RESEARCH ARTICLE

Shear Wave Elastography in Evaluating Acute Kidney Allograft Dysfunction: Preliminary Results.

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Abstract

Background
In absence of pharmacological toxicity, allograft dysfunction is usually due to parenchymal inflammation and tubulointerstitial fibrosis, but its clinical signs are often non-specific and tend to appear when advanced damage has been established. We investigated whether Shear Wave Elastography (SWE), a new non-invasive ultrasound (US) based technique that estimates tissue stiffness, could provide early confident diagnosis of acute allograft dysfunction compared to biopsy (gold standard technique).

Methods
We designed a single Centre, case-controls, prospective, longitudinal and analytical study that included all kidney transplanted patients with acute allograft dysfunction referred for biopsy at our Institution for 21 months. Within 24 hours after laboratory tests an initial US and Doppler examination was performed. If non-parenchymal, urinary or vascular complications were encountered, the patient was considered as case. We gathered consecutive normal-functioning transplanted patients referred for routine follow-up. If no US abnormalities were encountered, they were classified as controls. 7 quantitative SWE measurements at each allograft´s cortical region were acquired (kilopascals (kPa). Within 24 hours, same-point allograft biopsies were performed by Nephrologists in cases. Once Pathology results were available statistical analysis were subsequently performed.

Results
26 patients (13 cases and 13 controls) were enrolled. Creatinine serum mean values were 4,18mEq/dL in cases and 1,84 in controls. SWE mean values were of 21,45 kPa in cases and 13,73 in controls. Biopsies were evaluable in all cases. Statistical analysis showed a positive relation between SWE and creatinine levels. No significance was found of SWE with anatomopathological results in terms of rejection/others, neither with rejection type.

Conclusions
SWE is a helpful, non-invasive tool for early diagnosis of kidney allograft dysfunction. Patients with higher elasticity values, in absence of clinical or analytical manifestations, should be included in an increased surveillance program since parenchymal disorders may be incipient. However further studies, with larger cohorts, are necessary to validate these findings.

Keywords: Kidney allograft; Shear Wave Elastography; Ultrasound; Acute allograft dysfunction; Kidney transplant.

1. Introduction

Kidney transplantation is the treatment of choice in patients with end-stage renal disease since it allows better life quality and offers better survival advantages compared to hemodialysis (1). Significant allograft survival rates have progressively been achieved in early stages during last decades, although long-term allograft survival remains unchanged in Europe (2).

Renal allograft dysfunction is defined as increase of serum creatinine baseline levels of 15% (3). Different publications indicate it occurs most frequently after 1 year following transplantation with a reported incidence of long-term allograft failure of 4% per year (4). Early allograft dysfunction encounters during the first 3 months after implantation and can be due to vascular thrombosis, urologic pathology, thrombotic microangiopathy or rejection (5).

Allograft rejection is caused by inflammation with specific pathologic changes due to the recipient's immune system recognizing the non-self-antigen in the allograft. Acute rejection can occur any time after transplant although it is usually encountered within days to weeks after surgery (6) and has been identified as the main cause of renal graft dysfunction during the first year after transplantation (7) affecting almost 15% of patients during this period (8). Acute rejection can be divided in antibody-mediated rejection, which causes glomerulitis or peritubular capilaritis; and T-cell mediated rejection, which causes lymphocytic infiltration of the tubules, interstitium and occasionally the arterial intima (9).

Chronic allograft dysfunction occurs at least 3 months after transplantation. It is a multifactorial process that leads to progressive glomerular sclerosis, interstitial fibrosis, and tubular atrophy. It is usually due to glomerulonephritis recurrence, artery stenosis, calcineurin inhibitor´s toxicity or post-transplant glomerulopathy (10). However, several entities such as calcineurin inhibitors, BK virus toxicity or rejection can be encountered in both, early and delayed stages of allograft dysfunction (11).

Chronic rejection usually develops beyond 12 months post-transplantation (in absence of acute rejection, drug toxicity or other causes of nephropathy) and it can either be chronic antibody-mediated or T-cells mediated. It usually associates chronic inflammatory phenomena that leads to interstitial fibrosis and finally to tubular atrophy (8).

Clinical manifestations of acute kidney graft dysfunction are often non-specific (increase of creatinine levels, proteinuria, reduction in urine output) (5) and usually appear when advanced and/or irreversible parenchymal damage has already been established (12).

Although allograft biopsy remains to be the gold-standard technique for diagnosis of acute and chronic graft dysfunction (once underlying pathology or justifying treatments have been ruled out) (13), it is an invasive tool with severe potential technical complications (active bleeding, hematoma, or arteriovenous fistula development). Well-known limitations of biopsy are its low specificity due to similar anatomopathological appearance of different entities (14), the absence of international accepted classifications, insufficient sample obtainment, and the lack of pathologist's standardization within its interpretation.

Ultrasound (US) is a safe, non-invasive, repeatable and safe diagnosis technique that provides real-time information of kidney vessels, excretory system, cortical thickness, corticomedullar differentiation and allograft surrounding structures. It can be bed-side performed at intensive care units and doesn´t use non-ionizing radiation or nephrotoxic contrast (15). Increased cortical thickness, higher arterial resistance indexes or mild corticomedullar differentiation loss are often encountered US findings in allograft dysfunction patients. Unfortunately, these are non-specific and tend to overlap with each other (16). Therefore, US becomes of limited use when evaluating these patients.

Up to date, the role of further advanced US techniques such as contrast enhanced US (CEUS) still remains unclear (17), but since persistent dysfunction may lead to loss of allograft´s function and, eventually, to allograft failure; reliable and non-invasive diagnosis techniques are required in order to provide early and confident diagnosis of graft dysfunction etiology.

Two Dimension-Shear Wave elastography (SWE) is the most recently developed elastography technique. It uses acoustic radiation force by focused ultrasonic beams to induce mechanical vibrations. The induced tissue displacement by these mechanical vibrations, creates waves which spread through the tissue of interest. Propagation of these resulting shear waves, captured by high frequency US imaging sequences, enables the assessment of tissue elasticity (18). Elasticity loss or increase of allograft´s stiffness due to inflammation and fibrosis can therefore be detected with a non-invasive tool. This modality of elastography has already been approved by the FDA for diffuse hepatopathy differentiation from liver cirrhosis (19), and it seems to have promising applications in characterizing breast, thyroid and native kidneys solid lesions as benign or possibly malignant (20).

SWE acquisition is based on is a fully integrated software in the US machine without the need of any additional special probe or device. SWE values are shown both in a color map (qualitative display), and in a quantitative manner (kilopascals (kPa) or meters per second display). Since SWE acquisition is less sensitive to probe´s pressure than other elastography modalities, it has higher interobserver reproducibility and agreement than with Fibroscan or Strain elastography (21).

Prompt recognition and evaluation of allograft dysfunction is vital since in early stages, it can be reversible. Tissular inflammation and tubulointerstitial fibrosis are the underlying substrates of early and delayed graft dysfunction. Therefore, a tissue stiffness raisal due to edema and fibrosis should theoretically be encountered in these patients, and higher SWE values should be obtained in these patients when compared to normal functioning grafts.

Recent published investigations suggest SWE can accurately correlate with kidney fibrosis (22) but up to date, no consent has been established regarding the potential role of this imaging modality in diagnosis of allograft dysfunction (23).

2). Objectives

Main objective:

To determine if kidney transplanted patients with acute elevation of creatinine serum levels have higher mean SWE values when compared to normal-functioning allografts.

Secondary objective:

To investigate if SWE mean values in acute kidney allograft dysfunction patients can be related to allograft´s biopsy results.

3). Material and Methods

We designed a prospective, longitudinal, non-blind and analytical study that included all kidney transplanted patients in our Centre that developed acute allograft dysfunction from January 2018 up to September 2019 (21 months). Patients submitted to our Radiology Department for US evaluation prior to allograft´s biopsy where considered as cases. Consecutive patients with normal allograft function submitted to our Department for routine follow-up US, were included as controls.

All US examinations were performed by the same experienced 10-years US Senior Radiologist with an US Aplio 500 Platinum device (Canon Medical Systems, Japan) using a low frequency (3.5 MHz) convex probe (PVT-375BT).

We designed a SWE standard acquisition program for all patients with a gain range of 70-85dB, and a standard Region of Interest (ROI) measuring box of 55 x 40mm. Sterile gel was used when the patient presented a recent surgery wound (Transonic Gel, Ref. G-15E, TELIC TAU), whereas conventional US gel was used for the rest of the patients (Transonic Gel, TELIC TAU).

Inclusion criteria:

Age > 16 years.
Transplantation performed in our Centre.
Cases were defined as acute allograft dysfunction patients (creatinine values over 2,2 mEq/dL., or over 15% among basal) referred for US evaluation prior to biopsy.
Controls were defined as normal functioning allograft patients (creatinine values inferior to 2,2 mEq/dL. (as standardized in our Centre).

Exclusion criteria:

Age < 16 years.
Transplantation performed in another Centre.
Concomitant organ transplantation.
US diagnosis of hydronephrosis, nearby graft collections, arterial or venous (stenosis or thrombosis), allograft infarction (corticomedullar microvasculature defect confirmed with CEUS or other imaging modalities).
Proven pharmacological toxicity (with specific blood tests).
Non-informed consent for biopsy performance.
Acute allograft dysfunction patients who weren´t candidates for biopsy.
Critically ill patients.
No valuable SWE measurements (interquartile (IQR) range in measurements over 30%).

Epidemiological data (age, sex, time from transplantation and creatinine levels) was collected from every patient included in our study.

We initially performed a conventional B-Mode, Color Doppler and Pulsed Doppler US in order to rule out vascular pathology, obstructive uropathy or nearby fluid collections on every patient (table 1). Patients who developed acute allograft failure but were not biopsy candidates (e.g.: severe coagulopathy) were not included since we could not compare elasticity values with the gold standard diagnosis technique.

Once the patient was classified as case or control, allograft SWE was acquired as follows: Supine positioning of the patient. Both arms placement under the patient's neck. Gel and convex probe placement superficially to graft´s location (right/left iliac fossa), and B mode US longitudinal imaging of the graft (in order to minimize anisotropy artefact) was obtained.

Immediately, SWE mode activation was done at the control panel, and once the region of interest (ROI measuring box appeared at the screen, it was placed at the graft´s cortical region (at 3mm depth from kidney´s capsule) in the interpolar or medial pole (where acoustic window was more favorable). The patient was subsequently asked to remain breathless during 3 seconds before acquisition of 3 color propagation maps was done. Then the patient was allowed to breathe normally while the operator performed stiffness measures on each map at the US machine.

A final number of 7 measures were collected per patient with the ROI ´s size predefined in "3", all of them with IQR inferior to 30%. A digital and automated spreadsheet was generated at the US machine, gathering all valid SWE measurements from each patient including mean, median, standard deviation and IQR. These SWE values were exported to a final Excel table containing the whole epidemiological information of all the patients gathered in the study.

Within the first 24h after US examination and SWE acquisition, a same-point US-guided allograft biopsy was performed by Nephrologists at the Nephrology department (obtaining 3 cylinders per patient). Biopsy was subsequently evaluated by two Senior Pathologists. Results were classified into 3 groups: cellular rejection, humoral rejection and others (disease recurrence, ischemic lesion or chronic graft nephropathy). These reports were added to the above mentioned Excel table.

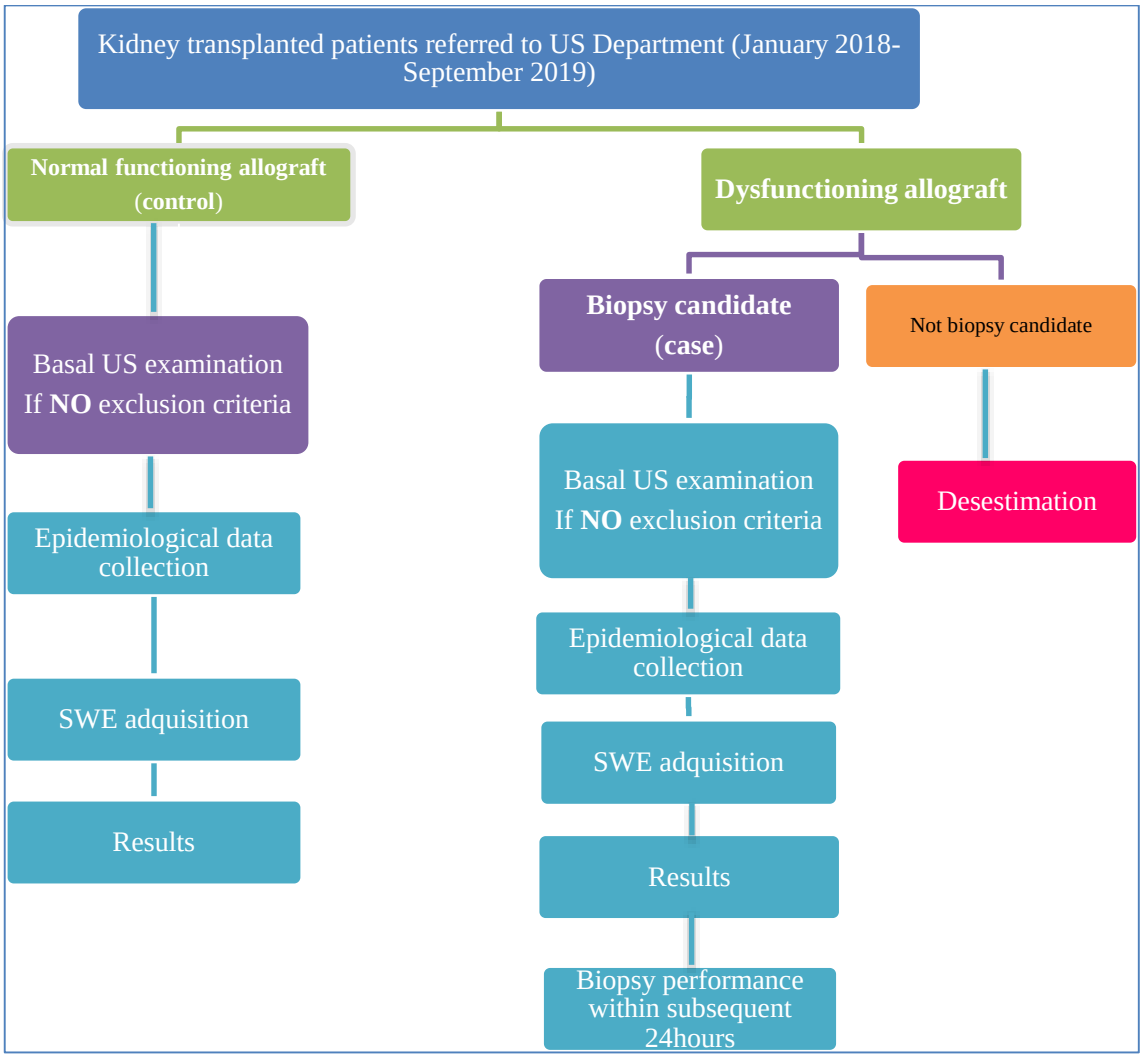
Finally, statistical tests were performed in order to evaluate the potential relationship of mean SWE values of allograft dysfunction patients and normal functioning allograft, with creatinine values and with biopsy results (classified rejection/others).

Statistical software (SPSS version 19.0, IBM) was used for all statistical analyses. Mann-Whitney U-Test was applied to evaluate the association of creatinine values and stiffness (SWE) between cases and controls patients. Spearman's rank correlation coefficient (non-parametric test) was subsequently used to measure the relationship between creatinine levels and kidney stiffness/SWE values. Since our study population (*n*) was low and we couldn´t assure variables followed a complete normal distribution, parametric tests (such as Pearson coefficient) were not be suitable for this investigation.

We performed ROC curve and area under curve (AUC) analysis to assess the performance of SWE in diagnosing allograft dysfunction and to compare the discriminative power of creatinine values versus SWE for this same diagnosis. *P* values of 0,05 or less were considered to indicate statistical significance.

This investigation has been designed and performed conforming to the principles of the Declaration of Helsinki. This study has been approved by the Institutional Review Board of our Centre. Informed consent was gathered from every patient prior to US evaluation and biopsy performance.

Table 1. Study protocol.



4). Results

17 cases were finally enrolled in this investigation. Invalid SWE measurements (IQR>30%) were reported in 2 patients. In 2 more cases, the final Pathology report was not conclusive due to Pathologist´s disagreement. Therefore, the final total number of cases included was 13 (mean age 55,2 years).

13 consecutive controls were collected (mean age 49,3 years).

Epidemiological data of our study population is shown here below (table 2) and biopsy results are exposed in table 3.

SWE values obtained in cases and in controls, and well as their corresponding creatinine values are show in table 4.

Table 2.

INCLUDED CASES Nº	**13**	**INCLUDED CONTROLS Nº**	**13**
Gender	5 men 8 women	**Gender**	8 men 5 women
Age range	27-78 years	**Age range**	26-72 years
Creatinine mean values	4,18mEq/dL	**Creatinine mean values**	1,84mEq/dL
SWE mean values	21,45 kPa (SD 0,6- 4,5)	**SWE mean values**	13,73 kPa (SD 0,8-3,8)

Table 3.

BIOPSY RESULTS	**NUMBER OF PATIENTS**
Cellular rejection	**6**
Humoral rejection	**4**
Others	**1** Graft chronic nephropathy
	1 Disease recurrence
	1 Acute ischemic lesion
TOTAL	**13**

A significant difference was observed for creatinine values between cases and groups, being higher in the cases group (p=0,001). Kidney stiffness was significantly higher in the cases group (p=0.022) than in controls. This means, that SWE demonstrates that allografts with acute dysfunction tend to be stiffer that normal functioning ones.

Spearman´s rank showed a weak association between creatinine and stiffness with a value of r_s=0,269 (p=0,184); which is non-significant. This means, that according to our results we cannot establish a linear relation between creatinine and SWE values.

Further analysis resulted in that SWE values showed an acceptable discriminatory capacity for the diagnosis of allograft dysfunction [with AUC 0,763 (CI 0,575-0,952)]. Although creatinine levels have a superior discriminative capacity for this diagnosis [AUC 0,899 (CI 0,765-1); p=0,001], both tests presented values greater than 0,75, and in neither of them the confidence interval obtained included the non-discrimination value (0,5). This means, SWE is strong enough to be considered a useful diagnosis tool.

Further statistical tests did not reveal significant association of kidney stiffness (SWE) with biopsy results classified as rejection or others. We did neither obtain statistical significance when investigating

the potential relation of SWE to rejection type classified as humoral o cellular (*p* was superior to 0,05).

Table 4.

CASE Nº	Creatinine value (mEq/dL.)	SWE mean value (kPa)	BIOPSY RESULT	CONTROL Nº	Creatinine value (mEq/dL.)	SWE mean value (kPa)
1	2,35	25	Cellular rejection	**1**	1,47	14,7
2	3,70	16,67	Humoral rejection	**2**	1,89	12,5
3	3,55	12,7	Cellular rejection	**3**	1,73	16,6
4	3,15	14,7	Cellular rejection	**4**	1,72	9,9
5	8,41	17,97	Cellular rejection	**5**	2,14	18,2
6	5,01	24,05	Cellular rejection	**6**	1,84	19
7	4,31	25,10	Humoral rejection	**7**	1,75	12,4
8	3,56	28,5	Humoral rejection	**8**	1,07	11,4
9	2,42	11,45	Cellular rejection	**9**	1,53	12,9
10	3,1	24,1	Chronic allograft nephropathy	**10**	2,01	15,3
11	4,05	8,7	Disease recurrence Nonspecific changes	**11**	1,88	11
12	4,33	45,8	Acute ischemic tubulopathy	**12**	2,18	14,3
13	1,53	23,3	Humoral rejection	**13**	2,47	7,6

5). Discussion

Early detection of allograft dysfunction is mandatory for prompt treatment instauration. In absence of vascular abnormalities of pharmacological toxicity, it is usually based on serum creatinine levels determination and biopsy. We conducted this study to determine if SWE could be considered a reliable and non-invasive tool in early diagnosis of acute allograft dysfunction.

We found a significant elevation of mean SWE values in allograft dysfunction patients (21,45 kPa) compared to normal functioning allograft´s (13,73 kPa). Creatinine mean values were also significantly elevated in cases (4,18 mEq/dL.) compared to controls (1,84 mEq/dL.).

Statistical tests revealed a positive (although nonlinear) correlation between creatinine values and allograft's stiffness between both groups. According to this result, SWE could be considered as an independent and quantitative criterion to predict and early diagnose potential allograft dysfunction, even when creatinine increase doesn´t reach 15% over baseline values. This means patients with mild or no elevation of creatinine levels, but with increased SWE values should undergo an increased surveillance program in order to early detect possible incipient dysfunction.

On the contrary, statistical tests did not demonstrate a significant correlation between SWE mean values and pathological results classified as rejection/others nor to the type or rejection, classified as cellular or humoral. Therefore, according to our results, SWE could not be considered as a reliable tool in depicting the underlying etiology of allograft´s dysfunction up-to-date.

As a final conclusion we could state that SWE could be considered as a sensible non-invasive tool in early detecting acute graft failure but with low specificity, and therefore it cannot replace biopsy.

As future research**,** we suggest close monitoring of every control in order to detect if early SWE changes do correlate with potential misfunctioning. This is, each patient will be converted into case and obtained results could be compared with himself (control). Then we could potentially evaluate the strength of SWE in detecting acute allograft failure in an exquisite manner. Moreover, we could extend this investigation to other variables and determine the whether stiffness can correlate with other variables such as main artery resistance index and/or proteinuria values.

SWE remains a promising diagnosing modality in evaluating kidney transplant patients although more time and experience, and studies with larger cohorts are needed to refine its possible applicability's.

6). Limitations

Our study includes a small sample of patients. This could be the reason why we only obtained statistical significance in a single variable. New investigations with a higher patient cohorts are needed in order to minimize size bias and establish new correlations with variables that were almost near to p= 0,05.

Moreover, there is no international consent regarding what mean SWE values should be established as a cut-off point to diagnose graft´s parenchymal disorder.

This threshold could help to early diagnose patients before dysfunction is established (SWE high-end values) and could improve and narrow the selection of biopsy candidates.

Interobserver US agreement could not be evaluated, since all examinations were performed by the same Radiologist.

Our Centre Pathologists still lack consent when applying Banff's classification. Although current publications suggest its possible positive correlation with SWE values, we could not confirm nor establish any relation according to this categorization (24).

7). Interest Conflict Statement

No affiliations with or involvement in any organization or entity with any financial interest (such as honoraria, educational grants, participation in speakers' bureaus, membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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