Utility of Doppler Ultrasound as the Primary Imaging Modality in Renal Graft Dysfunction

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Abstract

Background: Doppler ultrasonography is a noninvasive imaging modality with no ionizing radiation or contrast administration that can be applied for renal transplant regardless of renal functions. It is routinely used by many clinicians to diagnose graft dysfunction postoperatively and during long-term follow-up to identify its possible etiology and also to guide graft biopsy.

Aim of the Work: To explore the utility of Doppler ultrasound as the primary modality in the assessment of renal graft dysfunction with main correlation with renal biopsy.

Material and Methods: The subject of this study was 79 consecutive live-related renal graft patients presented with graft dysfunction. Initial assessment was done by ultrasound (US) in all patients using power, Color and Pulsed Doppler with serial US in suspected acute rejection and acute tubular necrosis. Renal biopsy was done in 55 patients, MAG3 scintigraphy done in 42 patients. MM and CT done in case of graft-related masses (n=2). MR Angiography (MRA) and catheter angiography (n=2) were done when renal artery stenosis (TRAS) was diagnosed on US.

Results: Patient's age range was 25-62 years. Out of 55 patients with graft dysfunction underwent biopsy, 3 patients revealed recurrence of original disease, 5 acute tubular necrosis (ATN), 21 acute rejection, chronic rejection (n=14) and collections (n=10). Renal graft mass (undifferentiated carcinoma) was discovered (n=1), compressing adrenal mass (n=1) revealed by US (n=2), unenhanced CT (n=1) unenhanced MRI (n=1). As regard parenchymal complications, Doppler/Biopsy agreement was 87.57% in chronic graft rejection, recurrence of original disease (66.7%), acute rejection (57.14%) and the least was ATN (40%). Peritransplant collection (one abscess, 2 lymphoceles, 8 seroma and hematoma), were depicted on US and proven by aspiration ultrasound-guided biopsy (n=10) and MM (n=2) with 100% agreement. Vascular complications (n=3) were vascular thrombosis (n=1) and TRAS (n=2). TRAS was diagnosed by Doppler in 2 patients and proven by Angiography (n=2) and MRA (n=2) and confirmed by relief of signs on follow-up Doppler US after PTA (percutaneous transluminal angioplasty).

Conclusion: Doppler ultrasound is a safe sensitive non-invasive procedure in assement of Renal Graft dysfunction particularly when using serial PI and RI measurements in addition to Power Doppler parameters described. Doppler US is still having low specificity in differentiating parenchymal entities of graft dysfunction with better value in follow-up and in patient's selection for biopsy. It has high sensitivity in diagnosing vascular complications and peri-graft collections.

Key Words: Renal transplantation — Doppler ultrasound — renal graft imaging — Graft dysfunction.

Introduction

RENAL graft is now the gold standard for treatment of renal failure. The most common graft dysfunction indicator is rising creatinine ill. Graft dysfunction has many medical causes such as acute rejection, chronic rejection and acute tubular necrosis [2]. Early and accurate diagnosis of renal graft dysfunction soon after transplantation is the key to prompt institution of appropriate treatment [3]. Many causes of graft dysfunction are treatable, making prompt detection and diagnosis of complications essential. Sensitive, noninvasive imaging procedures, which do not use iodinated contrast media, are therefore highly desirable to evaluate graft function [4]. Color Doppler Sonography has been established as part of the routine follow-up after kidney transplantation [5]. Doppler US has traditionally been the initial investigation of graft dysfunction. US offer many advantages, particularly during the postoperative period, when it can be performed portably regardless of renal function and can guide percutaneous procedures [4]. The superficial location of the renal transplant allows normal corticomедullary differentiation with the pyramids relatively hypoechogenic to cortex. Main transplant artery examination may be time consuming due to twists and the requirement of precise
angle correction. Therefore accurate velocity readings cannot be overemphasized [7]. The intra-renal branches and the main renal vein are normally easily visualized [8]. Spectral Doppler signals from segmental and interlobar vessels show normal fast systolic upstroke with subsequent slow delay in diastole, forward flow being maintained until next systole. Thus, resistance index values of 0.8 or lower are expected, although the precise reading must be taken within clinical context [9]. The most common Doppler indices used to assess the blood flow within the graft are the pulsatility index (PI), resistive index (RI), and the acceleration time (AT) [10]. An isolated elevated RI has limited value and is nonspecific [11]. Power Doppler images (PDI) were obtained parallel to the longitudinal axis with a gain setting just below the background noise to avoid motion artifacts. The distance between the most peripheral vessels and the renal capsule was measured in each examination. This distance is referred to as the peripheral vessel distance (PVD) measured in millimeters [12].

Sonographically, post-transplant complications can be divided into four major categories: Perinephric collections, Parenchymal abnormalities, collecting system abnormalities, vascular abnormalities [11]. Acute rejection (AR) shows diffuse renal enlargement, cortical thickening, increased or decreased cortical echogenicity, loss of corticomедullary differentiation, prominent pyramids, and thickening of collecting system. All can be seen in the setting of diminished renal function. Although elevated RI at the arcuate arteries was previously described as an accurate method of detecting AR, it has been subsequently shown that RI increase can also be seen in various other conditions as ATN, renal vein thrombosis, graft infection, compressive perinephric collections and obstructive hydrenephrosis [6].

Normal RI in transplanted kidney should be below 0.70 to 0.80 [13]. An elevated RI (>0.8) is now used as a nonspecific parameter of renal dysfunction [6,13]. API of <1.5 or RI <0.7 can be regarded as normal, whilst a PI >1.8 or RI of 0.9 should be regarded as abnormal. Although both ATN an AR cause PI & RI rise, the likelihood of AR is greater with higher levels. Complete absence of diastolic flow or reversal in the majority of cases is due to AR [14,15]. Serial measurement of RI & PI in conjunction with clinical & biochemical findings are useful in early transplant period and guide clinicians whether to refrain or to proceed to biopsy [16].

Ultrasound features of chronic rejection include increased transplant echogenicity and reduction in normal intra-renal vessels number [7]. The kidney showed diminished perfusion with increased RI similar to atrophic native kidney, and cortical thickness will be decreased [17].

Renal artery stenosis (TRAS) occurs usually at surgical anastomosis site, clinically manifests as persistent hypertension and/or graft dysfunction, although in many cases discovered during routine examination [6]. Doppler criteria for diagnosing TRAS include: 1. Direct indicator: PSV at site of stenosis >2.5 m/s which is different from a PSV of 1.8m/s as the criteria for diagnosis of native kidney renal artery stenosis and (B) PSV ratio of the renal artery at stenosis to iliac artery >3.5; and 2. Indirect indicator at intrarenal segmental arteries of Parvus-tardus waveform (AT, >0.07 seconds; and AI, <3m/s2) of intrarenal artery distal to stenosis [12,18]. After TRAS sonographic diagnosis, MRI or angio-computed tomography is indicated to confirm the diagnosis before PTA treatment [11]. The normal value of AT is defined as 0.07 sec. Every increase in the AT is suspicious for severe proximal stenosis [29]. An abnormal Doppler spectrum that better reflects the changes in downstream circulation to a TRAS appears at the level of the interlobar instead of segmental arteries because the former is farther away from the turbulence caused by stenotic site high-velocity “jet” [18].

Peritransplant collections have been reported in 50% of renal transplant recipients. Because sonographic characteristics of all Peritransplant collections are nonspecific, ultrasound-guided percutaneous aspiration may be necessary to exclude urinary leak. Drainage is often performed under US-guidance because of high risk for secondary infection attributable to immunosuppression [19]. Immunosuppressive therapy places transplant Recipient at 100 times the normal risk for developing cancer, in particular skin cancers and lymphomas. Immunosuppression Degree and duration are important risk factors for development of malignancy. Post-transplantation lymphoproliferative disorder (PTLD), is a complication occurring in 0.9-2.5% of renal transplant recipients [20]. Primary renal cell carcinoma should be considered when a focal mass is noted by US [19].

Renal scintigraphy perfusion and renogram patterns highly suggestive of specific allograft pathologies seemed to provide useful information distinguishing early postoperative renal allograft pathologies [21]. Biopsy is still required to distin-
guish AR from ATN, and immunosuppressant's serum levels are required to diagnose overdosage.

Material and Methods

In Ultrasound Unit, King Khalid University Hospital, King Saud University, Riyadh Saudi Arabia from 2011 — 2012 the subjects of this study were 79 consecutive patients live-related graft dysfunction (38 males, 41 females). Initial assessment was done in all patients (n=79) by US using Power, Color and Pulsed Doppler. Renal biopsy was done in 55 patients to clarify different etiologies (Fig. 1), MAG3 renal scintigraphy done in 42 patients, MRI (n=4) and CT (n=3) done in case of morphological complication depicted on US. MRA and angiography (n=2) when graft renal artery stenosis was strongly suggested on Doppler US.

US were done using Philips-ATL HDI 5000 and Philips-ATL IU22 US machines, (Philips Ultrasound, Bothell, WA), 2-5MHz curvilinear probe. All exams are done by same radiologist (*) with fixed parameters in all patients to avoid interobserver variations. Patients placed in supine position with angle of beam correction to examined vessels <60°. We start Doppler imaging with a low wall filter for slow flow in intrarenal vessels and then make adjustments accordingly. Routine graft CDUS includes observing morphologic characteristics on gray scale US, assessing vascularity with Color Doppler and quantitatively evaluating hemodynamic on Pulsed Doppler. Measurements are done in upper, mid and lower pole vessel with sample volume reduced allowing targeted interlobar vessels assessment. Common graft Doppler indices to assess blood flow are pulsatility index (PI), resistive index (RI), and acceleration time (AT). Other Doppler parameters are peak systolic velocity (PSV), PSV ratio of transplant renal artery/iliac artery and acceleration index (AI) of intrarenal arteries. Power Doppler US for renal parenchyma perfusion in instances of slow blood flow in graft. In case of clinical and Sonographic findings suggesting ATN versus AR, serial Doppler US was done every 48 hours for 3 times. Follow-up Doppler US was done for all graft dysfunction patients receiving medical treatment and for patients with TRAS after relief of findings post-PTA. At Doppler reporting time, examiner was blinded about biopsy findings.

US/Doppler diagnostic parameters used:

Normal doppler parameters:

- VI <0.70; PI <1; AT <0.07 sec.
- PVD (distance from most peripheral vessel to renal capsule on power Doppler ultrasound) = 2.9mm.

The intrarenal vein: Monophasic waveform with low velocity and a minimal respiratory variation with normal cardiac function.

Graft dysfunction:

- RI >0.9.
- PI >1.8.
- PVD more than 3.2mm with vascular blur on power Doppler.
- ATN persistent changes or slow rise (<10%) on serial examinations.

Acute rejection:

- Significant RI & PI rise (>10%) on serial 3 follow-up (48 hours gap).
- Reversal or loss of diastolic flow.

Vascular complications:

Suspected hemodynamically significant RAS (> 60%):
- PSV <25 cm/sec in interlobar vessels and >250 cm in main artery.
- RI in interlobar arteries <0.5
- AT of >0.6 second.
- Parvus-tardus flow (interlobar arteries).

MRA or Catheter Angiography was done. MRA was done when TRAS proven with additional PTA dilatation of stenotic area. Follow-up assessment of relief disturbed parameters done in all of those patients.

Vascular thrombosis: 1 case was discovered. Follow-up US done with no relief of ischemic signs with positive post-nephrectomy findings.

Collections and masses:

Described as regard site, size, echogenitity or sonographic pattern. CT, MRI done for those patients and aspiration was done for collections increasing in size (on follow-up) or when US findings are alerting for infection. US-guided tissue biopsy was done for all renal graft related masses. Histopathological Findings were correlated. Agreements of Doppler with Histopathological findings were compared (Table 1, Fig. 2).
**Statistical method:**

We used SPSS Statistical package 19.0 for data analysis. We used Fisher’s exact test and Chi-square test to compare Doppler ultrasound and biopsy findings and to assess for the agreement of findings. We assumed statistically significant difference if \( p < 0.05 \).

**Results**

79 consecutive patients, 38 male and 41 female presenting with renal graft dysfunction with age range of 25-62 years were examined by Doppler US. Out of 55 patients with graft dysfunction underwent biopsy with histopathological diagnosis of graft dysfunction etiology (Fig. 1), 3 patients revealed recurrence of original disease and 5 patients showed acute tubular necrosis (ATN), 21 acute rejections (n=21) (Fig. 3), chronic rejection (n=14). Renal graft-related mass (n=2) one renal graft mass (undifferentiated carcinoma) was discovered (n=1) (Fig. 4), compressing adnexal mass (n=1) revealed by US (n=2), unenhanced CT (n=1) unenhanced MRI (n=1). Peritransplant collection (1 abscess, 2 lymphoceles, 8 seromas, 1 urinomas and hematoma), were diagnosed on US, proven by ultrasound-guided biopsy (n=10) and MRI (n=2) with 100% agreement. TRAS was diagnosed by Doppler in 2 patients, proven by Angiography (n=2) and MRA (n=2).

Graft-related mass and collections are detected by US and proven by MRI, CT and biopsy in 100% of cases (n=2 and n=10 respectively). As regards parenchymal complications, based on renal biopsy (n=50), highest Doppler agreement (Table 1, Fig. 2) was in chronic graft rejection (87.57%) then recurrence of original disease (66.7%) then AR (71.4%) and the least was ATN (40%). Vascular complications were seen in 3 patients, 2 renal artery stenosis (proven by MRA in one patient and transcatheter angiography with therapeutic PTA in 2 patients) with 100% agreement and one case of intra-renal arterial thrombosis proven by post-nephrectomy pathological correlation.

![Fig. (1): Incidence of aetiology of graft dysfunction based on graft biopsy.](image1)

![Fig. (2): Percentage of agreement of doppler findings with renal graft biopsy.](image2)
Fig. (3): Renal transplantation patient with acutely raised blood creatinine diagnosed by US as acute rejection with high RI and PI and raised RI and PI >10% on Follow-up US (3 times every 48 hours). Biopsy revealed Acute rejection.

Fig. (4): Renal graft dysfunction. Left: US showed graft (TX) dysfunction with multiple left iliac fossa graft masses (M) with secondary hydronephrosis. Right: MM post-Gd. Contrast coronal T1WI showing multiple renal graft masses. Biopsy revealed undifferentiated renal graft carcinoma.

Discussion

Ultrasound is often the initial diagnostic modality as it is noninvasive, relatively inexpensive, does not require intravenous contrast, can be obtained at the bedside, and can often rapidly and accurately depict many of the common complications-most notably, vascular complications.

Color and spectral Doppler examination of the transplant provides an excellent noninvasive method to assess immediate and delayed vascular complications. Sonography also plays a key role in guiding percutaneous interventional diagnostic and therapeutic procedures [19].

Color Doppler is now essential for detection of intra- or extra renal arterial or venous abnormalities. Several sonographic findings have been reported in patients who have graft dysfunction, including poor corticomedullary differentiation, reduction in renal sinus echoes, and both increased and decreased echogenicity of the pyramids, urothelial thickening, and enlargement of the kidney. All these findings are nonspecific, however, and may be seen in patients who have acute rejection, ATN, infection, and cyclosporine toxicity, along with vascular complications. Additionally these sonographic findings often occur much later than the biochemical indicators of graft dysfunction, limiting their usefulness to allow early therapeutic intervention. The elevated RI results from any cause of interstitial edema, which is most reflected in the diastolic phase of the arterial waveform. A normal RI does not exclude graft dysfunction, however, and may be noted in up to 50% of
patients who have biopsy-proven rejection. Serial measurements of RI may be helpful to determine if the insult is worsening and to monitor therapeutic interventions. Power Doppler examination is more sensitive than RI evaluation for the detection of the vascular changes of graft dysfunction. Alterations in the small vessels within the cortex of the transplant (on power Doppler) such as patchy lack of peripheral cortical flow may be the earliest sign of parenchymal insults, such as rejection and cyclosporine toxicity. Measuring RI by quantitative Doppler ultrasonography seemed to be more suitable to yield a prognosis for the kidney graft rather than an exact diagnosis of the cause of graft dysfunction. Although imperfect at correctly grading significant histopathological damage, the RI provided recognition of the need for needle core biopsy.

Power Doppler US using high-frequency transducers to delineate cortical blood flow visualizes the dense cortical interlobular pedicles all the way to the cortex cortices.

There is a wide range of causes of renal graft dysfunction with AR as the comments cause in our series of cases (Fig. 1). Since there is a considerable overlap in the indices of patients with "normal" function, ATN and patients with AR, a single PI and RI value is of limited utility in the diagnosis. This explains low specificity and positive predictability of a single value of PI (cut-off point of 1.8) and RI (cut-off point of 0.8) in diagnosing AR in patients with ATN.

In case proven graft dysfunction by these parameters we used the PVD on color Doppler as a parameter for assessment of graft dysfunctions. Langer and Jones considered Power Doppler examination more sensitive than RI evaluation for detection of vascular changes of graft dysfunction. Alterations in the small vessels within the cortex of the transplant may be the earliest sign of parenchymal insults such as rejection and cyclosporine toxicity. These patients may show patchy flow or complete lack of cortical flow on power Doppler examination of the parenchyma. Similar to RI determinations, normal examination does not exclude graft dysfunction.

Venz et al. concluded that adding power Doppler ultrasound information (using PVD and peripheral vascular blur) to Doppler indices (mainly RI and PI) improves accuracy of color Doppler in diagnostic work-up of kidney transplant. In our study using statistical analysis showed that those values increased sensitivity in detecting graft dysfunction but it did not increase specificity in differentiation between different etiologies. Still serial examination plays a role in this respect particularly in differentiating ATN from AR but also specificity still low (p-value >0.05) (Fig. 3). For obvious reasons ultrasound has high sensitivity in detection peri-graft collections and mass (100% and proven by CT, MRI and Biopsy) (Fig. 4) but again as literature agreement, collection nature is still to be assessed by other means.

Since there is a considerable overlap in the indices of patients with "normal" function, ATN and patients with AR, a single PI and RI value is of limited utility in the diagnosis. Hollenbeck et al. reported that primary rejections were better identified by an increased PI over the preceding value than by an absolute PI value. Measurement of the increase in intra-renal indices using serial duplex scanning was more valuable than that of a single time observation. In these patients, the finding of a >10% increase over the previous PI and RI offered much better combination of good sensitivity and reliable specificity. We used this in our study increasing Doppler US and renal graft biopsy (used as the gold standard) into 57.14% in AR and 40% in ATN in our series (Table 1, Fig. 2). The higher agreement in chronic rejection (87.57%) is mainly attributed to other clear morphological changes (increased parenchymal echogenicity and significantly thinned parenchyma) rather than the serial Doppler values which are not significantly changed (Table 1, Fig. 2). Even with the use of serial examination and Power Doppler ultrasound signs, specificity mildly increased.

Although small in number, vascular complications namely TRAS (n=2) and intra-renal vascular thrombosis (n=1) were accurately diagnosed by Doppler US (100%) and confirmed by MRA and Catheter angiography in the former and confirmed in post-transplant nephrectomy in the later based mainly on the indirect downhill pulsed Doppler signs in interlobar vessels.

Conclusion:

Doppler ultrasound is the primary investigation in renal graft dysfunction due to absence of ionizing radiation and contrast administration. It has high sensitivity in vascular complications, peri-graft collection and masses. Its lower specificity in differentiating parenchymal entities can be increased by using power Doppler and serial assessment of PI in conjunction with RI parameter. Its clear value is in follow-up and also in patient's selection for biopsy.
References


