37- 84.5 kg) with a mean weight (59.66±16.69). As regards the renal histopathology results, 4 patients (14.28%) had mesangial glomerulonephritis, 15 patients (53.57%) had focal proliferative glomerulonephritis, 6 patients (21.42%) had diffuse proliferative glomerulonephritis, and 3 patients (10.71%) had membranous glomerulonephritis. In patients with impaired renal function the 99mTc-DTPA GFR values and C-G estimated GFR values was decreased significantly with P value <0.05, however, that GFR values obtained by the C-G estimated formula showed a total bias (– 15 ml/min/1.73m2) and relative bias (-21%). Whereas, the estimated GFR obtained by MDRD, and CKD-EPI equations are still markedly underestimating the GFR values, among the same group of patients with total bias (-28 & -26 ml/min/1.73m2) and relative bias (-40% & - 37%) respectively. MDRD as well as CKD-EPI equations for estimation of GFR tend to underestimate the GFR value among patients with impaired renal functions. In the patients group with preserved (normal or near normal renal function) the measured GFR by 99mTc-DTPA dynamic renal scintigraphy showed a comparable results to that obtained from the C-G equations total bias (-5 ml/min/1.73m2) and relative bias (-5%), whereas, the GFR values are much higher in equations of MDRD, and CKD-EPI with a total bias (+5 & + 10 ml/min/1.73m2) and a relative bias (+5% & +10%) respectively. MDRD as well as CKD-EPI equations for estimation of GFR tend to overestimate the GFR value among patients with normal or near normal renal functions. There was a significant decrease in the 99mTc-DTPA measured GFR value among patients with stage III and stage IV glomerulonephritis, with a P value < 0.05, Whereas, the GFR values obtained by the C-G formula showed significant decrease only among patients with stage IV glomerulonephritis (P value = 0.016). On the other hand, (MDRD & CKD-EPI formulae) showed insignificant decreased GFR values among patients with stage III & stage IV glomerulonephritis, but they showed significantly increased GFR values among patients with stage II & stage V glomerulonephritis.

Conclusion: 99mTc-DTPA as a glomerular agent provides a sensitive, physiological, reliable, accurate and reproducible method for assessment of renal function throughout different disease stages in patients with confirmed diagnosis of lupus nephritis (LN), when compared to other methods evaluating renal function in these patients. It provided a proper evaluation of the nephron function, including renal blood flow condition, the secretory function of the nephrons, as well as nephron's excretory function before and after intravenous diuretics injection. Besides, 99mTc-DMSA as a tubular agent provides a sensitive morphological image of the kidney that can help in estimation of the split function of both kidneys as well as evaluation of the disease course, compared to the traditional morphological imaging modalities (renal ultrasonography).

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1. Introduction:

Systemic lupus erythematous (SLE) is a prototypic autoimmune disease characterized by the production of antibodies to components of the cell nucleus in association with a diverse array of clinical manifestations. The typical age of onset of SLE falls during the reproductive years, and postpartum and during periods of rapid hormonal changes (Mok & Lau, 2003).

Lupus comprises a range of multisystem disorders involving the deposition of aberrant immune complexes into tissues. Inflammation occurs as a result of autoantibodies attacking organ systems (Childs, 2006).

The primary pathological findings in patients with SLE are those of inflammation, vasculitis, immune complex deposition, and vasculopathy. The exact etiology of SLE is unknown. SLE may coexist with other organ specific autoimmune diseases such as hemolytic anemia, immune thrombocytopenic purpura, and thyroiditis (Mok & Lau, 2003).

It causes inflammation in the tissues of the brain, endothelial cells, gastrointestinal, genitourinary, joints, kidneys, muscles, and skin (Childs, 2006). Renal disease is one of the most common and most serious manifestations of SLE. Systemic lupus erythematosus may present with renal manifestations that frequently are difficult to categorize and lupus nephritis is an important

predictor of poor outcome. The type and spectrum of renal injury may remain undiagnosed until full-blown nephritic and/or nephritic syndrome appears with increased risk of end-stage renal disease. These abnormalities occur within the first few years after the diagnosis of lupus is made on clinical grounds and with the support of laboratory tests in high-risk patients (Ortega et al., 2010).

Renal involvement in SLE adversely affects its ultimate prognosis in terms of patient survival and renal survival (survival without the need for renal replacement therapy) rates, as well as quality of life, including work disability (Mok et al., 1999). The glomerulus is the most common site of kidney involvement by lupus. However, the renal interstitium and tubules, as well as the vasculature, may also be affected (Cross & Jayne, 2005). Early recognition of renal disease and close monitoring for progress after treatment is an essential part of management.

The clinical course of SLE is characterized by periods of remissions and acute or chronic relapses. Despite the overall improvement in the care of SLE in the past two decades, the prognosis of lupus nephritis remains unsatisfactory. Up to 25% of patients still develop end-stage renal failure 10 years after onset of renal disease. Relapses occur frequently in patients with Lupus nephritis, so early disease relapse detection allows proper early treatment. Treatment is based on preventive measures, reversal of inflammation, and prevention of organ impairment and alleviation of symptoms (Ortega et al., 2010).

In order to improve the prognosis of lupus nephritis in SLE, more sensitive and specific diagnostic tools for the onset or relapse of renal disease activity in patients with SLE may allow earlier institution of treatment and even preventive strategies so that the efficacy of existing therapies can be enhanced while treatment-related complications can be minimized (Mok, 2010).

Renal biopsy is the gold standard for assessing renal activity and hence guiding the treatment. Early recognition of renal disease and close monitoring for progress after treatment is an essential part of management (Ortega et al., 2010). Here, we are trying to find a sensitive and accurate diagnostic tool for early detection of lupus nephritis or relapse. Many trials were used to assess nephron function through estimating the glomerular filtration rate (GFR). Calculation of GFR using an empirical mathematical formula has been encouraged as a simple, rapid and reliable means of assessing kidney function. But there are now fewer than 46 different prediction equations currently available, although the two most commonly used are the Cockcroft-Gault (C-G), and Modification of Diet in Renal Disease (MDRD) formulas (Levey et al., 1999), and more recently, Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Levey et al., 2009).

Estimation of GFR proven to be less prone to errors than using 24-hour urine collections for creatinine clearance and is recommended by guideline- issuing organizations like the National Kidney Foundation (NKF) that recommended to estimate GFR with prediction equations based on serum creatinine determinations (Botev et al., 2009).

The Cockcroft-Gault (C-G) formula is based on serum creatinine, age, sex and body weight (Cockcroft & Gault, 1976). Many MDRD equations were used; the most commonly used one is the abbreviated (simplified) 4-variable MDRD equation which relies entirely on determination of serum creatinine, eliminating the need for urea and albumin and so allows estimation of the GFR even if albumin is not checked. It provides computer-generated estimates of GFR with minimal impact on accuracy. (Levey et al., 2000).

CKD guidelines have provided definitions of CKD, and recommend an estimated glomerular filtration rate (GFR) as the best overall measure of kidney function. Unlike measures of creatinine or urea clearance, the MDRD equation does not require 24-hour urine collection, which is prone to errors and is inconvenient for patients (Levey et al., 2000).

The new Chronic Kidney Disease Epidemiology Collaboration Formula (CKD-EPI) equation was developed by Levey and his colleagues in 2009 in an effort to create a formula more accurate than the MDRD formula, especially when actual GFR is greater than 60 ml/min per 1.73 m2 (Levey et al., 2009).

Radionuclide renal studies can assess both renal function through the dynamic study with a glomerular agent like (99mTc-DTPA) and morphology through the static imaging using tubular agent like (99mTc- DMSA). Scintigraphy with 99mTc-dimercapto succinic acid (DMSA) is considered a reference method for assessment of parenchymal lesions and estimation of differential kidney function (Smokvina et al., 2005).

2. Patients & Methods:

This study was carried out on 28 SLE patients who were attending the outpatient clinic, or were admitted to the inpatient unit of the Rheumatology Department at King Fahd Specialist Hospital (KFSH) - Buraidah - Kingdom of Saudi Arabia (KSA).

All Patients fulfilled the updated revised criteria of the American College of Rheumatology for classification of Systemic Lupus Erythematosus (Hochberg, 1997). Clinical and laboratory evidence of renal disease was defined as varying combinations of the following: 3+ proteinuria, urine protein > 0.5

gm/24h, creatinine clearance < 60 ml/min, diastolic blood pressure > 90 mmHg or serum creatinine >150 µmol/l, (1.5 mg/dl).

The clinical disease activity was recorded using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). It is a weighted cumulative index of lupus disease activity. The SLEDAI is an index that measures disease activity by weighting the importance of each organ system involved. Activity categories have been defined on the basis of SLEDAI scores: no activity (SLEDAI = 0), mild activity (SLEDAI = 1-5), moderate activity (SLEDAI = 6-10), high activity (SLEDAI = 11-19), and very high activity (SLEDAI 20).

A flare of SLE has been defined as an increase in SLEDAI > 3, and a SLEDAI score > 5 is associated with a probability of initiating or changing therapy in more than50% of instances (Bombardier et al., 1992). Disease activity was recorded first at the time of renal biopsy and at the time of DTPA assessment.

All patients were diagnosed histopathologically by renal biopsy. These biopsies were performed during the course of assessment and management of the disease. Renal biopsy was done by ultrasound- guided percutaneous puncture and all renal biopsies were assessed by a pathologist and classified according to the abbreviated International Society of Nephrology/ Renal

Pathology Society (ISN/RPS) classification of lupus nephritis (2003):

Class I Minimal mesangial lupus nephritis.

Class II Mesangial proliferative lupus nephritis.

Class III Focal lupus nephritis (a).

Class IV Diffuse segmental (IV-S) or global (IV-G) lupus nephritis (b) Class V Membranous lupus nephritis (c).

Class VI Advanced sclerosing lupus nephritis.

(a) Indicate the proportion of glomeruli with active and with sclerotic lesions.

(b) Indicate the proportion of glomeruli with fibrinoid necrosis and cellular crescents.

(c) Class V may occur in combination with class III or IV in which case both will be diagnosed. Indicate and grade (mild, moderate, severe) tubular atrophy, interstitial inflammation and fibrosis, severity of arteriosclerosis or other vascular lesions (Weening et al., 2004).

All patients were subjected to thorough history taking, full clinical examination, and relevant laboratory investigations.

Laboratory investigations included: CBC, including hemoglobin levels, total leucocyte count, lymphocyte count, and platelet count, Erythrocyte

Sedimentation Rate (ESR) by Westergren method, complement levels (C3 and C4), antinuclear antibodies (ANA), anti-double stranded DNA antibodies (anti-dsDNA) using the indirect immunofluorescent antibody test, blood chemistry, including serum urea, serum creatinine, serum total proteins, serum albumin, serum calcium, serum phosphorus, routine urine analysis with microscopy for presence of pus cells, presence of RBCs , and abnormal sediments (casts). In addition, 24 hour urine proteins as well as creatinine clearance were done.

Ultrasonography (U/S) assessment for both kidneys was done by the aid of state of the art (General Electric Ultrasound Machine, Logic 9 model), and by using a deep probe (3-5 MHz). Images were taken while the patients were at supine as well as at lateral positions.

Estimation of glomerular filtration rate (GFR) using three formulae namely Cockcroft–Gault (C-G) Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD- EPI) Formulae was performed.

Glomerular filtration rate (GFR) is accepted as the best overall measure of kidney function. Normal values, which are related to age, sex, and body size, are approximately 130 ml per minute per 1.73 m2 in young men and 120 ml per minute per 1.73 m2 in young women, taking into consideration that mean values decline with a person's age.

The Cockcroft-Gault (C-G) formula is based on serum creatinine, age, sex and body weight (Cockcroft &Gault, 1976).

The CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula was developed by Levey and his colleagues in 2009 in an effort to create a formula more accurate than the MDRD formula, especially when actual GFR is greater than 60 ml/min per 1.73 m2 (Levey et al., 2009).

Measurement of GFR uses dynamic 99mTc-DTPA renal isotope scan: Individuals then underwent renal dynamic99mTc-DTPA and static 99mTc-DMSA studies with proper hydration confirmed before starting the study. Explanation of the technique of the study and all the recommended precautions was done before insertion of the IV line. Dynamic99mTc-DTPA renal isotope scan was performed as follows:
99mTc-DTPA was dosed at 100µCi/Kg (with total adult dose about 300MBq) was injected intravenously according to the following imaging protocol:

A pre-syringe image was taken for 60 seconds for the prepared radioactive dose before being injected inside the patient with detector posterior to the syringe).

Injection of the patient was done in the gamma camera room while the dynamic phases of the study were being taken by the aid of state of the art large field of view gamma camera fitted with low energy general purpose (LEGP) collimator, with energy peak at 99mTc (140 Kev and 20% window) and adjusted at

the region of interest (kidneys at posterior view). Serial dynamic images were taken every 1 second for 60 seconds. Then, second group dynamic images were taken every 15 seconds for 29 minutes. At the 10thminute, 40mg IV furosemide injection was done.

A post-syringe image was taken for 60 seconds for the residual99mTc- DTPA radioactive dose after being injected inside the patient with the detector being posterior to the syringe.

Patient's weight and height were taken for further processing of the imaging data for further evaluation of the GFR of the patient as well as split function of both kidneys by using (Gates' equation and technique).

Static 99mTc-DMSA scan was performed as follows:

1) Adjustment of the dose of the 99mTc-DMSA at 50µCi/Kg, with total adult dose about 100MBq = 2.7 mCi. Injection of the patient was done in the preparation (injection) room.
2) Wait for 120 minutes before taking anterior & posterior images for the patient in the gamma camera room by the aid of state of the art large field of view gamma camera fitted with LEGP collimator, with energy peak at 99mTc (140 Kev and 20% window).
3) Imaging field was adjusted in the kidney area (site of interest) taking into consideration the upper parts of the urinary bladder to appear at the bottom of the field of view. The duration of imaging was for 500-1000 K. count.

Exclusion Criteria:

Patients excluded from our study include: a patient with malnutrition, a patient under age of 16 years or more than 45 years, pregnant females or a patient with hyperthyroidism. In addition, a patient in remission or has a disease activity less than 6 according to SLEDAI score.

Statistical Methods:

The performance of C-G, MDRD, and CKD-EPI formulae was assessed by the following criteria, in which mGFR is deemed as the true value for comparison purposes:

Total bias = mean difference between eGFR and mGFR values.

Relative bias = mean percentage difference; that is, $[(eGFR - mGFR)/mGFR] \times 100$.

3. Results:

This study was carried out on 28 patients: 9 males (32.1%) and 19 females (67.9%). Their age ranged from 16 years to 44 years with mean age (23.57± 9.57 years), their height ranged from 147 - 169 cm with mean height (155.14±7.97), and their weight ranged from 37 - 84.5 Kg with mean weight (59.66±16.69). All patients had biopsy-proven lupus nephritis with disease duration ranging between 4weeks and 24 weeks with mean disease duration (16.9 ± 4.54weeks). According to SLEDAI score, eighteen patients (64.3%) had mild to moderate disease flare with SLEDAI score ranging between 6-10, and ten patients (35.7 %) had severe disease flare with SLEDAI score ≤ 11.

As regards the renal histopathology results; 15 patients (53.57%) had focal proliferative glomerulonephritis, 6 patients (21.42%) had diffuse proliferative glomerulonephritis, 4 patients (14.28%) had mesangial glomerulonephritis, and 3 patients (10.71%) had membranous glomerulonephritis.

Six out of the 28 patients (21.4%) had associated bronchial asthma. During the disease course, 6 out of the 28 patients (21.4%) developed diabetes. All patients in study group were normotensive.

Demographic results of our study revealed that the 24-hour urine protein level ranged between 0.71–7.22gm/day with mean (2.24 ± 2.10 gm/d), whereas, the total serum protein level ranged between 40.9 – 67.9 gm/dl with mean (52.78 ± 11.59), whereas serum albumin level ranged between 15-33gm/dl with mean (25.13±7.58µmol/l).

Serum creatinine level ranged between 85-209 µmol/l with a mean (125.4 ± 29.15), 24-hour urinary creatinine level ranged between 3680-8592mg/day with mean value (6135.2 ± 1206.84); whereas, the creatinine clearance ranged between 25-106ml/min, with mean (76.86 ± 17.43).

Immunological profile for patients of the study group revealed that the Anti- dsDNA serum level ranged from 64-787 U/mL, with mean (238.89± 195.76), whereas, serum Complement-3 (C3) ranged from 0.3-1.0 g/L with mean (0.71±0.28), and Complement-4 (C4) ranged from 0.8-1.0 g/L with mean (0.58±0.34), Table (1) showed this demographic data.

Table (2) showed the demographic data for the patients as regard the results of the total renal GFR estimated and/or measured by different methods, and revealed that the Total renal GFR calculated by Cockcroft-Gault (C-G) ranged from 34.62 – 106.64 ml/min/1.73m2 with mean value (76.31 ± 26.36), whereas this value ranged from 42-120 ml/min/1.73m2 with mean value (84 ± 24.02) when calculated by MDRD. By the CKD-EPI method, estimated total renal GFR value ranged from 48 – 132 ml/min/1.73m2 with mean value (100.92 ± 26.55). On Dynamic renal study to assess the renal GFR using 99mTc-DTPA, total renal GFR value ranged from 27-106 ml/min/1.73m2 with mean value (84.63 ± 24.9).

Table 1: *Demographic Data of Patients in the Study Group:*

Parameters	Minimum and Maximum	Average	Mean ± SD
Age in years	16-44	23.57	23.57± 9.57
Weight	37-84	47.50	
Height	147-169	153	155.15±7.89
Duration of Renal disease (weeks)	4-24	14	16.9 ± 4.54
24-h urinary protein (gm/day).	0.71 – 7.22	2.23	2.24 ± 2.10
Total serum protein (gm/dl)	40.9 - 67.9	52.78	52.78±11.59
Serum albumin (gm/dl)	15-33	25.13	25.13±7.58
Serum creatinine (umol/l)	85-209	125.4	125.4±29.15
creatinine24h urine (mg/day)	3680-8592	6135.5	6135.6±1206.84
Creatinine clearance	25-106	76.86	76.86±17.43
Anti-dsDNA	64.00-787.00	239	238.89±195.76
C3	0.30-1.0	0.7	0.71±0.28
C4	0.8-1.0	0.5	0.58±0.34

Table 2: *Demographic data of the total Glomerular Filtration Rate (GFR) estimated and/or measured by different modalities for study group:*

Parameters	Range	Mean ± SD
C-G - GFR	34.62-106.64	76.31±26.36
MDRD	42.00-120.00	84.00±24.02
CKDEPI	48.00-132.00	100.92±26.55
^{99m}Tc-DTPA TOTAL GFR	27-106	84.63±24.90
Split Lt kidney Function %	47-54	50.5±5.08
Split Rt kidney Function %	46-53	49.5±5.08
Rt kidney DTPA - GFR	27-54	38.24±12.93
Lt kidney DTP - GFR	26-53	41.37±12.30

In comparison between the total estimated and/or measured renal GFR by different methods and the renal function among patients included in the study revealed that: there was a significant decrease in the GFR values obtained by 99mTc-DTPA as well as C-G formula in patients with impaired renal function (serum creatinine > 135 µmol/min) P value < 0.05, whereas, the total renal GFR estimated by MDRD and CKD-EPI formulae, decrease insignificantly in patients with impaired renal function (serum creatinine > 135 µmol/min) p value > 0.05. All methods gives a significant normal GFR values in patients with preserved renal function P value = 0.0001 table (3).

Table 3: *Comparison between different methods of GFR estimation in view of renal function:*

Parameter	Patients with impaired renal function (18)	P value	Patients with preserved renal function (10)	P Value
Total ^{99m}Tc-DTPA - mGFR	70.31±7.86	0.002*	95.25±6.75	0.0001*
C-G – eGFR	54.94±3.14	0.049*	90.72±5.21	0.0001*
MDRD - eGFR	42.62±5.36	0.66	100.78±9.32	0.0001*
CKD-EPI- eGFR	44.28±7.64	0.55	110.97±8.61	0.0001*

*P value < 0.05 is considered to be significant.

Comparison between the GFR values obtained by different GFR estimation methods in patients with impaired renal function revealed that in patients with impaired renal function the 99mTc-DTPA GFR values and C-G estimated GFR values was decreased significantly with P value <0.05, however, that GFR values obtained by C-G estimated formula showed a total bias (– 15 ml/min/1.73m2) and relative bias (-21%). Whereas, the estimated GFR obtained by MDRD, and CKD-EPI equations are still markedly underestimating the GFR values, among the same group of patients with total bias (-28 & -26 ml/min/1.73m2) and relative bias (-40% & - 37%) respectively.

MDRD as well as CKD-EPI equations for estimation of GFR tend to underestimate the GFR value among patients with impaired renal functions table (4).

Table 4: *Comparison between different methods of GFR estimation in view of impaired renal function:*

Parameter	**Total ^{99m}Tc-DTPA –mGFR 70.31±7.86**	**P value**	**Total bias**	**Relative bias**
C-G eGFR	54.94±3.14	0.0409*	-15	-21%
MDRD eGFR	42.62±5.36	0.0001*	-28	-40%
CKD-EPI eGFR	44.28±7.64	0.00004*	-26	-37%

*P value < 0.05 is considered to be significant.

In patients group with preserved (normal or near normal renal function) the measured GFR by 99mTc-DTPA dynamic renal scintigraphy showed a comparable results to that obtained by the C-G equations total bias (-5 ml/min/1.73m2) and relative bias (-5%), whereas, the GFR values are much higher in equations of MDRD, and CKD-EPI with a total bias (+5 & + 10 ml/min/1.73m2) and a relative bias (+5% & +10%) respectively.

MDRD as well as CKD-EPI equations for estimation of GFR tend to overestimate the GFR value among patients with normal or near normal renal functions table (5).

Table 5: *Comparison between different methods of GFR estimation in view of normal renal function:*

Parameter	**Total 99m Tc- DTPA –mGFR 95.25±6.75**	**P value**	**Total bias**	**Relative bias**
C-G – eGFR	90.72±5.21	0.28	-5	-5%
MDRD - eGFR	100.78±9.32	0.07	+5	+5%
CKD-EPI- eGFR	110.97±8.61	0.076	+10	+10%

*P value < 0.05 is considered to be significant.

Comparison between the GFR values (obtained by different methods of estimated and/or measured GFR) and the renal histoptahological data revealed that: there was a significant decrease in the 99mTc-DTPA measured GFR value among patients with stage III and stage IV glomerulonephritis, with P value < 0.05, Whereas, the GFR values obtained by C-G formula showed significant decrease only among patients with stage IV glomerulonephritis (P value = 0.016). Both methods gave significant normal values among patients with stage II and stage V glomerulonephritis, P value = 0.0001. On the other hand, (MDRD & CKD-EPI formulae) showed insignificant decreased GFR values among patients with stage III & stage IV glomerulonephritis, but they showed significantly increased GFR values among patients with stage II & stage V glomerulonephritis table (6).

Table 6: *Comparison between different methods of GFR estimation in view of the histopathology results:*

Parameter	Stage II mesangial lupus nephritis (4)14.28%	Stage III focal lupus nephritis (15) 53.57%	Stage IV diffuse lupus nephritis (6) 21.42%	Stage V membranous lupus nephritis (3) 10.71%
Total 99mTc-DTPA – mGFR	93±2.4 P value =0.001*	75±5.3 P value =0.05*	64±3.6 P value= 0.0002*	103±2.9 P value = 0.0001*
C-G - eGFR	90±2.6 P value =0.0001*	55±1.7 P value =0.9	49±4.3 P value=0.016*	98±8.6 P value = 0.0001*
MDRD - eGFR	110±4.5 P value =0.001*	41±2.2 P value=0.33	37±1.6 P value=0.18	115±4.9 P value = 0.0001*
CKD-EPI-eGFR	120±6.5 P value= 0.001*	45±2.7 P value = 0.55	40±2.4 P value = 0.11	130±4.8 P value = 0.0001*

*P value < 0.05 is considered to be significant.

Case Presentation

A 31 years old female patient diagnosed as systemic lupus erythematous with diffuse proliferative glomerulonephritis and secondary antiphospholipid syndrome, as well as hypothyroidism secondary to autoimmune thyroiditis, under L-thyroxine 50ug daily. She developed high blood sugar level.

Patient is on: Cellcept 1gm PO BID, Prednisolone 40 mg PO OD, Hydroxychloroquine 200 mg PO BID, Folic Acid 2mg PO OD, Calcium Carbonate 1200 mg PO BID, Alpha Hydroxy Cholecalciferol 1 µg PO OD, L-Thyroxine 50 µg PO OD, ASA 81 mg PO OD, Omeprazole 40 mg PO OD.

At the time of the renal isotope scanning patient was admitted at the hospital with rapidly progressive glomerulonephritis and renal impairment. Laboratory studies were done for the patient and their results were as follow: WBC 8.1× 1000/uL, Hb 10.5 g/dL, PLT 360× 1000/uL, s. urea 13.8, s. creatinine 148, s. uric acid 414, creatinine clearance 28, total proteins 38.66, s. albumin 13.54, s. K 3.8, s. Ca 2.04, s. P 1.26, RBS 8.5, ESR 28 mm/Hr, C3 0.5, C4 0.28, anti-dsDNA 84.5, urinalysis 3+ albumin, Pus cells 10 cells / HPF, and 24- hour urinary proteins were 6 g/d.

Patient received IV pulse methylprednisolone at a dose 1 g/d for 5 consecutive days followed by high dose oral Prednisolone at a dose of 1mg/kg/day, together with IV pulse cyclophosphamide 0.75 g/ m2 BSA with gradual withdrawal of oral prednisolone later on after stabilization of renal function.

Estimated total renal GFR by (C-G) method = 61 ml/min. Estimated total renal GFR by (MDRD) method = 46ml/min. Estimated total renal GFR by (CKD-EPI) method = 49 ml/min.

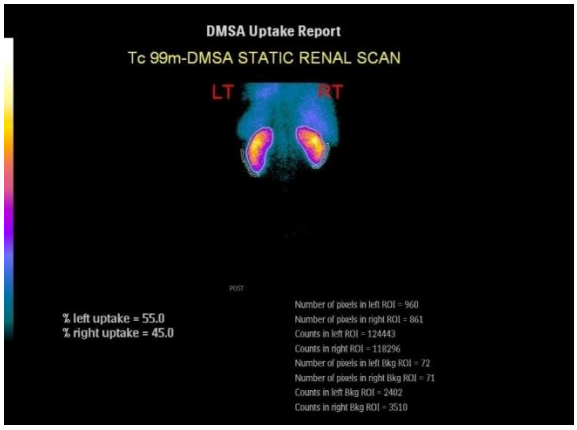

Figure 1(A): 99mTc-DMSA static image showed enhanced background radioactivity with fine heterogeneous cortical radiotracer distribution pattern at both kidneys (reflects parenchymal edema). Left kidney split function 55% & right kidney split function 45%.

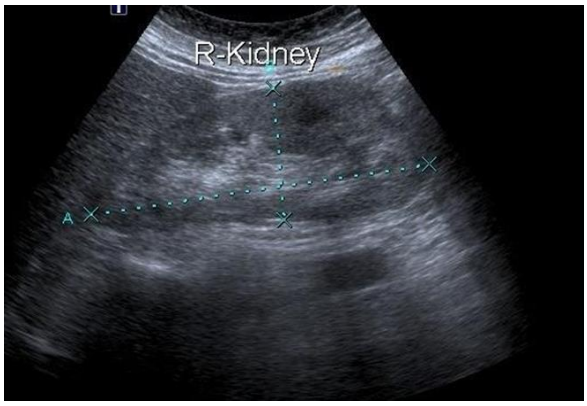

Figure 1(B): U/S both kidneys were of average size, normal site, and normal parenchymal thickness, echogenic Grade-1 nephropathy, with no calculi or backpressure changes.

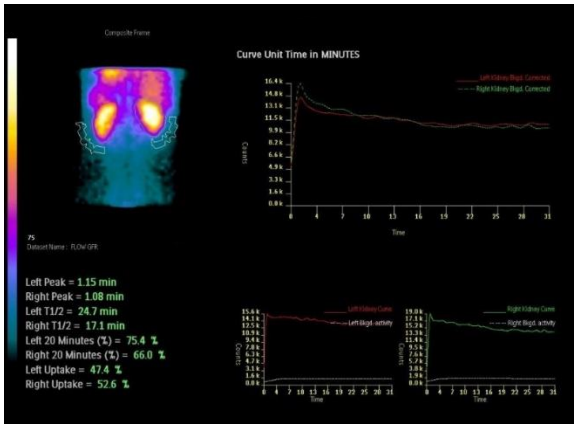

Figure 1(C): 99mTc-DTPA renogram curves showed proper perfusion of both kidneys (vascular phase), with suboptimal radiotracer handling (secretory phase) and prolonged parenchymal transit time of radioactivity as well as delayed clearance of radioactivity from both kidneys.

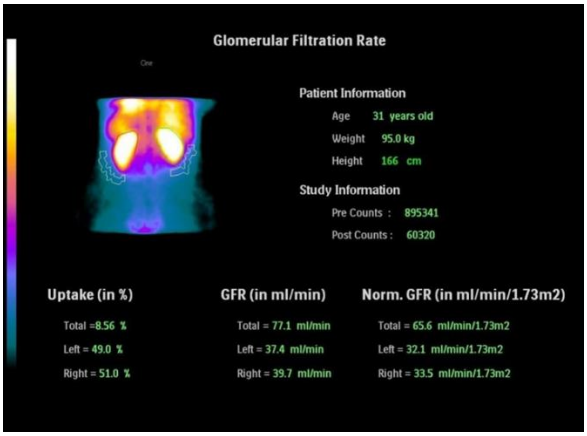

Figure 1(D):99mTc-DTPA GFR data showed, reduced total renal GFR= 77.1 ml/min, (normal range for her age and sex = 90-110 ml/min), left kidney's GFR = 37.4 ml/min and right kidney's GFR = 39.7 ml/min.

4. Discussion:

Lupus nephritis remains a common complication and major determinant of outcome in SLE (Ortega et al., 2010). Survival of patients with lupus nephritis has significantly improved over the last decades due to increasing treatment options than in the past. However, the optimal treatment of lupus nephritis is still a challenge to the clinician (Bertsias et al., 2008). Early management of lupus nephritis is dependent on early detection of nephritis in SLE patient (Lightstone, 2010).

The best overall index of renal function is considered to be the glomerular filtration rate (GFR) (Botev et al., 2009). Attributes of the GFR as an overall index include the following: (1) it is a direct measure of renal function. (2) It is reduced prior to the onset of symptoms of renal failure. (3)In chronic renal diseases, the reduction in GFR correlates with the severity of some of the structural features of the end-stage kidney, such as the extent of tubule-interstitial sclerosis (Levey, 1990).

The regular measurement of serum creatinine levels is easy to perform and is currently the most common method. However because creatinine is invariably reabsorbed by the renal tubules, serum creatinine and creatinine clearance measurements tend to underestimate the GFR in the context of hyper filtration and overestimate the GFR in the context of hypo filtration (Shemesh et al.,1985).

There are several methods for estimating GFR: A traditional method is to measure 24-hour creatinine clearance which tends to underestimate hyper filtration and overestimate low GFR levels. This

technique is subject to errors in urine collection unless great care is taken (NEBG for CKD, 2009).

Calculation of GFR using an empirical mathematical formula has been encouraged as a simple, rapid and reliable means of assessing kidney function. But there are now fewer than 46 different prediction equations currently available, although the two most commonly used are the Cockcroft-Gault (C-G), and Modification of Diet in Renal Disease (MDRD) formulas (Kemperman et al., 2002; Levey et al., 1999)and more recently, Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Levey et al., 2009).

Many organizations recommend the use of equations that estimate the glomerular filtration rate (GFR) to facilitate the detection, evaluation, and management of chronic kidney disease (CKD). Indeed, many clinical laboratories already report estimated GFR (eGFR) values whenever the serum creatinine level is measured (Stevens et al., 2006). In addition, for optimal approximation of GFR from serum creatinine measurements allowances need to be made for age, gender, height and weight of the individual. If the variables are taken into account, as in the Cockcroft-Gault (C-G) and Modification of Diet in Renal Disease (MDRD) equations, a satisfactory index of GFR can be achieved. This is particularly important in thin elderly female people whose baseline serum creatinine levels may be as low as 40-50 µM. In these people delay in referral until the serum creatinine rises above 110 µM would imply that more than 50% of kidney function had been lost (NEBG of CKD, 2009; Levey et al, 1999).

The C-G formula estimates creatinine clearance (CrCl) instead of GFR. Because creatinine is not only filtered by the glomeruli but also secreted by the tubules, CrCl overestimates the GFR (Shemesh et al., 1985). Besides, Cockcroft Gault (C-G) equations consistently overestimate measured GFR in people with normal renal function. It tends to underestimate GFR at levels less than 60 ml/min but is more accurate at higher levels (Botev et al., 2009).

The MDRD equation is based on serum creatinine, age and sex. The MDRD formula tends to underestimate GFR at levels greater than 60 ml/min but is more accurate at lower levels. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula was developed to address the systematic underestimation of the glomerular filtration rate (GFR) by the Modification of Diet in Renal Disease (MDRD) Study equation in patients with a relatively well-preserved kidney function (White et al., 2010).

Estimated GFR by Modification of Diet in Renal Disease (MDRD) Study equation and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) can be used in patients who are in the hospital. However, it is important to pay attention to potential inaccuracies due to the non-steady state of serum creatinine, co-morbidities that cause, and the use of medications that interfere with the measurement of serum creatinine (Botev et al., 2009).

The GFR estimates appear to provide a substantial improvement over the measurement of serum creatinine alone in the clinical assessment of kidney function. GFR estimates may be inaccurate in the non-steady state and in people in whom non-GFR determinants differ greatly from those in whom the estimating equation was developed. If GFR estimates are likely inaccurate or if decisions based on inaccurate estimates may have adverse consequences, a measured GFR (mGFR) is an important confirmatory test (Stevens & Levey, 2009).

The National Kidney Foundation recommends GFR estimates for the definition, classification, screening, and monitoring of kidney diseases. Prediction equations based on serum creatinine values were chosen both for adults Cockcroft-Gault (C-G) and Modification of Diet in Renal Disease (MDRD). Because these prediction equations based on serum creatinine may still have a high level of bias, depending on creatinine assay calibration, especially in the normal or near-normal GFR range (Soares et al., 2009).

The MDRD equation generally outperforms the C-G equation but, and low precision with, at best, approximately 80% of estimated GFR in the "Accuracy range" of 70-130% of the measured GFR value, even in patients with known CKD (Soares et al., 2009).

Recently, the National Kidney Disease Education Program (NKDEP) recommends reporting estimated GFR values greater than or equal to 60 mL/min/1.73 m2 simply as ⩽ 60 mL/min/1.73 m2, and not as an exact number when using the MDRD Study equation. For values below 60 mL/min/1.73 m2, the report should give the numerical estimate rounded to a whole number (e.g., "32 mL/min/1.73 m2").

There are three reasons for this recommendation:

Inter-laboratory differences in calibration of creatinine assays and the imprecision of the measurements have their greatest impact in the near-normal range and, therefore, lead to greater inaccuracies for values ⩽ 60 mL/min/1.73 m2 (Myers et al., 2006).

The MDRD Study equation has been most extensively evaluated in people with CKD and reduced GFR, and is less accurate for persons with normal or mildly impaired kidney function (Poggio et al., 2005; Rule et al, 2004; Lin et al, 2003; Bostom et al, 2002; Stoves et al, 2002).

Quantification of estimated GFR values below 60 mL/min/1.73m^2 has more clinical implications for classification of kidney function than values above this level (Myers et al., 2006). The new Chronic Kidney Disease Epidemiology Collaboration Formula (CKD-EPI) equation was developed to address the systematic underestimation of the glomerular filtration rate (GFR) by the Modification of Diet in Renal Disease (MDRD) Study equation in patients with a relatively well-preserved kidney function (White et al., 2010). It performed better than the Modification of Diet in Renal Disease Study (MDRD) equation, especially at higher GFR, with less bias and greater accuracy (Levey et al., 2009).

An accurate measure of GFR can be undertaken using low molecular weight markers of kidney function such as inulin, iohexolor technetium (Labeled DTPA)(Mathew & Australasian Creatinine Consensus Working Group 2005). Other methods for assessment of GFR include the renal inulin clearance (Cin) (K/DOQI, 2002). However, it cannot be used routinely in daily practice because of its complexity as a test. Previously, some studies reported that Cio overestimates Cin in normal subjects and lupus nephropathy (Petri et al., 1988), and 125I-iothalamate is excreted not only by glomerular filtration but also by tubular secretion (Botev et al., 2009).

As a consequence, alternative filtration markers and clearance methods have been developed and validated. The most widely used alternative filtration marker in the United States is 99mTechnetium labeled di-ethylene triamine Penta acetic acid (DTPA). 99mTc-DTPA is excreted almost entirely by glomerular filtration, 99mTc-DTPA is widely used for dynamic kidney imaging, and its clearance from circulation reflects the condition of the renal arterial blood flow (perfusion), as well as the glomerular filtration rate (GFR) (Vladisav & Bogicevic, 1997).

The 99mTc-DTPA renography which was introduced by Gates (Gates, 1982), is considered to be more accurate than 24 hours creatinine clearance and is recommended for clinical use in patients with reduced renal function (Petersen et al., 1999). In 99mTc-DTPA renography, the GFR is calculated without the need for blood or urine sampling (Prigent et al., 1999).

Besides, 99mTc-DTPA dynamic renal scintigraphy is generally the most important imaging methods routinely used for the evaluation of kidney function. Additionally, the diagnostic information about pre-renal as well as post-renal underlying pathology can be obtained simultaneously with renal scintigraphy and this information has a potential benefit for patient management. Also the capability of studying both kidneys separately offers a great benefit to assess the spit function of each kidney (Tansel et al., 2006), and to draw the treating physician's attention of for the most affected kidney to be the site of further investigation including biopsy aiming at reaching early and proper diagnosis.

Radionuclide renal studies can assess both renal function through the dynamic study with glomerular agent like (99mTc-DTPA) and morphology through the static imaging using tubular agent like (99mTc-DMSA). Considering mechanisms of renal handling of radiopharmaceuticals, the glomerular filtration rate is estimated by 99mTc-DTPA, measurement of absolute as well as split clearances of this radiopharmaceutical provides quantitative information concerning overall and split renal functions. The functional information given by radionuclide methods, are sensitive, reproducible, noninvasive, with low radiation burden to the patient make them favorable for both diagnostic and monitoring tools of various renal diseases (Bogicevic & Stefanovic, 1997).

In Parenchymal diseases: Urographic finding is often normal in patients with a relatively mild impairment of the renal function, while radionuclide methods are very sensitive, even in the initial stage of disease. Renal hypofunction is manifested by low radiopharmaceutical uptake, prolonged transit time and decreased clearance value. By using radiopharmaceuticals with different mechanisms of renal handling, it is possible to estimate the extent of renal dysfunction, as well as to monitor the changes characteristic for disease in the advanced stage. Dynamic kidney scintigraphy and determination of 99mTc-DTPA clearanceindicates impairment of both the glomerular and tubular function (Bogicevic et al., 1993; Bogicevic et al., 1989).

Determination of 99mTc-DMSA renal fixation showed decreased uptake in glomerulonephritis patients (Bogicevic & Stefanovic, 1997). Our study results showed that there was a significant decrease in the 99mTc-DTPA measured GFR value among patients with stage III and stage IV glomerulonephritis, with P value < 0.05, Whereas, the GFR values obtained by C-G formula showed significant decrease only among patients with stage IV glomerulonephritis (P value = 0.016). On the other hand, (MDRD & CKD-EPI formulae) showed insignificant decreased GFR values among patients with stage III & stage IV glomerulonephritis.

In patients with impaired renal function 99mTc-DTPA measured GFR values and C-G estimated GFR values was decreased significantly with P value <0.05, however, that GFR values obtained by C-G estimated formula showed a total bias (– 15 ml/min/1.73m2) and relative bias (-21%).

Whereas, the estimated GFR obtained by MDRD, and CKD-EPI equations are still markedly underestimating the GFR values, among the same group of patients with total bias (-28 & -26 ml/min/1.73m2) and relative bias (-40% & - 37%) respectively.

MDRD as well as CKD-EPI equations for estimation of GFR tend to underestimate the GFR value among patients with impaired renal functions. In patients group with preserved (normal or near normal renal function) the measured GFR by 99mTc-DTPA dynamic renal scintigraphy showed a comparable results to that obtained by the C-G equations total bias (-5 ml/min/1.73m2) and relative bias (-5%), whereas, the GFR values are much higher in equations of MDRD, and CKD-EPI with a total bias (+5 & + 10 ml/min/1.73m2) and a relative bias (+5% & +10%) respectively.

MDRD as well as CKD-EPI equations for estimation of GFR tend to overestimate the GFR value among patients with normal or near normal renal functions. Cirillo, in 2010 stated that estimates of GFR by equations of the Modification of Diet in Renal Disease (MDRD) study can be unreliable for high-normal GFR because that study did not enroll individuals without kidney disease. Moreover, GFR estimates can be biased by inter assay creatinine differences or unusual levels of creatinine generation (muscle mass) or of renal tubular creatinine secretion.

In the study of Botev and his colleagues in 2009, the C-G and MDRD formulae showed some limitations in their ability to properly estimate the mGFR by Cin. Both formulae had accuracy of approximately 70% of the GFR estimates within ± 30% of mGFR and approximately 60% of the population was classified correctly in the five GFR groups defined by the K/DOQI-CKD classification (Botev et al., 2009).

Dopuda and coworkers in 2008, in agreement with our results stated that, the most frequent method for the assessment of glomerular filtration rate (GFR) in clinical practice is clearance of creatinine and clearance of 99mTc-DTPA. Calculation of GFR is corrected for the background and depth of the kidney and finally expressed as a percentage of the net injected counts.

Soares and his colleagues in 2009, in agreement with our results stated that an extensive evaluation of the MDRD equation showed good accuracy in populations with low GFRs (<60mL/min/1.73m2), but worse performance for patients with near-normal GFRs, where underestimation is a problem. Therefore, the MDRD equation appears to be unsuitable for identifying early stages of kidney disease. In addition, other controversial issue with both C-G and MDRD equations is the influence of patient ethnicity. As regards the CKD-EPI, they stated that it performed better than MDRD study equation especially at higher GFR with less bias and greater accuracy.

Assadi and coworkers in 2008 showed the same results of our study that determination of GFR by the C-G method tended to overestimate or underestimate GFR but the DTPA-GFR method resulted in less error in estimation of GFR. Because of the low cost and negligible radiation burden, this method might be preferred for routine practice.

In the study by Prigent in 2008 he showed that prediction equations based on serum creatinine have limitations especially in the normal or near- normal GFR range. The MDRD equation generally outperforms the C-G equation but may still have a high level of bias, depending on creatinine assay calibration, and low precision with, at best, approximately 80% of estimated GFR in the "accuracy range" of 70-130% of the measured GFR value, even in patients with known CKD. According to Kidney Disease Improving Global Outcomes (KDIGO) recommendations, many indications remain for GFR measurements using a clearance method. In that context, it should be recalled that radiolabeled-tracer plasma or urinary clearance methods, are safe, simple, accurate and reproducible.

Kozlova and coworkers in 2002summarized our results and stated that the dynamic scintigraphy provides qualitative and quantitative assessment of renal circulation in patients with confirmed diagnosis of SLE. 99mTc-DTPA dynamic renal scintigraphy can evaluate the effective renal blood flow, which is commonly affected in SLE patients with symptoms of renal disorders.

In agreement with our results too, Prigent and his colleagues in 1999 showed that the 99mTc-DTPA renography is considered to be more accurate than 24 hours creatinine clearance and is recommended for clinical use in patients with reduced renal function. In 99mTc-DTPA renography, the GFR is calculated without the need for blood or urine sampling.

Conclusion

The results of this study concluded that99mTc-DTPA dynamic renal scintigraphy, is a physiological, sensitive, reliable, safe, simple, accurate and reproducible technique to evaluate renal GFR and hence renal function in patient with early lupus nephritis especially those with normal or near normal renal function. Also, it provides proper evaluation of each kidney separately, so it is easily to detect the most affected kidney which gives a good chance for the treating physician to properly investigate it especially if biopsy procedure is planned to be done and consequently allow proper

histopathological diagnosis, staging, as well as early treatment. For already diagnosed cases it has high accurate diagnostic value that is needed by clinicians as a guide for lupus nephritis therapy.Also99mTc-DTPA dynamic renal scan is a universal and simple technique that could assess the GFR without the need for any special equations for race or gender evaluation.

99mTc-DMSA static renal imaging can provide a good imaging marker for active undergoing inflammatory process through its effect on the renal parenchyma (parenchymal edema), as well as its role in assessment of split renal functional indices.

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