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Acoustic Radiation Force Impulse Imaging In Non-Invasive Assessment of Renal Histological Fibrosis

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Abstract: ***Introduction****: Chronic kidney disease (CKD) is defined as decreased glomerular filtration rate, raised urinary albumin excretion or both. CKD poses as a significant public health problem.Acoustic radiation force impulse (ARFI) imaging is a recently developed, non-invasive technique to quantitatively assess the mechanical stiffness properties of any organ tissue.*
Material & Methods*: A total of 200 patients underwent renal biopsy. ARFI readings with resistive index, cortical thickness and renal length were measured by two radiologists prior to biopsy. The biopsy specimen was processed and graded as per classification of Mayo clinic/Renal Pathology Society Consensus report on Pathological Classification, Diagnosis and Reporting.*
Results*: Majority of the population had IgA nephropathy(n=51;25.5%) followed by diabetic nephropathy (n=45; 22.5%). ARFI and total pathological score was inversely correlated. As ARFI value decreases, it is noticed that there is decrease in eGFR with a correlation co efficient of + 0. 279. The resistive index correlates well with total score with a correlation co efficient +0. 416. Renal length and total pathological score was inversely correlated. Resistive index is the best predictor of chronicity score among the ultrasound variables analyzed to detect chronicity.*
Conclusions*: ARFI is a good non - invasive tool for predicting chronicity in renal pathology specimens. It is a good predictor of changes in eGFR in acute and chronic kidney settings.*
Keywords*: chronic kidney disease, Acoustic radiation force impulse, renal histological fibrosis, evaluation*

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I. Introduction

Chronic kidney disease (CKD) is defined as decreased glomerular filtration rate, raised urinary albumin excretion or both[1]. CKD poses as a significant public health problem in developed countries and developing countries like India[2].The worldwide prevalence of CKD is approximately 8–16 %[3,4]. The reported prevalence of CKD in different regions of India varies from 1% to 13% , and recent data from the International Society of Nephrology's Kidney Disease Data Centre Study stated a prevalence of approximately 17%[5].

All patients suffering from CKD show a progressive decrease in the renal function with time. Renal fibrosis is the main process forming the basis for the progression of CKD, which is a relatively unvarying response. This process mainly involves glomerulosclerosis, interstitial fibrosis, tubular atrophy, as well as alterations in renal vasculature[6]. Renal fibrosis requires an industrious management as well as treatment strategy comprising of sensitive monitoring and specific treatment for renal fibrosis that would lead to a large scale medical, social as well as economic benefit. Renal biopsy is considered as the best method to assess the severity of renal fibrosis as well as the other related pathologic changes. The disadvantages of renal biopsy include sampling errors during pathological processing, invasive, as well as impractical for longitudinal monitoring. Also, for a developing nation like India, the access to biopsy assessment is not easy and the technical finesse involved in this procedure may not be easily available. Therefore, there is a crucial need to develop some alternatives which are reproducible as well as non-invasive[7]. There is a grave need to develop new diagnostic options with high sensitivity and reproducibility.

Acoustic radiation force impulse (ARFI) imaging is a recently developed, non-invasive technique to quantitatively assess the mechanical stiffness properties of any organ tissue. It is a recently developed, internal technique which is dynamic and that superimposes data concerning tissue elasticity to a conventional grey-scale image produced by commercial ultrasound (USG) scanners[8]. It uses low duration, high intensity pulses of

acoustic radiation force to produce focused displacements in the tissue and conventional ultrasound beams to track the dynamic response of the tissue. Acoustic radiation force is an outcome from a momentum transfer from the moving ultrasonic wave to the tissue through which it is propagating due to scattering mechanisms as well as absorption. It utilizes acoustic radiation force to transiently deform soft tissues in the area of interest and the dynamic displacement response of those tissues is measured ultrasonically and is utilized to estimate the tissue's mechanical properties[9].Since the force of acoustic impulse induces mechanical vibrations automatically, ARFI is operator independent and can determine tissue elasticity quantitatively. It overwhelms the intrinsic limitations of the strain elastography which can only control the relative and the qualitative elasticity.

ARFI has been used by physicians in the assessment of various organs such as breast, testis prostate, and thyroid and has also been used to detect elasticity in the graft kidneys of renal transplant recipients[10]. The major reason of renal transplant failure is chronic allograft nephropathy which is related with features of interstitial fibrosis and tubular atrophy.Some studies have verified ARFI as an accurate, promising and repeatable approach in liver fibrosis grading. However, there is a paucity of data related to the published literature that have assessed ARFI as a non-invasive tool in detection of renal tissue fibrosis in CKD patients. One such study by Stock et al. reported a remarkable correlation between shear wave velocity (SWV) and renal allograft fibrosis and backed the finding that SWV may have potential for assessing the grade of fibrosis in renal transplant [11]. However, the literature search done pertaining to availability of any Indian study related to the topic revealed lack of published evidence.

We hypothesized that the change in renal parenchyma stiffness indicated by ARFI might be a useful sign for detecting CKD. Hence, this study was planned by the Nephrology department of Government General Hospital in Guntur to investigate the stiffness value obtained by ARFI quantification and to correlate with renal histological findings. Another important objective of this study was to ascertain whether ARFI can be used as an effective non- invasive tool for evaluating renal histological fibrosis in comparison with ultrasound parameters.

II. Material And Methods:

Study Site: Department of Nephrology and Radiology, Government General Hospital, Guntur Medical College, Guntur.
Study Population: All patients who were undergoing native renal biopsy.
Study Design: Prospective observational study.
Sample Size: 200
Study period: September 2017 to April 2019.
Inclusion Criteria: All patients who undergo native renal biopsy with informed consent. (Age group-18-65 years)
Exclusion Criteria: Unwillingness of the patient, Patients who have undergone renal transplant, Patients having hydronephrosis, cyst, suspected renal artery stenosis and Pathology specimen containing less than 10 glomeruli.

III. Methods

The patients who are undergoing renal biopsy were enrolled in the study.They had their routine blood and urine investigations before the study (serum creatinine, urea, serum albumin) which were used in our study.The ultrasound parameters were evaluated 15 minutes prior to renal biopsy in the ultrasound room.

- The ultrasound parameter measurements including ARFI was given by two experienced radiologists with experience of 10 years in the field of radiology and 5 years' experience in handling ARFI measurements.
- ARFI quantification given as shear wave velocity was performed to measure renal parenchymal stiffness along with Ultrasound parameters like corticalthickness, renal length and resistive index before biopsy.
- Ultrasound was done in real time B mode. The ultrasound machine was EPIQ 7 Philips –High End Machine and the transducer was a 3 MHZ transducer focusing on the lower pole of the kidney. 15 readings of shear wave velocity (ARFI) were taken during the study in each patient and the average value was taken for final analysis. The patient was asked to hold breath for 10 seconds while taking readings for ARFI. The ARFI value is computed by software installed in the ultrasound machine based on the tissue elasticity.
- The renal length is the distance measured between the uppermost edge of the upper pole of the kidney to the lower most edge of the lower pole in ultrasound. Two readings were taken by two radiologists each and the average was taken as the final reading. The renal length is expressed in centimeters in this study
- The cortical thickness is the distance between the cortex –perirenal fat interface(capsule) and the sinus pyramidal apex interface. The average of the reading taken by two radiologistswas taken as the final value of cortical thickness in this study. The cortical thickness is expressed in centimeters.
- The renal resistive index is a doppler measurement which is measured as Peak systolic velocity-end diastolic velocity/Peak systolic velocity. It was measured at arcuate arteries (at the cortico-medullary

junction) and the mean reading given by two radiologistswas taken as the final value of resistive index in this study.

- The eGFR expressed in ml/min is calculated in the study is by using the MDRD 6 variableequation which includes age, sex, creatinine, race, albumin and blood urea nitrogen.Diagnostic performance of ARFI imaging and Ultrasound parameters was compared to the histological scores at renal biopsy and eGFR values.
- Renal biopsy of the lower pole of the kidney parenchyma was performed using an 18G needle fixed to automatic spring-loaded biopsy gun. under ultrasonic guidance. A 2.2- cm kidney tissue biopsy was obtained and sent for pathological evaluation in two containers one containing 10% formalin and another bit in a biopsy box having normal saline soaked gauze.

Our study involved 60 volunteers without renal pathology enrolled to decide upon a control value for ARFI in the ultrasound machine. The age group enrolled for control group was between 18-70 years. These control patients were any random individual who visited the ultrasound department for routine health assessment.

Pathological Staging: The pathological specimen was immediately taken to pathology lab in two containers (one containing formalin and other biopsy container containing saline soaked gauze)**.** Kidney tissue obtained by needle biopsy was fixed in 4 % buffered formaldehyde. After embedding in paraffin, 2-µmthick serial sections were cut and haematoxylin and eosinstaining and the periodic acid silver methenamine method were applied for assessment of the glomerulosclerosis and tubular atrophy. In addition, a Masson–Goldner's trichromemethod was performed to quantify interstitial fibrosis.

Staining's were performed according to standard protocols.The specimen which didn't contain a minimum of 10 glomeruli were not included since it was considered inadequate for pathological interpretation as per guidelines given by S.K Agrawal et al for renal biopsy adequacy [12].

- The pathological scoring of interstitial fibrosis was done as per the guidelines of the Mayo clinic/Renal Pathology Society Consensus report on Pathological Classification, Diagnosis and Reporting of Glomerulonephritis. (Author: Sanjeev Sethi, Mark Hass et al.[13,14])
- The pathological scoring was done by experienced pathologist of at least 10 years blinded to the clinical diagnosis and radiological findings.
- The pathological score has various components like glomerulosclerosis, vascular score, interstitial fibrosis and tubular atrophy which are predictors of chronicity in renal pathology.
- The pathological score used in thisstudy is a gold standard reference parameter to evaluate the performance of various ultrasound parameters including ARFI in its effectiveness and credibility to non- invasively determine the interstitial fibrosis and tubular atrophy visualized in the pathology slides.

Statistical analysis:

Data entry was done in MS excel spreadsheet.Data analysis was done in SPSS software version 16.0All p values less than 0.05 was considered statistically significant.All continuous variables were expressed as mean plus minus standard deviation if they are normally distributed.Non normally distributed continuous variables were expressed by median (inter quartile range).

Comparison of normally distributed continuous variables were done by independent sample 't' test.Non normally distributed continuous variables were compared by Mann Whitney U test.Comparison of categorical variables, if any, were done by Chi Square test or Fischer's exact test. Pearson's correlation co efficient was computed to know the association between binary variables.ROC curve was drawn to find out cut of values of ARFI.

IV. Results

Among the 200 patients enrolled in the study predominantly 40%(n=80) belonged to the age group between 46-60 years,30%(n=60) belonged to the 31-45 years age bracket.64%(n=128) were male and 36%(n=72) were females.

Majority of the population had IgAnephropathy(n=51;25.5%) followed by diabetic nephropathy (n=45;22.5%). 91 patients had an eGFR greater than 60 ml/min/m^2.which is followed by 40 patients having an eGFR between 0-14 ml/min/m^2. Nearly 50% of patients had had renal length greater than 10 cm on ultrasound measurement. Nearly three fourth (72%) had resistive index between 0.61-0.8.

More than three fourth (77%) had cortical thickness between 0.6-0.8 cm followed by 35 patients (17.5%) having cortical thickness between 0.9-1 cm. There were 116 patients with ARFI value ranging between 0.81-1 m/sec followed 58 patients with ARFI between 0.51-0.8 m/sec.

50.5%(n=101) having glomerulosclerosis between 10-25% on biopsy followed by 44.5%(n=89) having glomerulosclerosis <10%. Majority 90%(n=180) had intimal thickening less than thickness of media.There were 41.5%(n=83) having interstitial fibrosis less than 10% on biopsy and there were 47.5%(n=95) having tubular atrophy between 10-25% on biopsy.

Among 200 patients, mild chronic changes on biopsy as per pathological scoring was seen in 44.5%(n=89) followed by minimal chronic changes on biopsy in 38%(n=76). The third group is constituted by moderate chronic changes with 61 patients (30.5%) followed by 9.6%(n-24) which is the group having severe chronic changes.

Correlation between ARFI and total pathological score:

ARFI and the total pathological score corelate inversely that is if the ARFI value increases the total pathological score decreases and vice versa with a correlation co efficient of -0. 286.The 2 tailed tests conducted on these two variables computed a p value of 0.0001 which is statistically very significant. Also, ARFI value is statistically significant in all groups of chronicity scoring with a p value less than 0.05 in all groups (ANOVA Test).Even an intergroup analysis comparing the changes of ARFI as chronicity score changes yields a statistical significance within all groups with a P value always less than 0.05. (ANOVA Test). ARFI value is statistically significant with p value less than 0.05 even separately analysing the grade of interstitial fibrosis and tubular atrophy.

Correlation between ARFI and eGFR

As ARFI value decreases, it is noticed that there is decrease in eGFR with a correlation co efficient of + 0. 279.The 2 tailed tests used to analyse ARFI and eGFR concluded that ARFI is a good predictor of eGFR with a p value less than 0.05(p=0.0001).

Correlation between Resistive index, total score and eGFR

The resistive index correlates well with total score with a correlation co efficient +0. 416.The resistive index decreases as the total score decreases and vice versa. The two tailed test concludes that resistive index is a good predictor of chronicity with p value less than 0.05(p-0.0001).As the resistive index increases the eGFR decreased with negative correlation co efficient of -0.412.A two tailed test indicates that resistive index is good predictor of changes in eGFR with p value less than 0.05(p=0.0001).

Correlation between renal length and total score

The renal length and the total score have a correlation co efficient of -0.342 which indicates that as length increases, the total pathological score is less (it is an inversely proportional parameter). The two tailed test concludes that renal length is a sensitive indicator for changes in the chronicity index as scored in the renal biopsy samples. Even renal length is a good indicator for the changes in eGFR as computed with the two tailed tests with p value less than 0.05(p=0.008).

Regression analysis of various parameters in relation to chronicity score

On regression analysis using total chronicity score as a constant variable neutralizing all other factors it is found that resistive index (p=0.0001) and renal length (p=0.0004) are better parameters in predicting chronicity and interstitial fibrosis and tubular atrophy than ARFI(p=0.004) and cortical thickness(p=0.007). Resistive index is the best predictor of chronicity score among the ultrasound variables analyzed to detect chronicity.

Regression analysis of various parameters in relation to eGFR

On regression analysis using eGFR as a constant variable neutralizing all other factors it is found that resistive index (p=0.0001) and ARFI (p=0.001) are sensitive parameters in predicting changes in eGFR. Renal length (p=0.137) and cortical thickness(p=0.879) are statistically insignificant which denotes that they are not equivalent and sensitive predictors as compared to resistive index and ARFI. Resistive index is the best variable among the four modalities in accurately predicting the changes in eGFR.

V. Discussion

The mean age of the study population in our study was 45.34± 11.8 years. In comparison the study done by Wang et al [15]. the mean age in their study was 37.1±13.4 years. However, the study done by Guo et al[16]. calculated the mean age of the study group in different classes of chronic kidney disease was computed.The gender distribution in our patients were males contributing 64%(n=128) and females contributing around 36%(n=72). Compared to other study done by Wang et al.[15]we had higher proportion of males compared to females which is in accordance with gender ratio of our hospital outpatient registration which is 2:1.

The average resistive index in our study was 0.62± 0.05. The study done by Suguira et al.[17] in 2009 had an average renal resistive index of 0.69±0.10 which is very similar to our study.

In the study done by Radermacher et al[18] he found a significant association of renal resistive index with eGFR with a p value of 0.01. His study showed that an RI greater than 0.70 is associated with significant decline of renal function and increased mortality. In our study also we found a significant association of resistive index and e GFR with a p value of 0.0001 which was statistically significant. It corroborates with findings of Radermacher et al[18]that renal resistive index is sensitive indicator of declining renal function.

Splendiani et al[19]also showed that resistive index greater than 0.70 was predictor of poor renal outcome. It showed that it very well co related with trend of eGFR decline with p value less than 0.001during a follow up period of 5.93 years. This is similar to out observation where we found that resistive index and eGFR had a good co relation with a P value less than 0.0001.

The resistive index also correlates well with total pathological score with a correlation co efficient +0. 416.The resistive index decreases as the total score decreases and vice versa. The two tailed test concludes that resistive index is a good predictor of chronicity with p value less than 0.05(p-0.0001). As the resistive index increases the eGFR decreased with negative correlation co efficient of -0. 412.. A two tailed test indicates that resistive index is good predictor of changes in eGFR with p value less than 0.05(p=0.0001). This result is similar to the findings of Suguira et al.[17]. The study done by of Suguira et al.[17] showed that there were significant differences in the decrease in GFR on the basis of resistive index at 24 months.

VI. Conclusion

ARFI is a good non - invasive tool for predicting chronicity in renal pathology specimens.It is a good predictor of changes in eGFR in acute and chronic kidney settings.ARFI can used in future as an effective tool for evaluating patients in whom renal biopsy is contraindicated or is very risky.It should be incorporated as a radiological tool in routine practice in the near future along with conventional ultrasound parameter for evaluation of renal pathologies.ARFI values can be used to stage chronic kidney diseases in the near future. However large-scale studies in this perspective needs to done.

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