Role of Nuclear Medicine in Renal Transplantation

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ABSTRACT

Background: Precise diagnosis of renal transplant complications is very important as many complications are potentially treatable if detected early. CT, MR imaging, and nuclear medicine studies play a complimentary role. Nuclear medicine renal scans (using radioactive 99mTc DTPA or 51Cr-EDTA) are considered the gold standard for the evaluation of kidney function because of their accuracy

Objective: To spotlight on the important role of nuclear medicine on the preparation of both donor and recipient, follow up and early detection of any abnormality in the transplanted kidney with smooth noninvasive techniques.

Conclusion: Renal scintigraphy (RS) has its merits for the evaluation of complications after kidney transplantation, especially for urological and/or vascular complications. Early diagnosis of vascular and urological complications can contribute to a more specific surgical intervention and better post-transplant outcomes. RS should be used in case of non-acute complications, and if the ultrasound (US) provides insufficient results. Radionuclide imaging has the unique advantage of relating perfusion to function. Comparative studies between renal scintigraphy and Doppler sonography seem to have similar performance in the evaluation of renal transplant perfusion.

Keywords: Nuclear medicine, Renal transplantation

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INTRODUCTION

The kidney is a very important filtering organ of the body. When the kidney reaches stage 5 chronic kidney disease, its mean end-stage renal failure, renal transplantation is the preeminent therapy. Although it is the best option of treatment, lack of kidney donors is still challenging. Therefore, all efforts should be directed toward the long term survival of the transplanted kidney. However, graft dysfunction (e.g., acute rejection) is one of the serious barriers to prolong the survival rate of the transplanted kidney. Currently, the gold standard of diagnosis of graft dysfunction is renal biopsy. Although biopsy is helpful, it is not preferred due to it is invasive nature, high morbidity rates, and it is expensive. Therefore, noninvasive imaging modalities have become the subject of research and interest, giving the promise to replace, or at least to decrease, the use of biopsy in diagnosing graft dysfunction [1].

Although renal transplantation is the treatment choice, it is still associated with many complications. These complications can be divided into two subgroups, that is, parenchymal complications include acute tubular necrosis (ATN), delayed graft function (DGF), antibody-mediated rejection (ABMR), or T–cell-mediated rejection (TCMR), and damage caused by nephrotoxic drugs, surgical complications are rare and include decreased blood caused by anastomotic complications, vascular thrombosis, hematoma, fluid collection, or lymphoceles, ureteral obstruction or urinary leak[2].

Detection of the changes in the transplanted kidney function is very important to make the appropriate management. Accurate and noninvasive diagnostic measures take an important place in the early diagnosis of functional impairment. Renal ultrasonography (US), radionuclide imaging, CT, and MRI provide anatomical and functional information for the differential diagnosis of renal graft dysfunction as a result of surgical or parenchymal complications. Renal scintigraphy is a modality capable of measure graft function, not only qualitatively but also quantitatively. For this purpose, the most commonly used tracers are iothalamate, 51Cr-EDTA, and 99mTc-DTPA, which their plasma clearance reflects the glomerular filtration rate. 131-OIH has been used for the measurement of effective renal plasma flow (ERPF) for a long time; however, since 1990, 131-OIH has been replaced by other tubular agents such as 99mTc-MAG3 and 99mTc-EC [2].

A renal scan is very important to determine as accurately as possible the renal function in potential living renal transplant donors, especially those with limited renal function (Cr Cl <90 mL/m/1.73 m2), age older than 50 years, and cardiovascular risk factors that might favor development of long-term kidney diseases [3]. Following nephrectomy months to years, donors experience a 25–40% absolute reduction in their glomerular filtration rate (GFR) compared to their pre-donation level [4]. Compensation on the part of the remaining kidney reaches 70% of initial function [5].

Picture of Transplant Complications by renal scan

Table (1): Common scintigraphic findings and onset of complications[2].

Complication	Onset	Scintigraphic Finding
Surgical complications		
Renal artery thrombosis	First week	Absence of perfusion and function
Renal venous thrombosis	First week	Absence of perfusion and function
Hematoma	First week	Photopenic area
Seroma	First week	Photopenic area
Urinoma or urinary leak	1-3 wk	Radionuclide accumulation outside the kidney and collecting system
Ureteral obstruction	1-3 wk or up to 1 y	Tracer retention in the collecting system unresponsive to diuretic administration
Lymphocele	1-2 mo	Photopenic area
Renal artery stenosis	3-24 mo	Decreased uptake and prolonged renal retention
Parenchymal complications		
Hyperacute rejection	Immediately	Absence of perfusion and function
ATN	First week	Preserved perfusion and decreased function
Acute rejection	First week-1 mo	Decreased perfusion and function
Calcineurin toxicity	2-3 mo	Decreased perfusion and function
Chronic rejection	>3 mo	Decreased perfusion and function

A) Nephrological complications:

-Rejection:

-Accelerated acute rejection: The rejection occurs within the first week. The imaging features are the same as acute rejection. It is managed by immunosuppressants [6].
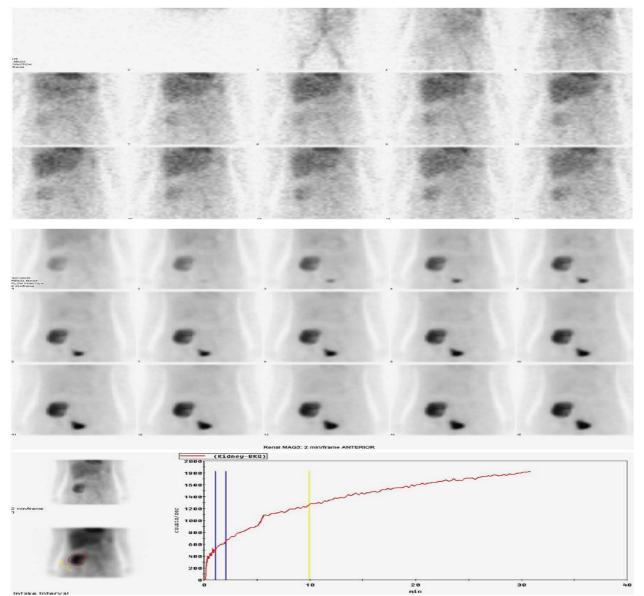
-Acute rejection: It is a cell-mediated reaction, clinically, there is an elevation of creatinine, oliguria, fever, graft swelling, and tenderness. The sonographic findings are non-specific and can be seen in other nephrological complications [6].

Radionuclide studies show decreased renal perfusion and function. There is the attenuation of the early rapid increase in activity, decreased peak activity and the prolonged delay between peak activity in aorta and transplant. These findings are seen with slightly reduced intensity in other nephrological complications. If the isotope study is normal in the early postoperative phase and becomes abnormal subsequently, acute rejection can be diagnosed with confidence[6].

-Chronic rejection: - occurs in a progressive manner and results in late graft loss. Radionuclide studies can show rapid uptake and washout[6].

-Acute Tubular Necrosis (ATN):- in up to 15% of patients after renal transplantation, it occurs more commonly among cadaveric transplants. Overall it has no impact on patient or graft survival as it is expected to resolve in several weeks [7]. There is no imaging specific pattern for the diagnosis of ATN. US findings are a non-specific marker of graft dysfunction, seen on both, ATN and rejection [8]. With radionuclide imaging. It is characterized by relatively good perfusion of the graft with poor filtration function of 99mTc-DTPA. When 99mTc-MAG3 is used, uptake of the tracer may be preserved or delayed and diminished, but there is progressive parenchymal concentration and retention, which are due to the absence of excretion, impaired urine flow, and tracer washout [9]. Comparison with baseline renal scintigraphy, performed within a couple of days after transplantation, provide information to determine whether the function is improving or deterring [10].

Table (2) Comparison of acute rejection and vasomotor nephropathy [11].

Disease	Baseline scan	Follow-up scan	Perfusion	Renal transit time
Acute rejection	Normal	Worseness	Decrease	Increase
Vasomotor nephropathy (acute tubular necrosis)	Abnormal	Improve	Normal	Increase

Fig. (1): The classical scintigraphic findings of ATN include preserved or only mildly reduced perfusion but delayed uptake and excretion of tubular secretion agent, such as Tc-99m MAG3, with progressive accumulation of the radiotracer in the renal cortex[11].

- **Cyclosporine toxicity**:- Similarly there is no specific imaging pattern for drug toxicity though this condition can be distinguished from ATN by measuring cyclosporine level and its time of occurrence as it characteristically occurs several weeks after renal transplantation, at this time acute tubular necrosis should have resolved. Scintigraphy in spite of its limited ability to distinguish between the various parenchymal pathologies, in the context of declining graft function, it's helpful to ensure the presence of blood flow to the graft, and the absence of a urinary leak or obstruction [11].
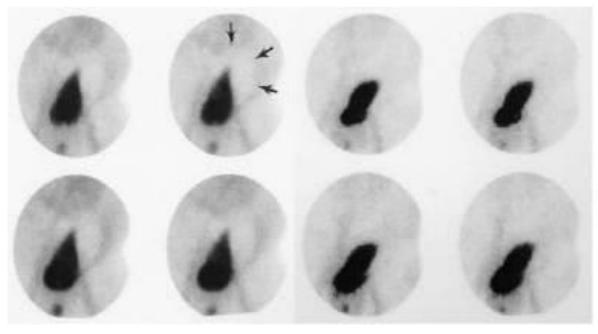
-Infection: - Infections are a common cause of morbidity and mortality after transplantation, and infections rank second as the cause of death in patients with allograft function. Renal cortical 99mTc-dimercaptosuccinic acid (DMSA) scintigraphy is more sensitive for the detection of pyelonephritis than sonography [12]. Pyelonephritis and scarring are recognized by focal areas of decreased 99mTc-DMSA uptake in the renal parenchyma; however, a focal abnormality is not specific for pyelonephritis or a renal scar since any process that replaces, injures, or destroys normal cortical parenchyma will result in an abnormal scan [13].

B) Urological Complications: - the prevalence of urologic complications varied from10% to 25%, with a mortality rate ranging from 20% to 30%. Currently, urologic complication rates are 4%–8% with very low patient mortality. In many instances, the US cannot differentiate obstructive hydronephrosis from a dilated, patulous, non-obstructed collecting system. In these cases, a Tc-99MAG3 renal scan with a diuretic (Furosemide scan) may be helpful to differentiate a non-obstructed dilated collecting system from an obstructed system [14].

- Perinephric fluid accumulation: - is less frequent after renal transplantation and occurs in up to 50% of cases. These collections include urinomas or hematomas in the early post-transplant period, and abscesses or lymphoceles, in the following months. The importance of perinephric fluid collection depends on its size, growth rate and the site of occurrence [15].

- Lymphocele: - are typically seen 4–8 weeks after surgery. They are the most common post-transplant fluid collection (1–15%) and occur as a result of a lymphatic leak or obstruction due to incomplete dissection of pelvic lymphatics. RS of lymphocele presents as a persistent photopenic area, although a mild degree of filling-in on delayed imaging has been observed [16].
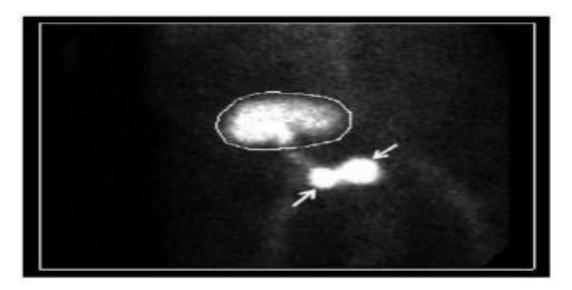

(a)   (b)

Fig. (2): Lymphocele. (a) Tc-99m MAG3 study demonstrate presence of the normal transplant in the right lower quadrant. (b) Views from another study performed 2 months later show that there is a large photopenic defect (arrows) compress the upper pole of the transplant [16].

-Urine Leak:-the incidence of urine leak is 0% –9.3%. Radionuclide imaging studies (Fig. 3) show extravasation of radiotracer into an area that was initially "cold". Delayed scintigrams should be obtained, since accumulation of radiotracer may be slow. But can be falsely negative in the case of slow/delayed graft function or if the bladder is decompressed by a Foley catheter [17].

Fig. (3): Diagnosis of a urine leak. Mag3 renogram shows a urine leak (top arrow) near the ureterovesical anastomosis. The isotope tracer has been excreted by the kidney (circle) and the bladder is contracted (bottom arrow) [17].

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Urinary Obstruction: occurring in 2%-10%. Kidney transplant obstruction (KTO) following renal transplantation still an important reversible cause of allograft dysfunction, requiring early diagnosis to prevent long- term graft damage. Scintigraphy may demonstrate urinary obstruction. In a patient with early partial obstruction, good perfusion and prompt uptake of the radiotracer may be present; however, in a patient with functionally significant hydronephrosis, radioactivity is retained in the collecting system. Delayed images (obtained 2–4 hours after injection) are helpful in differentiating an obstructed ureter from a dilated unobstructed one since an unobstructed system shows clearance into the bladder. Diuretic renography has proved useful for determining the functional significance of dilated collecting systems. Normal or slowly declining renogram curve effectively excluded KTO (sensitivity of 96%, the negative predictive value of 84%) [18].

-Hematomas/abscesses: are seen in the early postoperative period. Abscesses arise as a complication of surgery or pyelonephritis or secondary infection of urinoma, hematoma or lymphocele. RS demonstrates photopenic areas that do not fill up in delayed images [19].

-Urolithiasis/Nephrolithiasis:

The risk of nephrolithiasis is about 1 percent. RS diuretic renography used to evaluate the presence of obstruction or dilatation without obstruction. In the absence of obstruction, there is rapid drainage of radiotracer from the renal pelvis into the bladder to a minimal residual after 20 minutes. In quantitative terms, a drainage half-time, T½, of less than 10 minutes usually means the absence of obstruction. In an obstructed system, the drainage of radiotracer from the collecting system will be slow. In this case, a T½ of greater than 20 minutes indicates obstruction. T½ ranging between 10 and 20 minutes is usually considered an equivocal result, and a follow-up examination is typically performed to see if the drainage normalizes or becomes frankly obstructed and DMSA scan is used to evaluate renal parenchyma or presence of a renal scar [19].

-Vesicoureteral reflux: - a common complication that can take place early after graft surgery**.** As symptoms of reflux are non-specific, it is often diagnosed incidentally on Tc-99m MAG3 renography while investigating for a cause of graft failure. When reflux occurs, renography classically demonstrates a 'double peak' present on the time-activity curve. The first peak represents the start of the normal excretory phase while the second peak is caused by the re-entrance of the tracer into the kidney as a result of reflux from the bladder. Visually, the radiotracer is excreted from the renal parenchyma and cleared from the collecting system initially. At the time of reflux, the kidney appears to fill again with the radiotracer, sometimes preceded by radiotracer activity seen in the distal ureter (Fig. 4). In patients with suspected vesicoureteric reflux, an indirect micturating cystogram can be performed to confirm the diagnosis. As the bladder empties, tracer reflux into the kidney manifests as a single peak in the time-activity curve (Fig. 4) [20]**.**
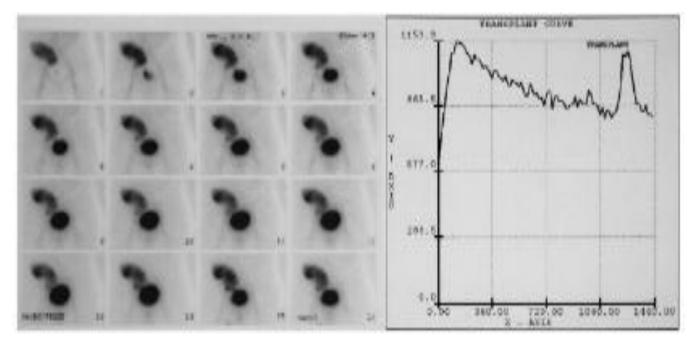

Fig. (4): Renal curve of vesicoureteral reflux [20].

C) Vascular complications: - it occurs in 10% of renal transplant recipients and it is considered an important cause of renal graft dysfunction and graft loss [21]. Vascular complications were divided into 2 groups; early ones occurring within the first-month post-transplantation, namely renal artery or vein thrombosis, versus those from the first month to years after transplantation, such as renal artery stenosis [22].

-Renal artery stenosis: - the most-common complication, occurring among 3%–23% of transplantations [23], which usually occur during the first 12 months after transplant [24]. If renal artery stenosis is not diagnosed. It can lead to continued renal dysfunction, resistant hypertension, and eventual allograft deterioration [25]. Therefore, noninvasive imaging such as USG, magnetic resonance angiography, and radionuclide renal scans are warranted to evaluate for renal artery stenosis. The gold standard for the diagnosis of RAS is angiography [26]. The major drawbacks of angiography are complications such as contrast-induced nephropathy and thromboembolism [27].

The US and renal scans go together as far as the evaluation of the renal transplant is needed in the early postoperative period. Tc-99 DTPA is a parenchymal agent and is used to evaluate renal blood flow, perfusion, and perfusion defects. Sometimes, a captopril renal scan radionuclide scan with angiotensin-converting esterase inhibitors may help to evaluate suspected renal artery stenosis (RAS) of the transplant renal artery [28]. Decreased GFR and tubular flow after the administration of an ACE inhibitor will result in decreased uptake and prolonged cortical retention of Tc-99m DTPA. Tc-99m MAG-3 images will show only increased and prolonged cortical activity [29]. Due to the retention of the tracer in the renal tubules secondary to decreased GFR and decreased urine flow through the tubules. Rarely, uptake of Tc-99m MAG-3 may actually decrease, presumably due to a fall in blood pressure below a critical level required to maintain perfusion in the stenotic kidney [29].

Scintigraphic studies are interpreted by comparing the baseline images with captopril images. The following changes after ACE inhibition are considered significant for renovascular hypertension: increase in renal parenchymal retention by at least 15%, delay in collecting system visualization by at least 2 min, an increase in cortical time to peak by at least 2 min if Tc-99m MAG-3 is used and decrease in initial cortical uptake by at least 10% and then prolonged cortical retention if Tc-99mDTPA is used. Test results can be interpreted as high, intermediate, or low probability for RVH[30].

High-probability result (>90%): Marked change of the renogram curve following ACE inhibition, compared with baseline findings. Intermediate-probability result: Abnormal baseline findings which is unchanged after ACE inhibition. Low-probability result

(<10%): Normal captopril renography or abnormal baseline findings that improve after ACE inhibition [30].

- Renal artery thrombosis (Infarction):-it occurs in 0.4% to 3.5% of recipients. Patients typically present with an acute reduction in urine output and an increase in serum creatinine. Arterial thrombosis most commonly occurs in the immediate postoperative period but may occur at any time following the transplant [31]. At the ultrasound, contrast-enhanced CT, and contrast-enhanced MR imaging, renal artery thrombosis appears as the absence of flow in the transplant main renal artery and branch vessels. Unfortunately, the graft is typically lost once arterial thrombosis occurs [32]. At technetium-99m dynamic radionuclide studies, a photopenic region may be seen. However, these findings are not specific, since hyperacute or accelerated acute rejection can have similar clinical, Doppler US, and scintigraphic features [33]. DMSA scintigraphy demonstrates focal perfusion defect(s) in the affected kidney(s) [34].

-Renal vein thrombosis:-Transplant renal vein thrombosis occurs in 0.55% to 4% of patients [35]. Scintigraphic findings are similar to renal artery thrombosis.

CONCLUSION

Renal scintigraphy has its merits for the evaluation of complications after kidney transplantation, especially for urological and/or vascular complications. Early diagnosis of vascular and urological complications can contribute to a more specific surgical intervention and better post-transplant outcomes. RS should be used in case of non-acute complications, and if the US provides insufficient results. Radionuclide imaging has the unique advantage of relating perfusion to function. Comparative studies between renal scintigraphy and Doppler sonography seem to have similar performance in the evaluation of renal transplant perfusion. However, scintigraphy has the added advantage of providing functional information. As regards patient management in most transplant centers, the first response to the deterioration of transplant function is the initiation of pulse steroid treatment. In cases of subclinical rejection or borderline cases, the decision to treat or not may be based on functional impairment detected on scintigraphy. In cases of acute rejection, starting treatment with steroids or more aggressive lines like monoclonal antibody induction therapy may be based on RS findings.

RECOMMENDATIONS

-Using nuclear medicine in measurement of donor GFR as it consider the gold standard for evaluation of renal function.

- A base line study performed within 24–48 h of transplantation provides important prognostic information in addition to its role in evaluating graft perfusion in the immediate postoperative setting; and it

has a role in the prediction of long term allograft function. Quantitative assessment of Tc-99m DTPA perfusion scintigraphy performed within 2 days after transplantation is useful in the prediction of long-term graft function up to 5 years and is superior to measurement of intra-renal resistance index by Doppler ultrasonography.

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