“ROLE OF ULTRASONOGRAPHY AND ELASTOGRAPHY IN RENAL PARENCHYMAL DISEASE IN DIABETIC AND HYPERTENSIVE PATIENTS”

BY

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DISSERTATION SUBMITTED TO SRI DEVARAJ URS ACADEMY OF HIGHEREDUCATION AND RESEARCH, KOLAR, KARNATAKA

In partial fulfilment of the requirements for the degree of

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IN
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Under the Guidance of

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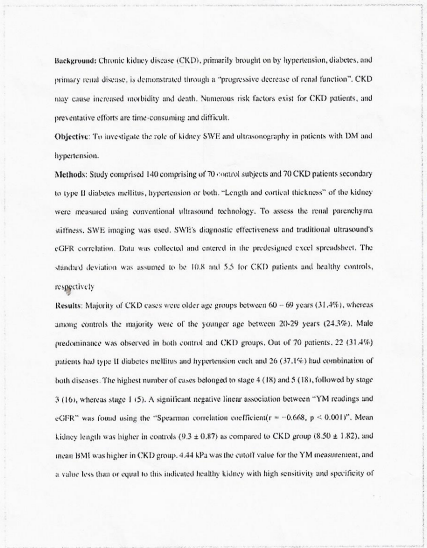

Background: Chronic kidney disease (CKD), primarily brought on by hypertension, diabetes, and primary renal disease, is demonstrated through a "progressive decrease of renal function". CKD may cause increased morbidity and death. Numerous risk factors exist for CKD patients, and preventative efforts are time-consuming and difficult.

Objective: To investigate the role of kidney SWE and ultrasonography in patients with DM and hypertension.

Methods: Study comprised 140 comprising of 70 control subjects and 70 CKD patients secondary to type II diabetes mellitus, hypertension or both. "Length and cortical thickness" of the kidney were measured using conventional ultrasound technology. To assess the renal parenchyma stiffness, SWE imaging was used. SWE's diagnostic effectiveness and traditional ultrasound's eGFR correlation. Data was collected and entered in the predesigned excel spreadsheet. The standard deviation was assumed to be 10.8 and 5.5 for CKD patients and healthy controls, respectively

Results: Majority of CKD cases were older age groups between 60 – 69 years (31.4%), whereas among controls the majority were of the younger age between 20-29 years (24.3%). Male predominance was observed in both control and CKD groups. Out of 70 patients, 22 (31.4%) patients had type II diabetes mellitus and hypertension each and 26 (37.1%) had combination of both diseases. The highest number of cases belonged to stage 4 (18) and 5 (18), followed by stage 3 (16), whereas stage 1 (5). A significant negative linear association between "YM readings and eGFR" was found using the "Spearman correlation coefficient($r = -0.668$, $p < 0.001$)". Mean kidney length was higher in controls (9.3 ± 0.87) as compared to CKD group (8.50 ± 1.82), and mean BMI was higher in CKD group. 4.44 kPa was the cutoff value for the YM measurement, and a value less than or equal to this indicated healthy kidney with high sensitivity and specificity of

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LIST OF ABBREVIATIONS

ABBREVIATIONS
CKD - Chronic kidney disease
SWE - Shear wave Elastography
T2DM - Type 2 Diabetes Mellitus
eGFR - Estimated glomerular filtration rate
DKD - Diabetic kidney disease
MRI = Magnetic resonance imaging
CT - Computed tomography
US - Ultrasound
CIN - Contrast induced nephropathy
RRT - Renal replacement therapy
HN - Hypertensive nephroangiosclerosis
ESRD - End stage renal disease
ARFI - Acoustic radiation force impulse
ROI - Region of interest
CS - Cortical stiffness

KDOQI - Kidney disease outcome quality index
ADPKD - Autosomal dominant polycystic kidney disease
AML - Angiomyolipoma
RCC - Renal cell carcinoma
VTQ - Virtual touch quantification
BMI - Body Mass index
HUN - Hydroureteronephrosis
AUROC - Area under region of curve

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ROLE OF ULTRASONOGRAPHY AND ELASTOGRPAHY IN RENAL PARENCHYMAL DISEASE IN DIABETIC AND HYPERTENSIVE PATIENTS

ABSTRACT

Background: Chronic kidney disease (CKD), primarily brought on by hypertension, diabetes, and primary renal disease, is demonstrated through a "progressive decrease of renal function". CKD may cause increased morbidity and death. Numerous risk factors exist for CKD patients, and preventive efforts are time-consuming and difficult.

Objective: To investigate the role of kidney SWE and ultrasonography in patients with DM and hypertension.

Methods: Study comprised 140 cases consisting of 70 control subjects and 70 CKD patients secondary to type II diabetes mellitus, hypertension or both. "Length and cortical thickness" of the kidney were measured using conventional ultrasound technology. To assess the renal parenchyma stiffness, SWE imaging was used. SWE's diagnostic effectiveness and traditional ultrasound's eGFR correlate. Data was collected and entered in the predesigned excel spreadsheet. The standard deviation was assumed to be 10.8 and 5.5 for CKD patients and healthy controls, respectively.

Results: Majority of CKD cases were older age groups between 60 – 69 years (31.4%), whereas among controls the majority were of the younger age group between 20-29 years (24.3%). Male predominance was observed in both control and CKD groups. Out of 70 patients, 22 (31.4%) patients had type II diabetes mellitus and hypertension each and 26 (37.1%) had combination of both diseases. The highest number of cases belonged to stage 4 (18) and 5 (18), followed by stage 3 (16) and stage 1 (5). A significant negative linear association between "YM readings and eGFR" was found using the "Spearman correlation coefficient($r = -0.668$, $p < 0.001$)". Mean kidney

length was higher in controls (9.3 ± 0.87) as compared to CKD group (8.50 ± 1.82), and mean BMI was higher in CKD group. 4.44 kPa was the cutoff value for the YM measurement, and a value less than or equal to this indicated healthy kidney with high sensitivity and specificity of 90.0% and 77.1%. For the bipolar kidney length, we found the best possible cut-off of 9.0 cm with a sensitivity of 44.3% and specificity of 40.0% to differentiate control and cases. Mean values of YM were found to be higher in Stage 5 CKD (9.71 ± 2.61) patients followed by Stage 4 (8.85 ± 1.74), Stage 3 (7.58 ± 1.26), Stage 2 (6.36 ± 1.28) and Stage 1 (3.85 ± 0.30). "Tukey post-hoc multiple comparison" test revealed that there was "statistically significant difference in means between stages 1, 3 and 5, and stages 2, 4 and 5". However, no statistical significance was noted between different stages. As the stage of CKD increases, the CS increases up till CKD 5. To an extent, reversible and non-reversible stages may be differentiated by the stiffness values which are significantly different between CKD stage 2 v/s 5 and 3 v/s 5. However, the ability to differentiate between individual stages was poor.

Setting a threshold between healthy and unhealthy renal parenchyma could aid in the early detection and treatment of CKD.

Conclusion: SWE was more effective at identifying CKD than "renal length and cortical thickness". A cut-off value of 4.44 kPa was used to determine whether a kidney was diseased or not.

Keywords: Elastography, Ultrasound, CKD, Diabetes, Hypertension, Correlation

INTRODUCTION

INTRODUCTION

Patients with T2DM for an extended period of time frequently get diabetic kidney disease (DKD).[1] If prompt diagnosis and therapy are given, it can be managed or even reversed. Early on "albuminuria, estimated glomerular filtration rate (eGFR), and serum creatinine" were less accurate indications.[2] Before nephropathy, cortical cells undergo the initial pathophysiologic alterations.[3] The basal membrane thickening is the first histologic change, and in the subsequent three to five years, the afferent and efferent arterioles are hyalinized. Within 15 years of the disease's beginning, the mesangial volume has increased.[3] Early diagnosis is important for DM patients' prognosis because 20–30% of them eventually develop nephropathy.[3]

Biopsy offers a conclusive diagnosis, but it also comes with potentially fatal risks. Both MRI and CT can assess the kidney's morphology and functional state. But they come with some drawbacks, like greater expenses, extended appointment times, radiation exposure and CIN. The evaluation of the kidney with ultrasound (US) is noninvasive, accessible, affordable, and routinely employed. US results like decreased renal size, increased parenchymal echogenicity, and parenchymal thickness, may be beneficial, particularly in advanced stages.[4] Although reversible, the early phases are where the majority of diagnostic issues manifest. The aforementioned criterias are unreliable and may stay within normal limits in hyper infiltration stages.[5] A noninvasive technique is necessary for the early phases of DKD evaluation.

The 2nd and 3rd most frequent reason for RRT in Europe, the USA, and Japan, respectively, is "hypertensive nephroangiosclerosis (HN)"[6], which represents progression of arterial hypertension.[6-8] Epidemiological statistics showed that over the previous 20 years, HN has drastically increased in Europe and he USA. About 15% of new cases of "end-stage renal disease (ESRD)" in Europe and 28% of new cases with the condition in the US had HN as the cause.[9-10] According to Mahmoodi et al., there is a direct link between cardiovascular illness, renal involvement, and high blood pressure.[11] Microalbuminuria and macroalbuminuria are related to cardiovascular events.[12]. Micro / macroalbuminuria are also responsible for CKD[13]. Less patients get benifited from histopathological study, where the diagnosis of HN is made based on a routine tests. As a result, epidemiological data from various medical facilities varied greatly "in Europe, between 5 and 33% of ESRD cases had HN as the cause".[10]

Vasculature, glomeruli, and tubulointerstitium are all involved in the kidney injury brought on by hypertension. Intrarenal arteries exhibit media thickness due to smooth muscle cell hyperplasia and increasing intimal thickening and fibrosis brought on by collagen deposition. A hyalinization process is visible in afferent arterioles. Glomerular involvement can have a variety of morphologies, including normal, ischemic, destroyed, with collapsed capillaries, or hypertrophied. Tubular atrophy and interstitial fibrosis are two additional characteristics of hypertensive kidney damage. These histological alterations develop from "asymptomatic organ damage to symptomatic organ damage", with the appearance of CKD. However, if the kidney

involvement is detected early and the patients receive the proper treatment, its progression might be halted.[9,14] Renal function is impacted by these changes in renal morphology. The initial alterations that characterise the developing kidney injury in HN are an increase in albuminuria and a decrease in glomerular filtration rate.[14] However, ultrasonographic "B-mode and Doppler" studies also play a significant role in the diagnosis of HN in addition to serum and urine biomarkers. B-mode ultrasonography assesses the morphology and location of the kidneys - "kidney length, parenchyma thickness and echogenicity". But regrettably, abnormalities in ultrasonography only become apparent later in the course of the disease.[9,14,15]

Studies have shown that renal USG can detect changes in size, echogenicity, and cortical thickness of the screened kidney. Shear wave elastography (SWE), an advanced, noninvasive, and straightforward sonographic technique, has been developed to quantitatively detect the onset of parenchymal fibrosis based on stiffness. In SWE, the tissues are bent temporarily by an acoustic radiation force applied by the transducer. The waves which get deformed, also known as shear waves, radiate perpendicular to the US beam and are measured in m/s and transformed into a "**quantitative stiffness score in kPa using Young's modulus**". Low speed signifies a soft medium, whereas high speed denotes a hard one. Shear wave elastography (SWE) has begun to be utilised on DM patients and has lately gained popularity as a method. A non-invasive, affordable, and reliable USG approach is shear wave elastography.[16-18] Systemic and

demographic factors had little impact on cortical stiffness (CS), which was evaluated by SWE, and it is correlated with renal parenchyma disease and fibrosis.[16-19]

By means of colour duplex, both internal renal venous and arterial vascularisation are measured using Doppler and power Doppler ultrasound, giving information regarding kidney function.[20,21] A novel ultrasonographic technique called "Acoustic Radiation Force Impulse Elastography (ARFI)", which measures elastic compliance changes as shear wave velocity, can be used to diagnose abnormal renal morphology. In ARFI, the transducer's acoustic pulses cause microscopic displacements (1–20 m) in the tissue being studied. Micrometric displacements are measured using the ROI's square shape. Shear waves are created by displacement and are propagated away from the ROI. These waves are collected by the same transducer and are displayed as m/s. ARFI are does not differ with operators and is effective in deep organ analysis.[22-24]

SWE measurements of nephrogenic cortical stiffness in patients with T2 DM and hypertensive patients have been shown to increase.[18, 25, 26, 27]

As far as we are aware, there isn't much evidence currently available in the literature about the changes in CS in T2 DM and hypertensive patients.

"We conducted this study to gain a better understanding of the role of kidney SWE and ultrasonography in patients with diabetes and hypertension".

AIMS & OBJECTIVES

AIMS & OBJECTIVES

Objectives

1. Comparison of renal parenchymal stiffness between healthy subjects and patients with chronic kidney disease due to type II diabetes mellitus and hypertension, using shear wave elastography.
2. Staging of chronic kidney disease based on renal parenchymal stiffness and its correlation with estimated glomerular filtration rate (eGFR).

REVIEW OF

LITERATURE

REVIEW OF LITERATURE

Anatomy and Physiology

CKD is recognised as having damaged kidneys or an "estimated glomerular filtration rate (eGFR) of less than 60 ml/min/1.73 $mt^{2"}$.[28] regardless of the underlying etiology. It is a disorder marked by a gradual loss of kidney function that ultimately calls for renal replacement therapy (dialysis or transplantation). The presence of pathologic aberrations in urine sediment, or renal biopsies are all regarded as indicators of kidney disease. Based on "2012 KDIGO CKD classification", the disease is divided into 6 groups "G1 to G5 with G3 dividing into 3a and 3b". Each stage of CKD is based on the "urinary albumin-creatinine ratio in (mg/gm) or (mg/mmol)" in an early-morning spot urine sample. These three stages of albuminuria are labelled as A1, A2, and A3.[29]

"The 6 categories include:

- G1: GFR 90 ml/min per 1.73 m2 and above
- G2: GFR 60 to 89 ml/min per 1.73 m2
- G3a: GFR 45 to 59 ml/min per 1.73 m2
- G3b: GFR 30 to 44 ml/min per 1.73 m2
- G4: GFR 15 to 29 ml/min per 1.73 m2
- G5: GFR less than 15 ml/min per 1.73 m2 or treatment by dialysis

The three levels of albuminuria include an albumin-creatinine ratio (ACR)

- A1: ACR less than 30 mg/gm (less than 3.4 mg/mmol)
- A2: ACR 30 to 299 mg/gm (3.4 to 34 mg/mmol)

- A3: ACR greater than 300 mg/gm (greater than 34 mg/mmol)".

The more accurate CKD classification has helped uncovering prognostic clues for declining kidney function and rising albuminuria. The potential over diagnosis of CKD, particularly in the elderly is a drawback.

Etiology

The causes of CKD vary globally, and the most common primary diseases causing CKD and ultimately end-stage renal disease (ESRD) are as follows:[30]

- Primary glomerulonephritis (8.2%)
- Diabetes mellitus type 1 (3.9%)
- Hypertension (27.2%)
- Diabetes mellitus type 2 (30% to 50%)
- Chronic Tubulointerstitial nephritis (3.6%)
- Secondary glomerulonephritis or vasculitis (2.1%)
- Plasma cell dyscrasias or neoplasm (2.1)
- Hereditary or cystic diseases (3.1%)
- Sickle Cell Nephropathy (SCN) which accounts for less than 1% of ESRD patients in the United States[31]

  Prerenal (lower renal perfusion pressure), intrinsic renal (pathology of the arteries, glomeruli, or tubules-interstitium), or postrenal disease processes can all lead to CKD (obstructive).

Epidemiology:

Due to the asymptomatic nature of early to moderate CKD, the incidence and prevalence is unknown. In the general community, CKD affects "10% to 14% of people".

A total of 2,546,700 (1% to 3%) and 2,968,600 (1% to 10%) life years were affected by CKD globally. According to the "Kidney Disease Outcomes Quality Initiative (KDOQI)", patients must be tested thrice over the course of three months, with 2/3 should be positive consistently. This is required for the designation of chronicity and CKD.[33]

Natural History and Progression of CKD

Compared to CKD patients referred to clinics, general population CKD patients have a distinct and varied natural history. The latter are named as 'community CKD'.

The elderly are mainly affected by demographic community CKD. Most individuals have long-term kidney-damaging illnesses that include diabetes, hypertension, and cardiovascular risk factors. After the age of 40 to 50 years, this population's typical GFR declines at a 'rate of 0.75 to 1 ml/min/year'.[34] In a community-based CKD, Kshirsagar et al. found that only 1% with G3 CKD and 20% of patients G4 CKD needed RRT, but 24% of G3 and 45% of G4 patients died primarily from cardiac causes. This finding suggests that cardiac events is the significant cause rather than progression to ESRD in community based CKD.[35]

Patients with referred CKD, in contrast to community CKD, typically present at a young age due to "hereditary (autosomal dominant polycystic kidney disease, or ADPKD) or acquired nephropathy (glomerulonephritis, diabetic nephropathy, or tubulointerstitial disease)" that results in consecutive renal damage and functional loss. The rate of progression of referred CKD varies from patient to patient and is dependent on the underlying disease process. According to reports, GFR decreases by "10 ml/min/year" on average in diabetic nephropathy. Patients with chronic proteinuria associated GN frequently advance more quickly than those with mild non-diabetic nephropathies. Patients with ADPKD. renal impairment, CKD stage G3b and beyond, may progress more swiftly than those with other nephropathies. In patients with hypertensive nephrosclerosis, Hypertension control decrease the disease progression.

There is virtually little utilisation of imagistic techniques for CKD early diagnosis or CKD progression assessment. The diagnosis of cystic kidney disorders, which make up a minor fraction of CKD causes, is aided by conventional ultrasound. Information obtained from ultrasonography is of limited value when it comes to the most common aetiologies of CKD (diabetes mellitus, arterial hypertension, glomerular disorders, or chronic tubulointerstitial illnesses). When CKD is in its advanced stages and the growth of fibrosis is causing the echogenicity of the renal cortex to increase, conventional ultrasound can be used to assess the renal size and parenchymal thickness, both of which are decreasing.[36]

However, the investigator's subjective observation of enhanced echogenicity cannot be quantified using traditional ultrasound. A technique based on ultrasonography that has demonstrated its effectiveness in evaluating fibrosis in various other organs (liver in both, diffuse[37,38] or focal lesions,[39] spleen,[40,41] thyroid[42,43] or prostate[44]) by measuring the stiffness of the tissue is elastography.

Imaging of Kidney - Ultrasound elastography (USE)

The imaging technique known as ultrasound elastography, which is sensitive to tissue stiffness, was initially introduced in the 1990s[1]. In recent years, it has been improved and extended further to allow for quantitative measurements of tissue stiffness. Elastography techniques make use of the soft tissues' altered elasticity brought on by particular pathological or physiological processes[2]. For instance, it is well known that many solid tumours mechanically differ from the surrounding healthy tissues. Similar to this, the liver stiffens more than normal tissues due to fibrosis brought on by chronic liver disorders. Thus, for diagnostic purposes, elastography techniques can be utilised to separate afflicted from normal tissue.

Conventional ultrasound (US), which also applies to USE is an affordable & adaptable modality that may be employed at the bedside. In recent years, USE has been investigated for a number of clinical applications and is imparted in clinical practice applications like the evaluation of liver fibrosis or the characterisation of breast lesions. By including stiffness as an additional quantifiable feature to current US imaging techniques we hope to get good results.

Principles and Techniques of Ultrasound Elastography

The USE physics and current methods are briefly summarised in the sections that follow. You can find more thorough discussions of elastography physics elsewhere.[4547]

Ultrasound elastography physics

"Elastography measures tissue elasticity, which is a tissue's propensity to resist deformation when subjected to a force or to regain its original shape when the force is removed. Because different quantities are reported depending on the elastography technique and vendor, it is crucial to understand the relationships between Young's modulus E, shear modulus G, and shear wave speed cS. Shear wave speed cS is directly measured by ultrasound shear wave imaging and either reported or converted to Young's modulus E".

Ultrasound elastography techniques

Based on the aforementioned principles, the US elastography techniques are classified into (Figure 1):

1) Strain imaging: This method assesses the Young's modulus E qualitatively by applying a "normal stress (n)" to the tissue and measuring the "normal strain (n)".

2) Shear wave imaging (SWI):

Tissue is subjected to a dynamic stress by means of a vibrating mechanical device in "1D transient elastography (1D-TE)" or "an acoustic radiation force in 2D shear wave elastography (pSWE) (2D-SWE)". Equation 9 evaluates and report the Young's modulus E or to measure the shear waves produced by the excitation parallel to the 1D

transient elastography excitation or perpendicular to the application of the acoustic radiation force.

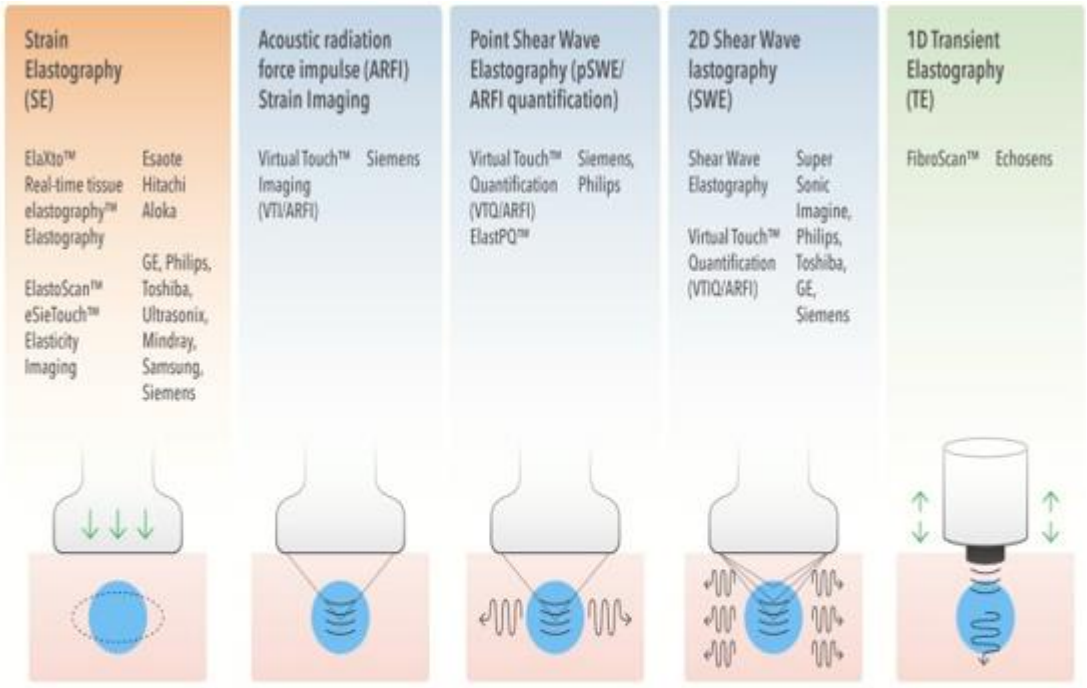

Figure 1: Ultrasound Elastography Techniques. Currently available USE techniques can be categorized by the measured physical quantity: 1) strain imaging (left), and 2) shear wave imaging (right). Excitations methods include quasi-static mechanically-induced displacement via active external compression or passively-induced physiologic motion (orange), dynamic mechanically-induced compression via a "thumping" transducer at the tissue surface to produce shear waves (green), and dynamic ultrasound-induced tissue displacement and shear waves by acoustic radiation force impulse excitation (blue).

Clinical Applications of Ultrasound Elastography in Kidney

Renal Fibrosis

The native and allograft kidneys demonstrate two types of renal fibrotic changes. The two types, CKD and interstitial fibrosis can be screened using USE. Both of these ailments have the potential to result in significant morbidity and expensive medical care. CKD is a common disease that affects about 14% of the population causing ESRD that calls for dialysis or a kidney transplant.[48] Failure of a kidney transplant may result from allograft renal interstitial disease. The current gold standard for staging renal

fibrosis is biopsy. Strain and shear wav elastography can be used to detect, stage and monitor renal fibrosis noninvasively.[49]

Strain imaging can be used to evaluate transplanted kidneys due to their superficial placement.[50] Patients with transplanted kidneys were examined by Orlacchio et al. using SE (Philips) and the results were compared with "severity of histopathologic fibrosis (F1=mild, F2=moderate, and F3=severe)". With an overall accuracy of 95%, "SE predicted degree of fibrosis in renal transplant patients, primarily for 'F2-F3' instances. Using a tissue mean elasticity cut-off value of 46 a.u. - arbitrary units" — the sensitivity, specificity, positive predictive value, and negative predictive value were 85.7%, 95.5%, 96%, and 84%, respectively, to identify F2-F3 tumours.[50]

Difficult external compressions on retroperitoneal organs like kidney gives inaccurate strain elastograms, however native kidneys are sometimes evaluated by strain elastograms.[49] "Strain elastograms was employed by Menzilcioglu et al. to compare kidneys in CKD and non-CKD patients".[51] They discovered that the "mean strain index value" of the renal parenchyma was considerably higher in CKD patients (1.8001) compared to healthy people (0.420.30) (p0.001). However, SE was unable to differentiate between various CKD stages.[52]

Since SWI does not rely on external compression, it is preferable to "strain imaging" for assessing kidney fibrosis (both native and allograft kidneys).[49] The majority of studies utilising SWI to assess CKD found that the renal parenchyma's shear

wave velocity was significantly lower in CKD patients than in healthy ones. Additionally, research has found a strong link between CKD biochemical markers and shear wave velocity. Guo et al. shown, for instance, that shear wave velocity substantially linked with estimated glomerular filtration rate, urea nitrogen, and serum creatinine using VTQ/ARFI[52] and Shear wave velocity substantially linked with serum creatinine and glomerular filtration rate, according to Hu et al.[53] However, Wang et al. demonstrated no difference in shear elastogram values between different hitological groups in 4G patients.

It's interesting to note that SWE and the development of CKD have been shown to be negatively correlated in SWI of renal fibrosis. For instance, Bob et al. demonstrated that as the CKD stage increased, the shear wave velocity dropped.[54] Other investigations that compared CKD to healthy kidneys reported that shear wave velocity was considerably lower in CKD. [52,53] These results are at odds with SWI liver fibrosis studies, which show that as liver fibrosis increases, shear wave velocity increases. The cause of this variation is still unknown. According to Asano et al hypothesis, the reduced renal blood flow in CKD patients reduces stiffness of kidney.[55]

Focal renal lesion

Because B-mode US characteristics are not unique to malignancy. Shear wave can also be used. For instance, whereas benign angiomyolipomas (AMLs) frequently show up as hyperechoic lesions. renal cell carcinoma (RCC) can also show up in around 10% of instances as such.[56] In 10% of cases, renal cell carcinoma may resemble benign cysts.[57]

Cross-sectional studies can be used for better characterization of above mentioned lesions[18,58-60]

Strain imaging to evaluate renal masses have produced encouraging results. It is difficult to compare different strain waves. In a study that evaluated “strain imaging in 28 AMLs and 19 RCCs”, two radiologists found that the strain ratios in AMLs were much lower than those in “RCCs (0.64 0.15 and 0.63 0.19, respectively)”, with the optimal “cut-off value of 0.3 (sensitivity = 95%, specificity = 100%)”.[58] Another strain index study between aggressive and dormant renal masses in 71 patients which concluded that “malignant masses are 2.8 times stiffer than benign masses with mean strain index values of 4.05 and 1.43, respectively.”. Additionally, they discovered that RCCs (4.30 2.27) had considerably higher strain index values than AMLs .

Studies evaluating renal masses with SWI have produced mixed outcomes. With significantly “lower mean shear wave velocities of AMLs (2.19 0.63 m/s) compared to RCCs (3.18 0.72 m/s)”; Goya et al VTQ/ARFI's assessment of 60 patients with renal masses indicated promising results. Additionally, they discovered that shear wave velocity readings “2.34 m/s (AUROC = 0.728)”, sensitivity and specificity of 88% & 54%, respectively, and could discriminate between benign and malignant tumours.[62] Shear wave velocities of “AMLs (2.49 0.63 m/s)” and “RCCs (particularly clear cell carcinoma; 2.46 0.45 m/s)” did not significantly differ, however, according to Guo et al., indicating that they may have similar physical characteristics.[60]

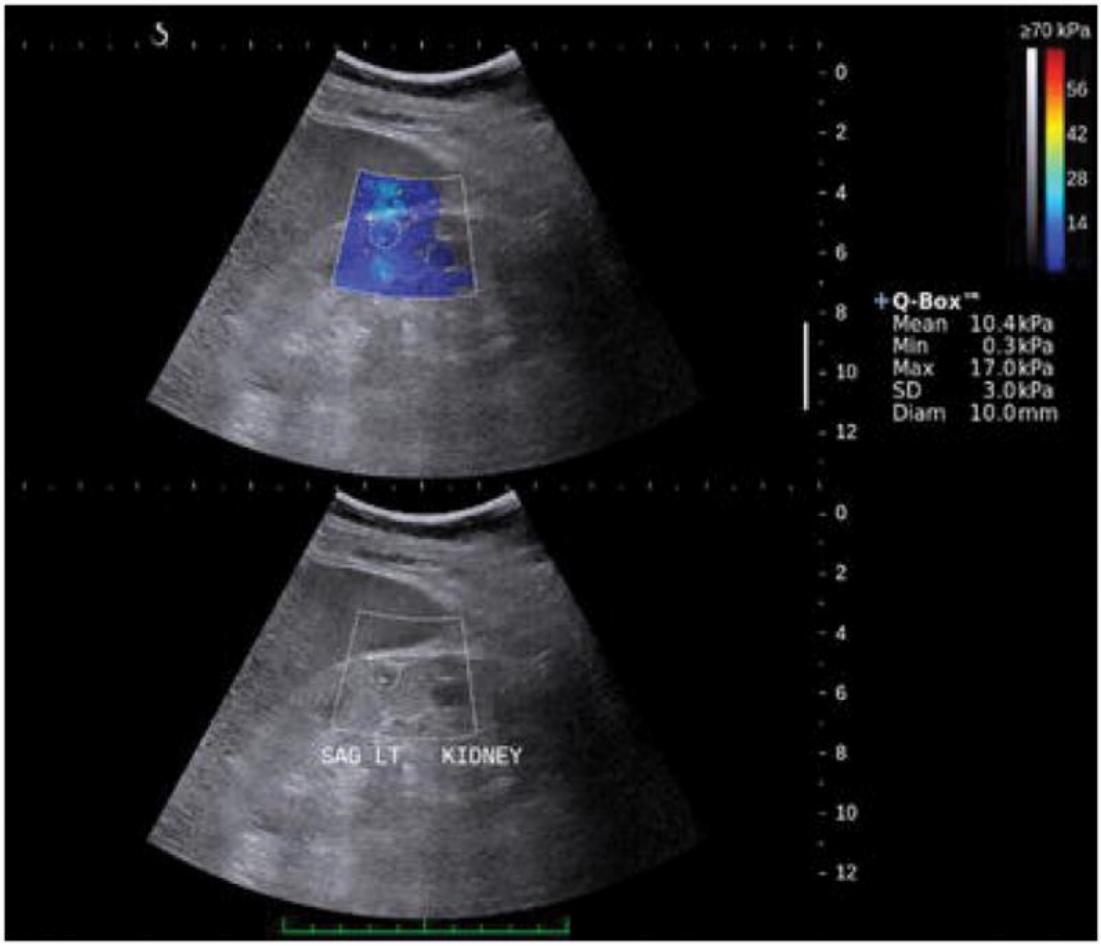

Figure 2 : Image showing strain elastography of kidney

In conclusion, shear wave in native and allograft kidneys demonstrated good results in the fibrosis detection becoming a substitute for biopsy. However, USE has not been accurate in identifying the various CKD stages[51,52] or grading fibrosis in transplanted kidneys.[63] To assess renal fibrosis staging and comprehend the connection between the advancement of fibrosis and kidney shear wave velocity, additional research involving larger numbers of patients is required. Additionally, only a small number of studies have, to date, employed USE to characterise focal renal masses (mainly AML vs RCC), with mixed results.

Leong SS et al (2018), investigated the Young's modulus (YM) produced from shear wave elastography as a marker to identify aberrant renal tissue identified by estimated glomerular filtration rate (eGFR). 106 people with CKD and 203 healthy controls participated in the study. With the help of conventional ultrasound equipment, the kidney's length and cortical thickness were measured. To assess the renal parenchymal stiffness, SWE imaging was used. With respect to eGFR, serum creatinine, urea levels, and SWE's diagnostic performance were all associated. According to the study's findings, there was a negative association between YM measures and eGFR as indicated by "Pearson's correlation coefficient (r = 0.576, p 0.0001)". Compared to conventional ultrasonography alone, the SWE's area under the receiver operating characteristic curve (0.87) was superior (0.35–0.37). A healthy kidney was indicated by the "cut-off value of less than or equal to 4.31 kPa (80.3% sensitivity, 79.5% specificity)". The study came to the conclusion that SWE was more effective at detecting CKD than renal length and cortical thickness. The ability to accurately determine whether a kidney was diseased or not depended on a value of 4.31 kPa or below.[64]

Yuksekkaya R et al (2022), undertook a study with the objective of objectively analysing the kidneys in participants with early T2DM renal disease. type 2 diabetic renal disease where 108 patients and control participants of 17 made up the entire study population. Patients were staged into 1 to 3 of diabetic renal disease based on eGFR and urine A:C ratio. Both shear wave elastography and grayscale ultrasonography were

carried out. It was noted the shear wave value, size & depth were analysed. Between participants with diabetic renal disease and healthy controls, these measures were compared. The findings showed that the mean shear wave elastography values in the group with diabetic renal disease were substantially higher (10.1561.75 kPa vs. 8.2411.4 kPa; p0.001). In subjects with stages 2 and 3 diabetic kidney disease compared to control subjects and in patients with stage 3 diabetic kidney disease compared to those with stage 1 diabetic kidney disease, the study produced statistically substantially greater shear wave elastography values (p 0.05 for all). It was discovered that a cutoff value of 9.23 kPa with a sensitivity of 67% and a specificity of 82% could accurately predict diabetic kidney disease in its early stages. According to the authors, routine therapy of patients with type 2 diabetes mellitus may include the use of shear wave elastography as a noninvasive, straightforward, and quantitative tool to give diagnostic data, particularly in the early stages of diabetic kidney disease.[65]

Bob F (2021) reviewed renal elastography's use in determining the severity of CKD. Point shear wave elastography (pSWE) and shear wave speed imaging (2D-SWE) are appropriate for the assessment of chronic kidney disease; however, the use of elastography in the assessment of the kidneys is more challenging than it is in the assessment of other organs due to the complex architecture of the kidneys, which is characterised by a high anisotropy, as well as the constrained size of the renal parenchyma, where the measurements are performed. Renal elastography is challenging, although the procedure has good reproducibility. While the values of renal

shear wave speed are mostly determined by age and gender in chronic kidney disease, renal stiffness is occasionally decreased in more advanced illness and is not primarily influenced by the development of fibrosis. According to research, a reduced renal blood flow is linked to a reduced kidney shear wave speed, which could account for why CKD patients typically have lower kidney stiffness. In this review, Bob F comes to the conclusion that elastography is a real-time imaging technique that could be helpful in the evaluation of the kidneys, but that more in-depth research and possibly even some improvements to the algorithms used to process the raw data from elastography machines are required before the technique can be used in clinical practise.[66]

According to shear wave elastography, patients with type 2 diabetes mellitus (DM) who develop diabetic nephropathy have increased renal cortical stiffness (CS) (SWE). With this background **Koc AS & Sumbul HE (2018),** conducted a study to examine the difference between type 2 DM patients with normal renal function and non-DM patients in renal CS as measured by SWE testing. In all, 103 individuals with or without type 2 DM were enrolled in the study (86 men, 17 women, mean age 63.2 11.8 years). All patients had an eGFR value greater than 60 ml/kg/1.73^2. The usual history, physical exam, and laboratory tests were carried out. Renal resistive index (RRI), renal pulsatility index (RPI), accelerated time (AT), and CS measurements were made in addition to standard renal ultrasonography (USG). According to the study's findings, 53 patients without type 2 DM and 55 patients with type 2 DM both participated in the study. Blood urea nitrogen, HbA1c, and blood glucose levels were all higher in patients

with type 2 DM (p 0.05 for each). Both groups with traditional renal USG had identical renal length, breadth, and echogenicity. In patients with type 2 DM, the thickness of the renal parenchyma was greater. When renal Doppler USG results were compared between two groups, RRI was identical. RPI and AT were greater in type 2 DM patients. Patients with type 2 DM had substantially higher CS values determined with renal SWE (p 0.05). According to the study's findings, type 2 DM patients with normal renal function have considerably higher cortical stiffness values than those without DM. The authors suggested that CS measurement be used to inform management and treatment plans in individuals with type 2 DM and normal renal function as part of routine nephropathy screening.[67]

Bob F et al (2017), examined how VTQ affected patients with diabetic renal disease, which is the main contributing factor to CKD. 164 patients made up the study group, including 84 without diabetes mellitus or renal illness and 80 with diabetic kidney disease (DKD). Five accurate VTQ measurements were taken in each kidney of each individual while they were in lateral decubitus, and the median value—which was calculated—was expressed in meters/second. "The median values in DKD patients were 2.21 0.71 m/s for the right kidney and 2.13 0.72 m/s for the left kidney", whereas statistically significant "higher values were observed in the normal controls at 2.58 0.78 m/s for the right kidney (p 5 0.0017) and 2.46 0.81 m/s for the left kidney (p 5 0.006)". DKD stages 1 and 2 and healthy controls had an estimated glomerular filtration rate (eGFR) of.60 mL/min, and those patients had a substantially faster renal shear wave

speed than those patients “(2.53 m/s vs. 2.09 m/s, p, 0.05)”. The eGFR and “VTQ values for the right kidney significantly correlated in the DKD group (r 5 0.28, p 5 0.04). The levels of proteinuria, the stage of diabetic retinopathy, or glycated haemoglobin did not correlate with the values of the VTQ. According to this study, shear wave speed values are much lower in patients with diabetic renal disease and eGFRs of 60 mL/min than they are in individuals with eGFRs. 60 mL/min (either healthy individuals or diabetics with DKD stages 1 and 2), and values drop as eGFR falls. However, VTQ is unaffected by proteinuria, diabetic retinopathy, or glycated haemoglobin”.[54] \

MATERIALS & METHODS

METHODLOGY

Source of data:

This is a hospital based study conducted in the Department of Radio-Diagnosis, R.L. Jalappa Hospital and Research Center attached to Sri Devaraj Urs Medical College, Tamaka, Kolar. The study included 70 chronic kidney disease (CKD) patients and 70 patients with age and gender matched non diabetic, non hypertensive controls with normal renal function test controls referred for ultrasound examination to the department of Radio-Diagnosis, who fulfilled the inclusion criteria.

Study design and method of collection of data (including sampling procedure if any):

The study was initiated after obtaining approval from the Institutional Ethics Committee of Jalappa Hospital and Research Center attached to Sri Devaraj Urs Medical College, Tamaka, Kolar. A preformed written consent form was taken from all patients fulfilling the inclusion criteria and explaining the objective, procedure and expected outcome in detail before the start of the study.

The patients were included for the study based on the inclusion and exclusion criteria mentioned as follows: -

Inclusion criteria:

Controls - Healthy Volunteers

Healthy volunteers were chosen as controls with inclusion criteria as follows being age >18 yrs.

Cases – CKD patients:

Cases included CKD patients referred to our department for imaging of kidneys with inclusion criteria as follows:

- Age >18 years
- Cases of chronic kidney disease secondary to type II diabetes mellitus or hypertension or both.

Exclusion criteria:

- BMI >35 or any condition that impedes visualization of kidneys.
- Diabetes mellitus, hypertension or any other systemic disease that might influence renal function.
- Presence of kidney lesions – renal cysts/stones/mass/HUN/solitary kidney.

Examination protocol:

Patients evaluation: Following parameters was measured/collected.

- Height
- Weight
- BMI
- Blood pressure
- HbA1c

Evaluation of renal function: Following lab values were obtained within 1 month of undergoing elastography.

- Blood urea nitrogen
- Serum creatinine
- Urinary protein

Sample size:

OpenEpi version 3.01 was used to determine the sample size (Open Source Epidemiologic Statistics for Public Health). The sample size was calculated using OpenEpi software version 3.01 (Open Source Epidemiologic Statistics for Public Health). Assuming alpha error of 5% (95% confidence limit), Power of 80% (β=0.20) and the ratio of cases and controls to be 1:1, the minimum required sample size was calculated to be 70 in each group and the total sample size is 140 (70 healthy controls and 70 CKD patients).

Sample size (n) = $\frac{Z^2(P*Q)}{d^2}$

where;

Z is the value for Confidence Interval

D is the absolute precision

P is the expected proportion (p = 0.70)

q=1-p (q = 0.30)

Protocol for data collection:

Quantification of kidney stiffness by shear wave elastography

All Ultra Sound (US) examinations was performed using Philips EPIQ5 system equipped with shear wave point quantification, ELASTPQ, using curvilinear broadband transducer C5-2. All patients were positioned in the left lateral posture, with right arm maximum abducted over the right kidney is measured and the opposite side was similarly treated. According to a recent US elastography guideline, patients are instructed to keep their breaths at mid-respiration level during acquisition to reduce breathing motion and prevent deep inspiration or expiration. Using a concentrated US beam, this method creates shear waves inside the tissue. The speed of propagation is

measured by the US machine while it tracks the shear-wave propagation using a method akin to Doppler. From there, the speed is utilised to calculate tissue stiffness, also known as the Young modulus (YM) of elasticity, in kilopascals (kPa).

The default setting for the measurement of the region of interest (ROI) was utilized. The size of the ROI is 15 x 5 mm. The middle third of the kidney, which corresponded to the area with the best representation of renal cortical parenchyma, was the location where the kidney stiffness measurement was carried out, with the sample line being directed radially. The amount of transducer compression used was kept to a minimum. In order to choose a kidney parenchymal ROI for analysis that is well observable within the cortex and free of renal pyramids or capsules, the quantified measurement was shown over a B-mode US picture. While the radiologist pressed a button to start the data capture, the patients were instructed to hold their breath while lying flat. The aforementioned methods seek to lessen the influence of renal anisotropy impacting measurement quality in order to increase the reproducibility of SWV measurements. Only tests with at least five independently validated measurements were deemed reliable. The mean stiffness value of the studied kidney was computed using 5 accurate consecutive measurements. The renal elasticity derived is correlated with the eGFR.

Precautions to be followed when doing elastography:

- Kidney displayed in longitudinal plane
- ROI size of 15 x 5 mm
- Located exclusively in cortical region
- Radially oriented middle 1/3rd of kidney.
- Excluding the vessels

Figure -3: EPIQ 5G Machine

RESULTS

RESULTS

A total of 140 adults comprising of 70 control subjects and 70 CKD patients secondary to type II diabetes mellitus, hypertension or both, were included in the study.

Age distribution:

Majority of CKD cases belonged to older age group between 60 – 69 years (31.4%), whereas among controls the majority belonged to younger age between 20-29 years (24.3%). (Figure 1)

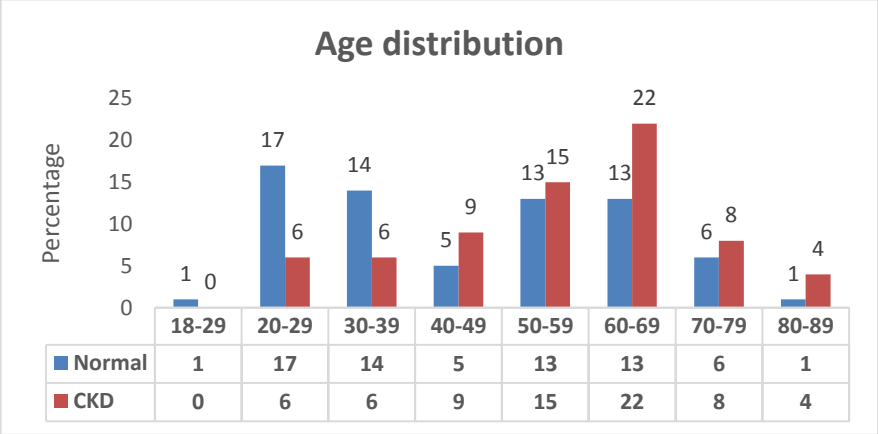

Figure 4: Bar chart – Age distribution.

Gender distribution:

The controls consisted of 47 males and 23 females, whereas the CKD group comprised of 43 males and 27 females. Male predominance was observed in both control and CKD groups. (Figure 2)

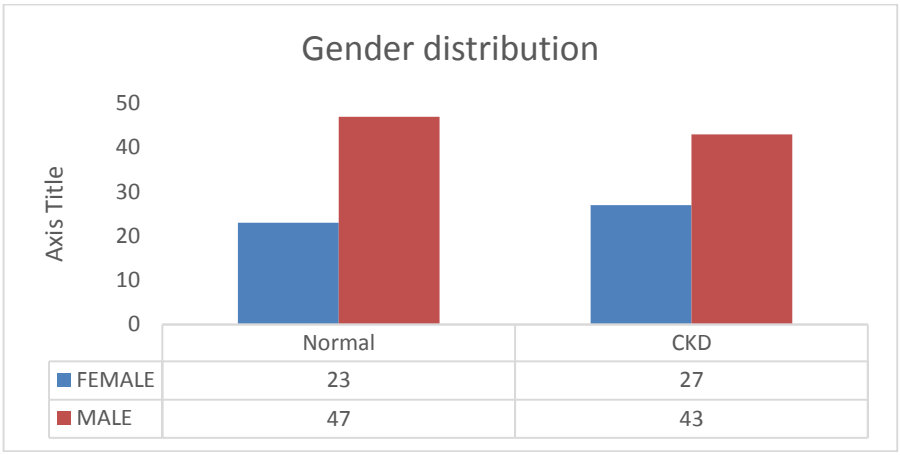

Figure 5: Bar chart - gender distribution

Etiology of CKD:

Our study included CKD cases secondary to type II diabetes mellitus, hypertension or both. Out of 70 patients, 22 (31.4%) patients had type II diabetes mellitus and hypertension each and 26 (37.1%) had combination of both diseases. (Figure 3)

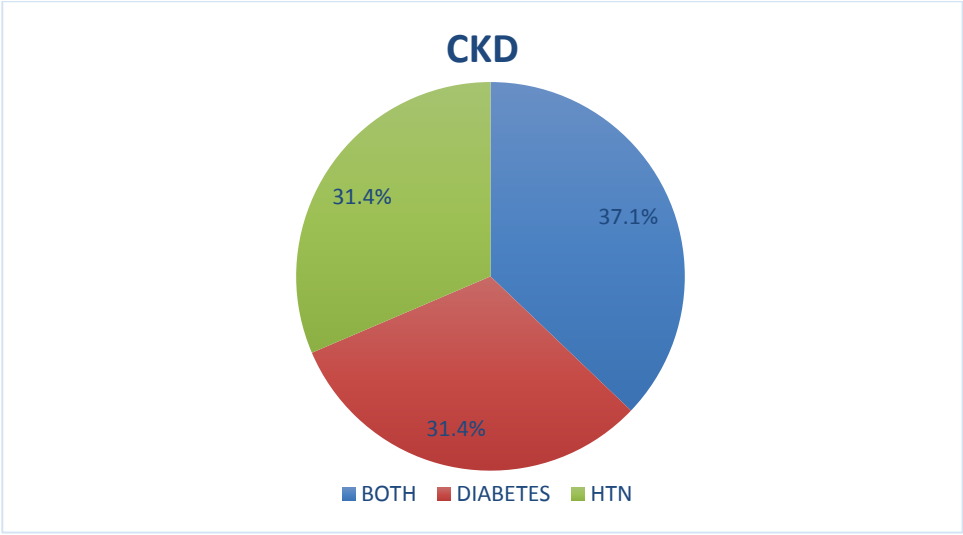

Figure 6: Pie chart showing the etiologies of CKD among the cases

Stages of CKD:

Among the 70 CKD cases, the distribution among the 5 stages is as shown in figure 4. The highest number of cases belonged to stage 4 (18) and 5 (18), followed by stage 3 (16) and stage 1 (5).

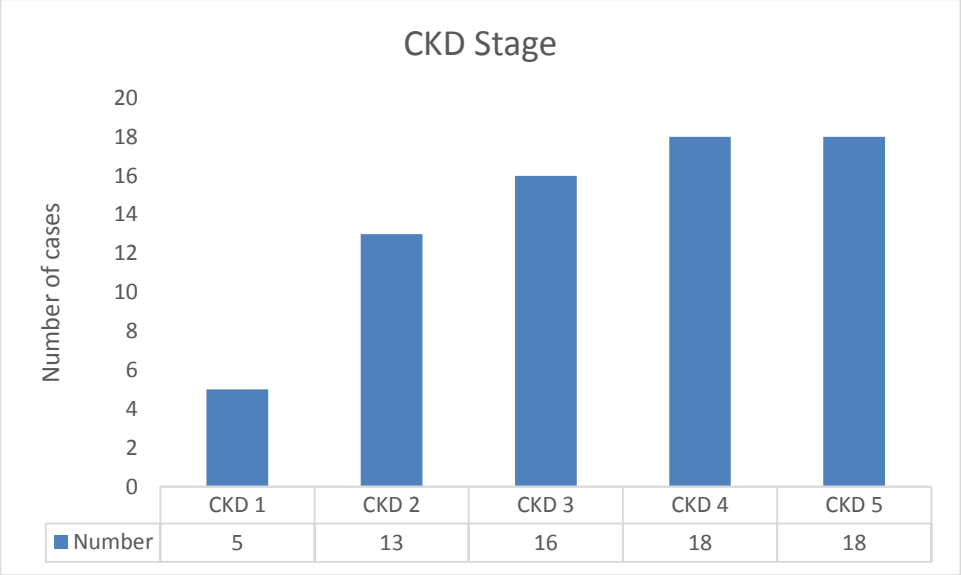

Figure 7: Distribution of cases across the CKD stages

Relationship between YM measurements and age and eGFR.

YM measurements showed no significant correlation with age among the controls, (Figure 5 and Table 1) but showed moderate positive correlation with age among the CKD group ($r = 0.293$, $p < 0.014$). (Figure 6 and Table 2)

The YM measurements and eGFR had a substantial negative linear association, according to the "Spearman correlation coefficient"($r = 0.668$, p 0.001). (Figure 7 and Table 3)

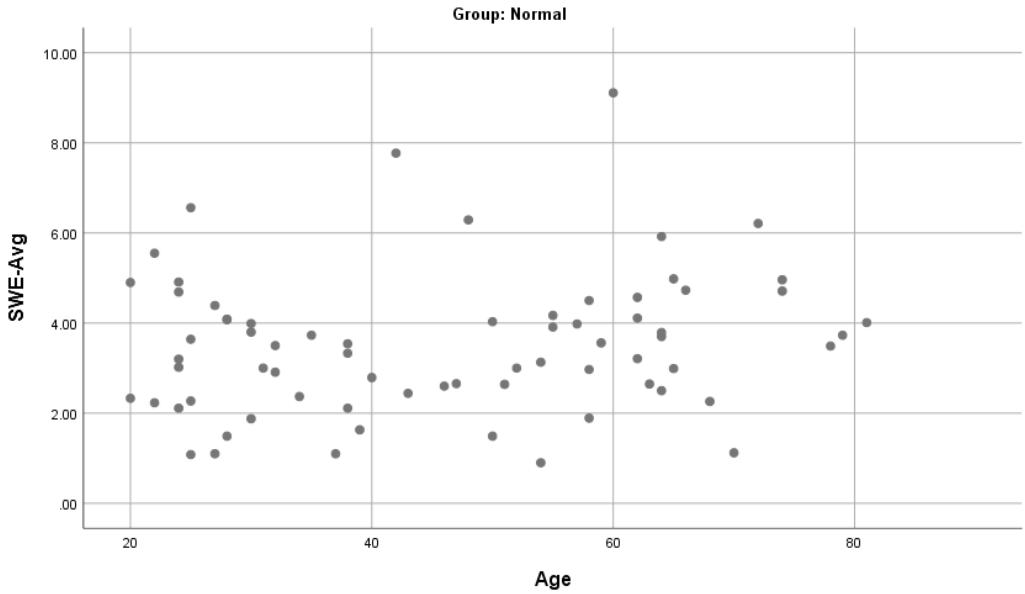

Figure 8: Simple scatter with fit line of age by SWE average among controls

Table 1: Spearman's rho correlation between age and YM measurements among controls

Correlations

Group				Age	SWE-Avg
Normal	Spearman's rho	Age	Correlation Coefficient	1.000	.170
			Sig. (2-tailed)	.	.161
			N	70	70
		SWE-Avg	Correlation Coefficient	.170	1.000
			Sig. (2-tailed)	.161	.
			N	70	70

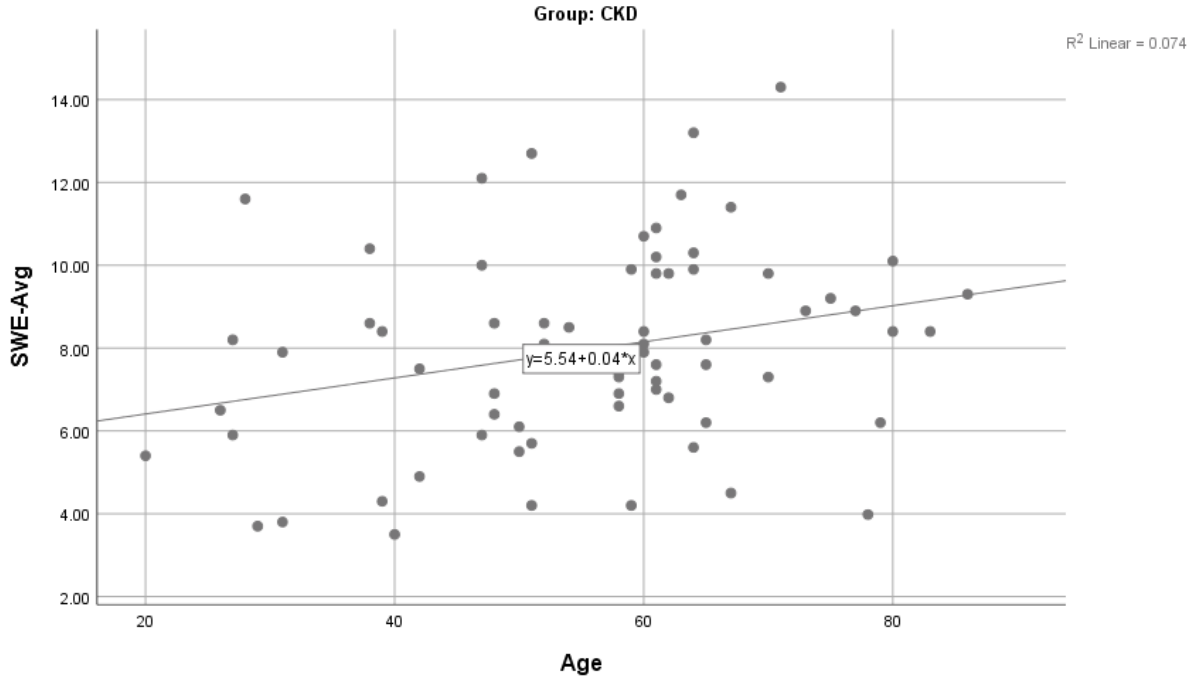

Figure 9: Scatter plot of YM measurements against age in CKD group

Table 2 Spearman's rho correlation between age and YM measurements among CKD group

Correlations

Group				Age	SWE-Avg
CKD	Spearman's rho	Age	Correlation Coefficient	1.000	.293*
			Sig. (2-tailed)	.	.014
			N	70	70
		SWE-Avg	Correlation Coefficient	.293*	1.000
			Sig. (2-tailed)	.014	.
			N	70	70

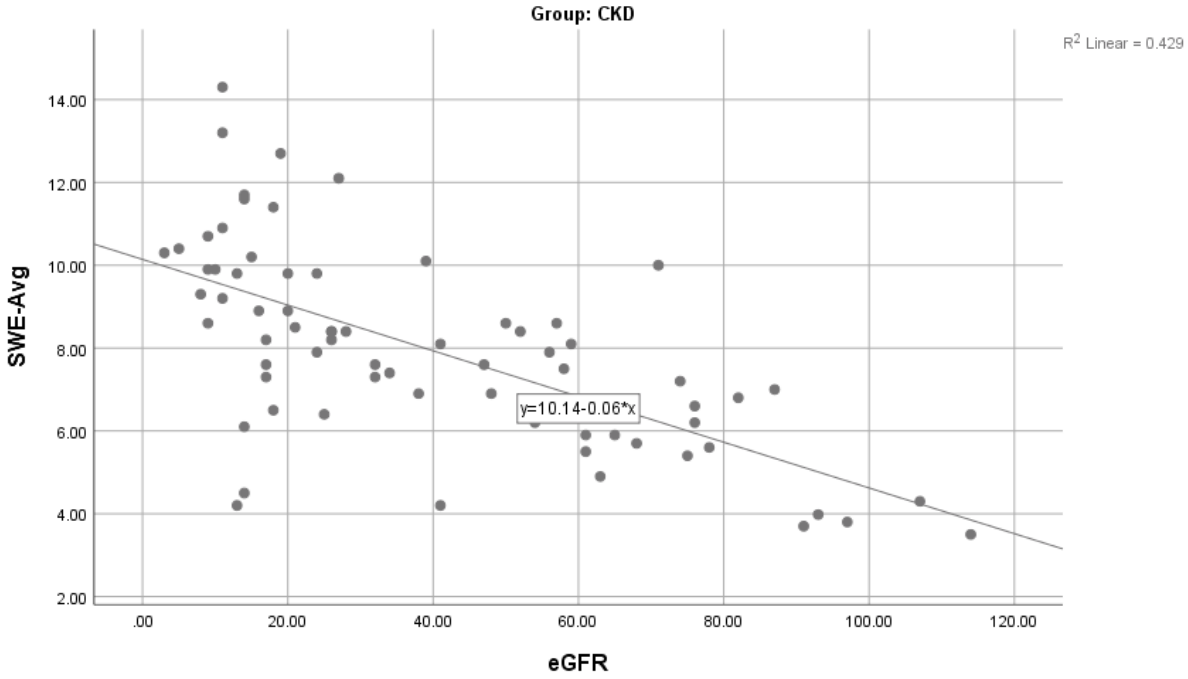

Figure 10: Scatter plot of YM measurements against eGFR in CKD group

Table 3 Spearman's rho correlation between eGFR and YM measurements among CKD group

Correlations

Group				eGFR	SWE-Avg
CKD	Spearman's rho	eGFR	Correlation Coefficient	1.000	-.668**
			Sig. (2-tailed)	.	.000
			N	70	70
		SWE-Avg	Correlation Coefficient	-.668**	1.000
			Sig. (2-tailed)	.000	.
			N	70	70

**. Correlation is significant at the 0.01 level (2-tailed).

Comparison of mean of different parameters between CKD and control groups

BMI were assessed comparing the two groups by "independent variable t test". (Table 4) YM measurements were greater in the CKD group (7.96 2.41) compared to control (3.51 1.56), showing increased stiffness within the CKD group, and were statistically significant with a p value of 0.001 in the comparison of mean YM measurements between the CKD and control groups. Mean kidney length was higher in controls (9.3 ± 0.87) as compared to CKD group (8.50 ± 1.82), and mean BMI was higher in CKD group as compared to controls. (Figure 8)

Table 4: Comparison of means of YM measurements, kidney length among controls and CKD group

	Controls	CKD	t	p value
YM (kPa)	3.51 ± 1.56	7.96 ± 2.41	-12.95	0.001
Kidney length (cm)	9.3 ± 0.87	8.50 ± 1.82	3.44	0.001

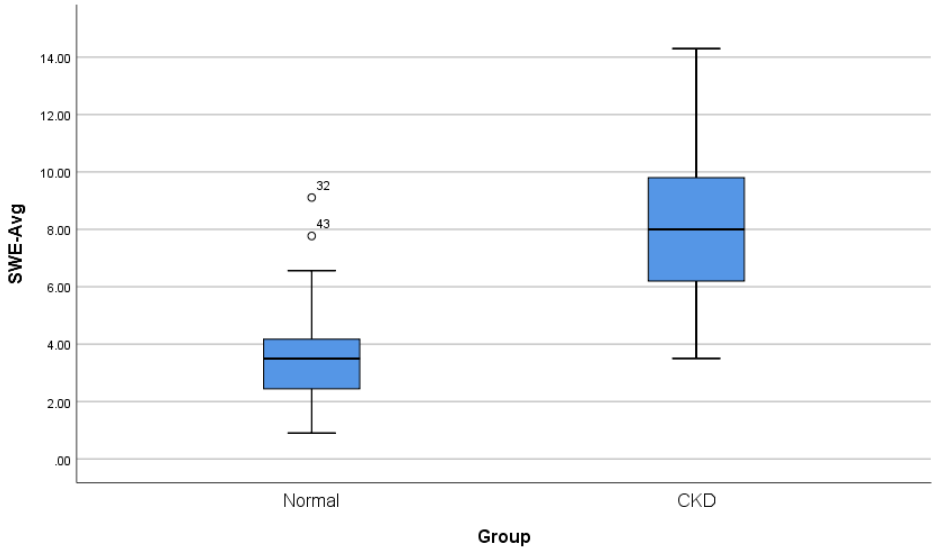

Figure 11: Boxplot showing mean YM measurements distribution among controls and CKD group

Comparison of ROC curves

YM's ROC curve for separating the CKD and control groups

ROC curves were used to assess the mean YM measurements between the control and patient groups. SWE had a 0.94 area under the ROC curve. We determined a cutoff value for YM measurements of 4.44 kPa, below which a kidney without disease was recommended. This resulted in sensitivity and specificity that were, respectively, 90.0% and 77.1%. (Figure 9 and Table 5)

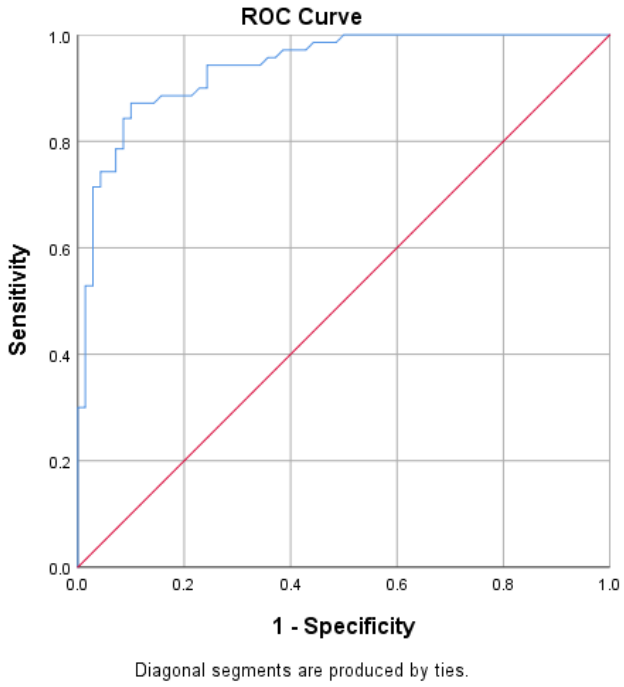

Figure 12: ROC curve of YM in distinguishing between CKD and control groups

Table 5: AUROC of YM in distinguishing between CKD and control groups

Area Under the Curve				
Test Result Variable(s): SWE-Avg				
			Asymptomatic 95% Confidence Interval	
Area	Std. Error[a]	Asymptomatic Sig.[b]	Lower Bound	Upper Bound
.940	.019	.000	.903	.977

ROC curve of length in distinguishing CKD and controls

For the bipolar kidney length, we found the best possible cut-off of 9.0 cm with a sensitivity of 44.3% and specificity of 40.0% to differentiate control and cases. The AUROC was poor (0.363). (Figure 10)

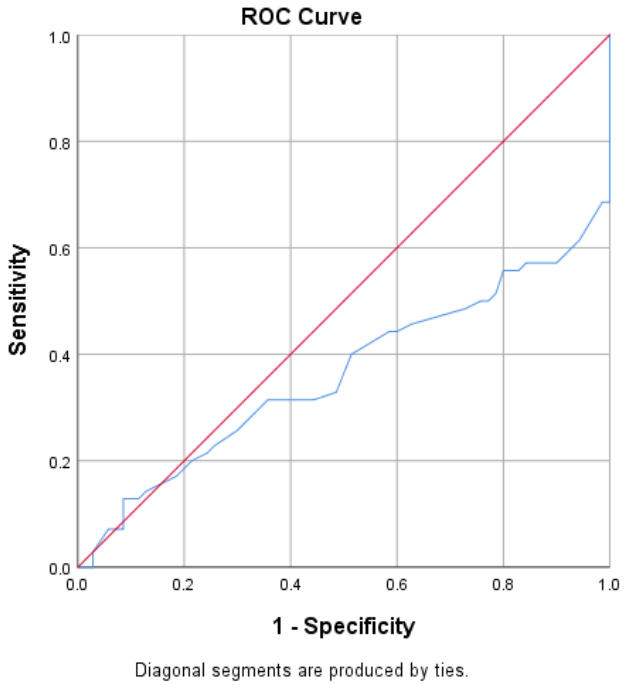

Figure 13: ROC curve of length in distinguishing CKD and controls

Correlation between CKD stage and YM measurements:

"One-way analysis of variance (ANOVA) tests" was used to see the changes of mean YM values according to the CKD stages. The mean values of YM were found to be higher in Stage 5 CKD (9.71 ± 2.61) patients followed by Stage 4 (8.85 ± 1.74), Stage 3 (7.58 ± 1.26), Stage 2 (6.36 ± 1.28) and Stage 1 (3.85 ± 0.30). (Figure 11, Table 6 and Figure 12)

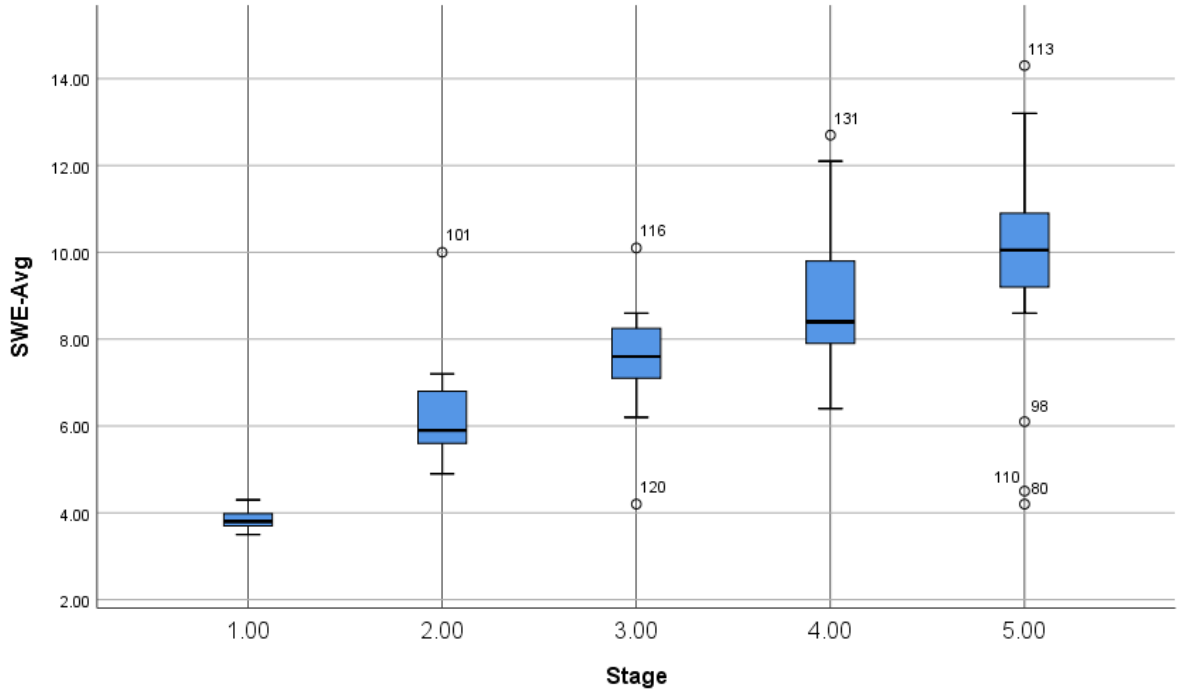

Figure 14: Boxplot showing the correlation between CKD stage and YM measurements

Table 6: Mean YM values of CKD stages

CKD Stage	Mean YM (kPa)	Std deviation
Stage 1	3.85	0.30
Stage 2	6.36	1.28
Stage 3	7.58	1.26
Stage 4	8.85	1.74
Stage 5	9.71	2.61

Figure 15: Line diagram showing CKD stage and YM measurements

Tukey post-hoc multiple comparison test between individual CKD stages

Post hoc Tukey significant difference tests were used to see the changes of mean YM values according to the CKD stages. “Tukey post-hoc multiple comparison” test revealed that there was statistically significant difference in means between stages 1, 3 and 5, and stages 2, 4 and 5, no other significant changes were observed in between the other CKD stages. (Table 7)

Our findings indicated that as the stage of CKD increases, the CS increases up till CKD 5. To an extent, reversible and non-reversible stages may be differentiated by the stiffness values which are significantly different between CKD stage 2 v/s 5 and 3 v/s 5. However, the ability to differentiate between individual stages was poor.

Table 7: Tukey post-hoc multiple comparison test between individual CKD stages

Multiple Comparisons						
Dependent Variable: SWE-Avg						
Tukey HSD						
					95% Confidence Interval	
(I) Stage	(J) Stage	Mean Difference (I-J)	Std. Error	Sig.	Lower Bound	Upper Bound
1.00	2.00	-2.50554	.95157	.076	-5.1755	.1644
	3.00	-3.73150*	.92646	.001	-6.3310	-1.1320
	4.00	-4.99956*	.91412	.000	-7.5644	-2.4347
	5.00	-5.85511*	.91412	.000	-8.4200	-3.2902
2.00	1.00	2.50554	.95157	.076	-.1644	5.1755
	3.00	-1.22596	.67519	.374	-3.1204	.6685
	4.00	-2.49402*	.65816	.003	-4.3407	-.6473
	5.00	-3.34957*	.65816	.000	-5.1963	-1.5029
3.00	1.00	3.73150*	.92646	.001	1.1320	6.3310
	2.00	1.22596	.67519	.374	-.6685	3.1204
	4.00	-1.26806	.62130	.259	-3.0113	.4752
	5.00	-2.12361*	.62130	.009	-3.8669	-.3803
4.00	1.00	4.99956*	.91412	.000	2.4347	7.5644
	2.00	2.49402*	.65816	.003	.6473	4.3407
	3.00	1.26806	.62130	.259	-.4752	3.0113
	5.00	-.85556	.60275	.618	-2.5468	.8357
5.00	1.00	5.85511*	.91412	.000	3.2902	8.4200
	2.00	3.34957*	.65816	.000	1.5029	5.1963
	3.00	2.12361*	.62130	.009	.3803	3.8669
	4.00	.85556	.60275	.618	-.8357	2.5468
*. The mean difference is significant at the 0.05 level.						

Measured mean values of YM were lower in the CKD group that had higher eGFR, with the exception being stage 1 which had a higher YM value than stage 2.

DISCUSSION

DISCUSSION

Worldwide, CKD incidence is currently relatively high. However, the course of CKD comprises of “significant fibrosis, tubular interstitial atrophy, and glomerular compartment sclerosis” independent of the underlying etiology. The advancement of CKD is followed by the deterioration of the kidney parenchyma and end-stage renal failure, which causes extensive tissue scarring. There may be morbidity and mortality as a result of the pathologic damage, which is permanent. As a result, CKD screening and early detection are crucial for taking action to prevent the disease from progressing to an expensive end-stage. Traditional techniques have been employed in the past to identify and assess renal diseases. These include conventional ultrasonography, CT, MRI, and blood sample biochemical analyses. These techniques do, however, come with some dangers, such as radiation exposure and CIN. Because it is safe, simple, and affordable to do, conventional renal ultrasonography is frequently employed in the initial evaluation. Evaluation of renal ultrasonography features such as “decreased renal size, increased parenchymal thickness, and higher parenchymal echogenicity” is straightforward. Nephropathy is frequently diagnosed using the marker of parenchymal echogenicity. This marker, nevertheless, is subjective, not quantitative, and frequently misses renal abnormalities. As a result, traditional renal ultrasonography is typically useless for determining how CKD is progressing.

A new ultrasonic method called shear wave elastography (SWE) is used to gauge tissue stiffness. SWE uses sensors to generate shear waves and non-invasively assess tissue stiffness. Studies conducted on humans and animals have revealed a link between the “presence of CKD and the SWE estimate of renal YM”.[17,69,70] Nephro-elastography technology is currently available; thanks to the development of an

unobtrusive quantitative study and the quick development of diagnostic methods for liver fibrosis. Application of elastography may be crucial in determining tissue stiffness as the prevalence of CKD rises. Using shear wave elastography, this study compared the renal parenchymal stiffness of individuals with CKD caused by T2DM and hypertension to that of people without these conditions (Control). Staging of chronic kidney disease based on renal parenchymal stiffness and its correlation with eGFR has also been studied.

Age distribution

For many years, it has been known that aging causes a decrease in kidney size and function.[23] In the current study, "the majority of CKD cases (31.4%) were in the older age range of 60 to 69 years", whereas the majority of controls (24.3%) were in the younger age group of 20 to 29 years. Leong et al. evaluated 309 persons in total for their study, "consisting of 106 patients and 203 control subjects". The average age of the CKD patients was 65.05 + 11.12, compared to the control groups' 50.94 + 12.71. (eGFR 60–89).[64]

Gender distribution

The controls included 47 males and 23 females, whereas the CKD group comprised of 43 males and 27 females. Male predominance was observed in both control and CKD groups was observed in our study. "Leong et al research's involved 309 adults (167 men and 142 females, with a mean age of 55), while the control group included 203 individuals (104 males and 99 females) who did not exhibit any clinical symptoms of renal illness".[64]

Etiology of CKD

Our study included CKD cases secondary to type II diabetes mellitus, hypertension or both. Out of 70 patients, 22 (31.4%) patients had type II diabetes mellitus and hypertension each and 26 (37.1%) had combination of both diseases. Koc and Sambul involved 46 male patients with Diabetes mellitus and 40 patients in control group.[5] Male predominance was also observed in the study of Bob et al.[66]

Stages of CKD

In the present study, among the 70 CKD cases, the highest number of cases belonged to stage 4 (18) and 5 (18), followed by stage 3 (16), whereas stage 1 (5) had lowest number of subjects. In the study of BOB et al. most of the patients (20) each were in stage 3 and 4 followed by Stage 1 (16 patients), Stage 2 (15 patients) and Stage 5 (9 patients).[66]

Relationship between YM measurements and age and eGFR.

A progressive buildup of harmful connective tissue in the kidney parenchyma known as tubulointerstitial renal fibrosis appears to be the main factor contributing to the decline in renal function. A falling eGFR as a result of progressive interstitial injury suggests an inverse relationship between serum creatinine and eGFR.[71] Plasma proteins may be pushed out into the tubule and urine by hyperfiltration, resulting in tubulointerstitial injury at the glomerulus.[72] Inflammation and fibrosis may develop as a result of protein reuptake at the tubules. Shear wave travels less swiftly in fibrosed tissue.[51,53] eGFR was inversely linked with the amount of renal fibrosis, which in itself is clearly relevant to the transmission of shear waves.

The study revealed that YM measurements showed no correlation with age among the controls, but showed moderate positive correlation with age among the CKD group ($r = 0.293$, $p < 0.014$) and Samir et al's finding that there was no discernible relationship between YM measurement and age confirmed this. The study's tiny sample size may be one reason for this. However, Leong et al and Yang et al researches revealed a substantial correlation between this observation and YM measurements and age. As kidneys became older, glomerulosclerosis, interstitial fibrosis, tubular atrophy, and arteriosclerosis began to emerge.[64]

In our research, the YM measurements and eGFR had a substantial "negative linear connection (Spearman coefficient: r = 0.668, p 0.001)". According to Hu et al., renal length and parenchymal thickness show a lesser connection with eGFR than SWE does.[53] Guo et al, who observed a "positive correlation between shear wave velocity (SWV) and eGFR", showed contrary results. It is still unknown why these differences exist.[52]

Comparison of mean of different parameters between CKD and control groups

Comparison of mean YM measurements between CKD and control groups revealed higher YM values in CKD group (7.96 ± 2.41) compared to control (3.51 ± 1.56), indicating increased stiffness within the CKD group, and was statistically "significant with a p value of <0.001". Mean kidney length was higher in controls (9.3 ± 0 87) as compared to CKD group (8.50 ± 1.82), and mean BMI was higher in CKD group. In contrast to the study by Leong et al., no discernible difference was found between the aforementioned groups. "One-way analysis of variance" revealed a significant difference in YM measurements (F = 90.188, p 0.0001).[64]

Bob et al[66] discovered a link between stiffness and body mass index. Given that the diabetic patients in our group had a greater BMI than the healthy controls, measurement depth may have also contributed to the slower kidney shear wave speed in CKD patients.[66]

ROC curve of YM in distinguishing between CKD and control groups

"ROC curves were used for the analysis of mean YM between the control and sick groups in our study". SWE had a 0.94 AUROC. We determined cutoff value for YM measurements of 4.44 kPa, below which a kidney without disease was recommended. This produced results that were 90.0% and 77.1% more sensitive and specific than typical ultrasonography values. Leong also found comparable outcomes, with SWE having a greater area under the ROC curve (0.87) than measurements of "kidney length and cortical thickness" made using conventional ultrasonography.[4] A "cut-off value of 4.31 kPa", with 80.3 % as sensitivity and 79.5% as specificity of 80.3%, indicating that a less value reflects normal kidney. According to Bob et al., a kidney shear wave speed of 2.32 m/s foretells a drop in eGFR to 60 mL/min. However, this cutoff value has a low sensitivity (67.39%) and specificity (67.83%), making it challenging to predict renal involvement in diabetic individuals only using elastography.[66]

ROC curve of length in distinguishing CKD and controls

A predictor of CKD has also been found in the bipolar length of the kidney. In the present study, for the bipolar kidney length, we found the best possible cut-off of 9.0 cm with a sensitivity of 44.3% and specificity of 40.0% to differentiate control and cases. The AUROC was poor (0.363). However, compared to kidney volume, "Sanusi et al. claims that kidney length is not a reliable indicator of kidney abnormalities".[62]

Correlation between CKD stage and YM measurements

In our study ANOVA tests was used to witness mean YM according to the CKD stages. The mean values of YM were found to be higher in Stage 5 CKD (9.71 ± 2.61) patients followed by Stage 4 (8.85 ± 1.74), Stage 3 (7.58 ± 1.26), Stage 2 (6.36 ± 1.28) and Stage 1 (3.85 ± 0.30).

Tukey post-hoc multiple comparison test between individual CKD stages

"Post hoc Tukey significant difference tests were used to see the changes of mean YM values according to the CKD stages in the present study. "Tukey post-hoc multiple comparison test" revealed that there was statistically significant difference in means between stages 1, 3 and 5, and stages 2, 4 and 5, but there was no significant difference in between the other CKD stages.

Certain traditional renal USG results, such as decreased kidney size, decreased cortical thickness, and increased echogenicity in cortex, may be indicative of parenchymal disease in the kidney. The use of cortical stiffness (CS) measurements from SWE tests has increased recently.[18] The limitations of SWE include the test's sporadic availability in clinics and the absence of defined average results of CS in the patient population.. Regular USG results do not include renal SWE data, and only specific diseases and research quantify CS levels. SWE is a non-invasive, cost-effective, and reliable USG test that can be used to assess tissue elasticity[16]. Values for CS are given in kPa.[17,62,76] The most significant indicator of kidney disease is renal parenchymal fibrosis, which affects the mechanical characteristics of the kidneys and may be assessed objectively using SWE.[25] It has been demonstrated that renal SWE examination is helpful in staging diabetic nephropathy, determining renal fibrosis, identifying rejection of renal allografts, and in CKD patients.[77,78] Our findings indicated

that as the stage of CKD increases, the CS increases up till CKD 5. To an extent, reversible and non-reversible stages may be differentiated by the stiffness values which are significantly different between CKD stage 2 v/s 5 and 3 v/s 5. However, the ability to differentiate between individual stages was poor. Leong concluded that the test also revealed that because of the significant variation between the groups, it was challenging to discriminate between CKD 3rd, 4th, and 5th stages based on their YM measures.[64] In a study involving individuals with diabetic nephropathy, Hassan et al. discovered a substantial reduction in renal cortical thickness. According to the same study, grade 4 CKD patients' renal cortical thickness was lower than that of grade 3 CKD patients.[18] Similar findings were made by Koc and Sumbul et al., "who discovered that patients with type 2 DM had increased cortical thickness in addition to normal renal function".[67] This supports Soldo et al. in the literature.[79] Increased cortical stiffness results from the nephropathy that long-term diabetics experience.[3] The relationship between increasing "renal cortical parenchymal thickness" and CS is a result of nephron hypertrophy and increased CS from increased filtration.

Measured mean values of YM were lower in the CKD group that had higher eGFR, with the exception being stage 1 which had a higher YM value than stage 2. This is in accordance with the study of Leong et al. Tukey post hoc analysis showed that the group with greater eGFR had lower YM readings.[64]

Although the SWE results are promising, it is important to be aware of this novel technique's limitations, including bladder distention, intra- and inter-observer variation, and the position of the ROI. However, bladder that is excessively distended and has transmitted backpressure could result in a false-positive diagnosis of obstructive hydronephrosis.[25] According to a study by Sohn et al, hydronephrosis-related increased

pelvic pressure may exacerbate renal parenchymal stiffness.[81]

Nephrogenic tissue is anisotropic; as a result, not all axis orientations have the same qualities.[82] “The Henle and vasa recta in the medulla”, as well as the collecting ducts in the cortex and medulla, may respond differently to the placement of ultrasound beams on account of the varied shear wave propagation axes.[78] As a result, our findings demonstrated a considerable difference in YM readings when the ROI's location was modified, thereby changing the orientation of the beam to the tissue. Given that the ROI box location had a substantial impact on YM measurements, it is important to choose a fixed location for the ROI box during image capture to provide accurate and repeatable results, particularly when determining the usual range of stiffness for a given tissue. Because the renal medulla and sinus are easily excluded from the ROI box when it is positioned in the middle of the kidney during image capture, we advise doing so.

Preventing nephropathy brought on by diabetes is one of the most crucial objectives in DM care. Although the mainstays of treatment for achieving this goal are blood sugar and blood pressure control, it is still challenging to prevent this consequence. Reactive oxygen products, glycolyzed lipid, and elevated glucose levels were the main Metabolic issues lead to increased generation of inflammatory cells and fibrosis.[83-84] Glomerulosclerosis and acute interstitial fibrosis are caused by nephropathy, which also damages mesangial, endothelial, and epithelial cells. Interstitial fibrosis is the key identifying characteristic of nephropathy brought on by DM.[85] Prior to the onset of nephropathy, it is critical to identify alterations in mesangium, endothelial, and epithelial cells. Early identification of microalbuminuria is crucial for detecting diabetic nephropathy.[86,87] Although invasive, histological evaluation with kidney biopsy clearly demonstrates the continuing fibrosis but cannot

be employed. Noninvasive examinations have been favoured for this reason. SWE is a potential, non-invasive examination that can be utilised for this reason since it provides an objective indication of the renal elasticity or tissue stiffness.

CONCLUSION

Based on the present study results it was found that:

- SWE performed better than traditional ultrasonography in evaluating CKD.
- Patients who had T2 DM had considerably higher cortical stiffness values when measured with SWE.
- 4.44 kPa was selected as the cut-off value to distinguish between kidneys with illness and those without.
- In spite of its shortcomings, SWE-derived estimations of renal stiffness are a reliable, inexpensive technique for non-invasively adding diagnostic information to CKD.

SUMMARY

- The majority of CKD patients (31.4%) were in the 60–69 years age range, whereas the majority of controls (24.3%) were in the 20–29 years age range.
- The controls included 47 males and 23 females, whereas the CKD group comprised of 43 males and 27 females. Male predominance was observed in both control and CKD groups.
- Our study included CKD cases secondary to type II diabetes mellitus, hypertension or both. Out of 70 patients, 22 (31.4%) patients had type II diabetes mellitus and hypertension each and 26 (37.1%) had combination of both diseases.
- Among the 70 CKD cases, the highest number of cases belonged to stage 4 (18) and 5 (18), followed by stage 3 (16), whereas stage 1 (5) had lowest number of subjects.
- YM measurements showed no significant correlation with age among the controls, but showed moderate positive correlation with age among the CKD group ($r = 0.293$, $p < 0.014$).
- The YM measures and eGFR had a substantial negative linear connection, as indicated by the "Spearman correlation coefficient ($r = 0.668$, p 0.001)".
- When the mean YM measurements of the CKD and control groups were compared, it was found that the CKD group's YM readings were higher (7.96 2.41 vs. 3.51 1.56), showing increased stiffness within the CKD group. This finding was "statistically significant with a p value of 0.001".
- Mean kidney length was higher in controls (9.3 ± 0.87) as compared to CKD group (8.50 ± 1.82), and mean BMI was higher in CKD group.

- For SWE, AUROC was 0.94. We determined a cutoff value for YM measurements of 4.44 kPa, below which a kidney without disease was recommended. A sensitivity and specificity of 90.0% and 77.1% were obtained as a result.

- For the bipolar kidney length, we found the best possible cut-off of 9.0 cm with a sensitivity of 44.3% and specificity of 40.0% to differentiate control and cases. The AUROC was poor (0.363).
- The mean values of YM were found to be higher in Stage 5 CKD (9.71 ± 2.61) patients followed by Stage 4 (8.85 ± 1.74), Stage 3 (7.58 ± 1.26), Stage 2 (6.36 ± 1.28) and Stage 1 (3.85 ± 0.30).
- "Tukey post-hoc multiple comparison test" revealed "statistically significant difference in means between stages 1, 3 and 5, and stages 2, 4 and 5, But no significant difference in between the other CKD stages".
- Our findings indicated that as the stage of CKD increases, the stiffness increases up till CKD 5. To an extent, reversible and non-reversible stages may be differentiated by the stiffness values which are significantly different between CKD stage 2 v/s 5 and 3 v/s 5. However, the ability to differentiate between individual stages was poor.
- Stage 1 had a greater YM value than stage 2, although overall, measured mean YM levels were lower in the CKD group with higher eGFR.

IMAGE GALLERY

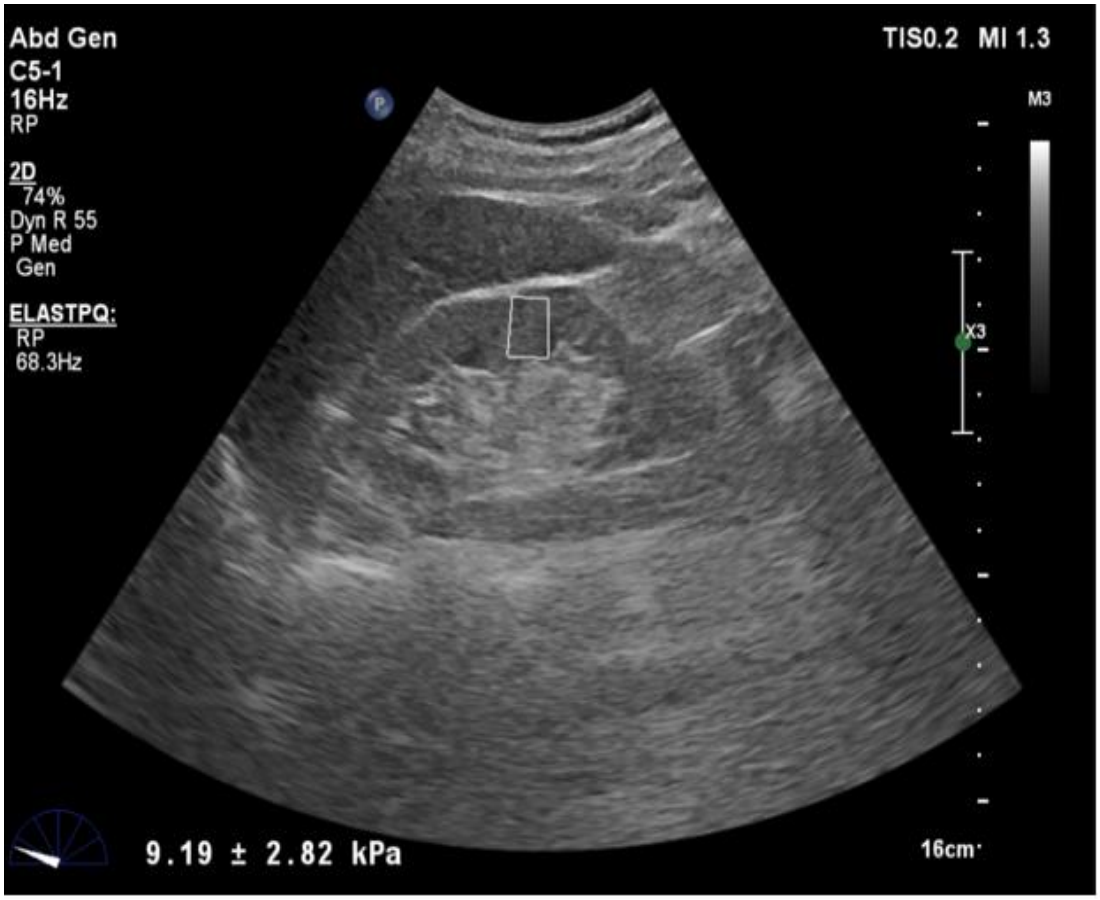

Fig 17: B-mode image and report showing the ROI placement in the cortex of a patient with CKD stage-5 with average YM measurement of 9.16 kPa

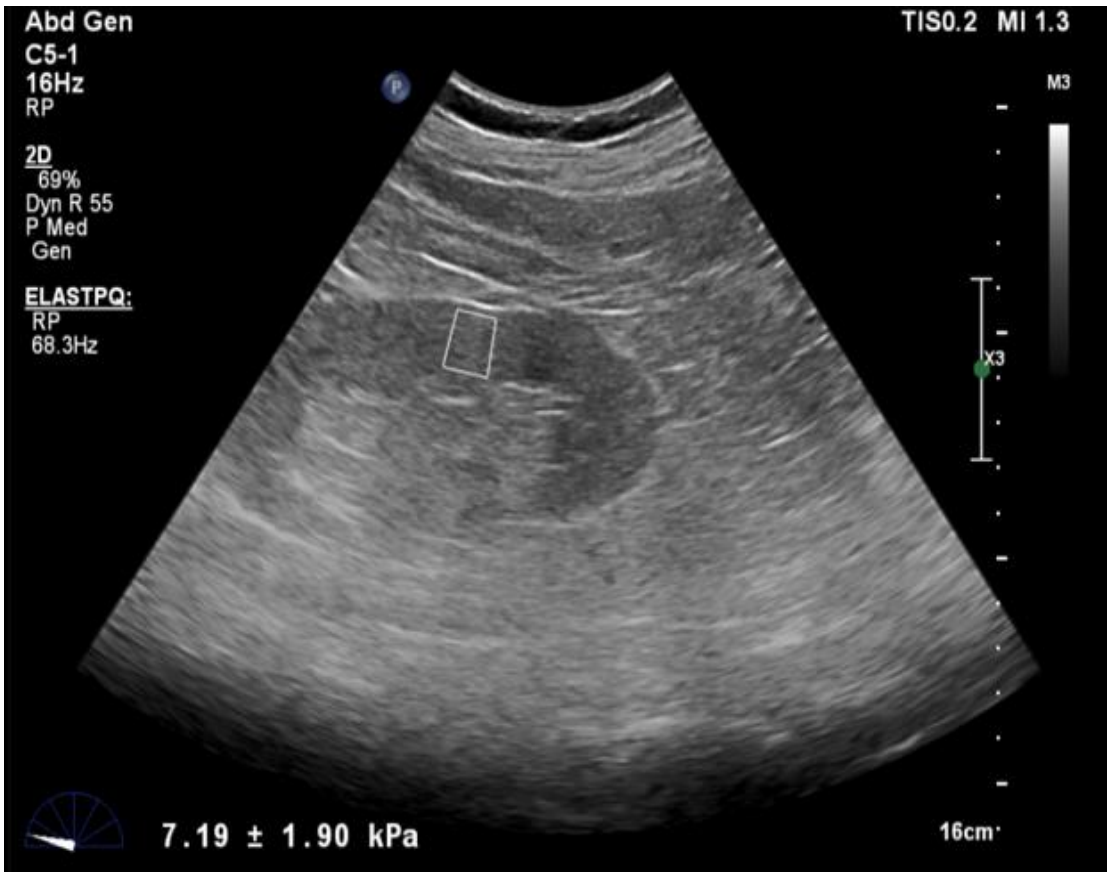

Fig 18: B-mode image and report showing the ROI placement in the cortex of a patient with CKD stage-4 with average YM measurement of 7.78 kPa

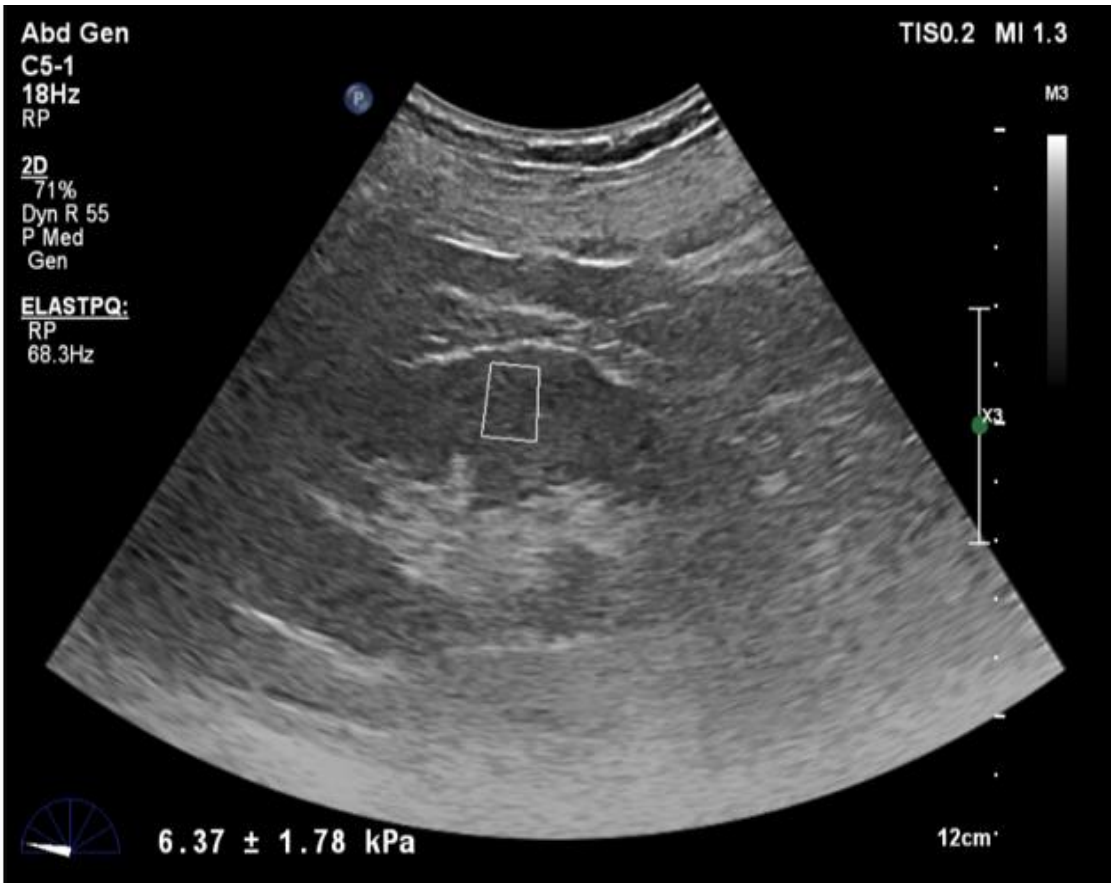

Fig 19: B-mode image and report showing the ROI placement in the cortex of a patient with CKD stage-3 with average YM measurement of 6.26 kPa

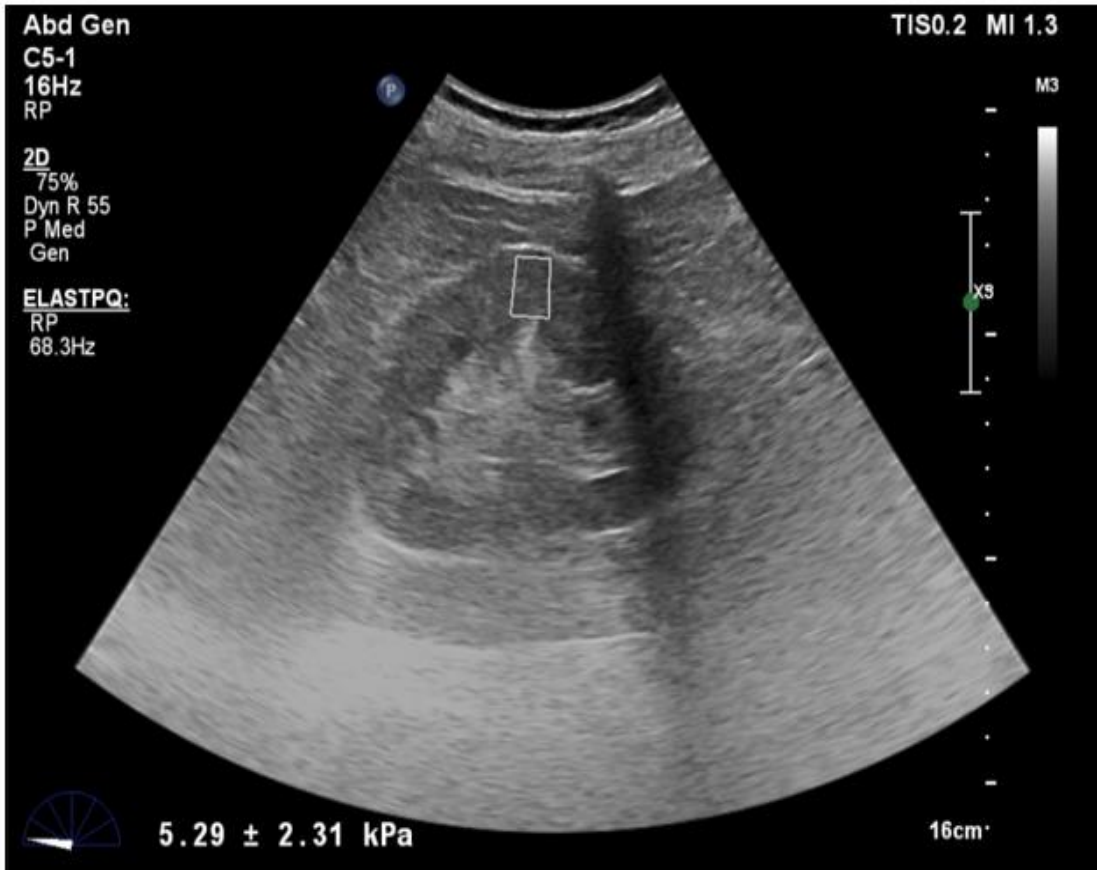

Fig 20: B-mode image and report showing the ROI placement in the cortex of a patient with CKD stage-2 with average YM measurement of 5.39 kPa

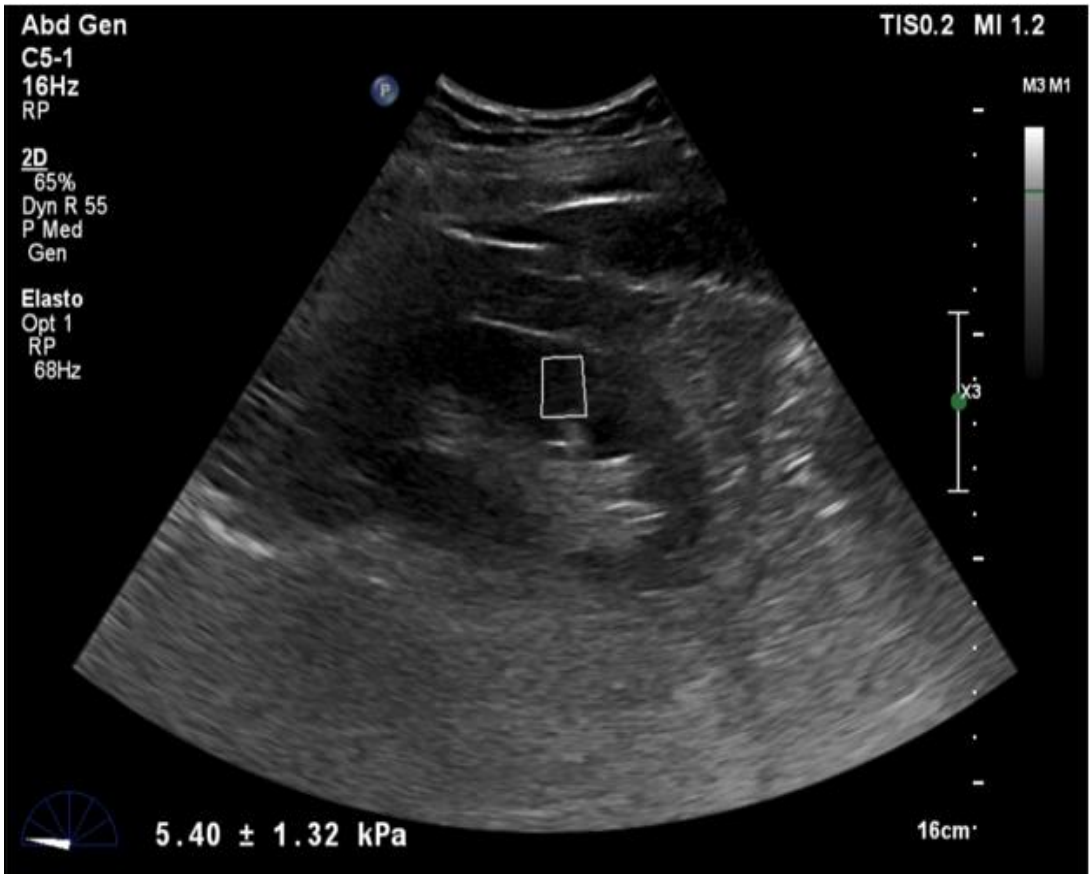

Fig 21: B-mode image and report showing the ROI placement in the cortex of a patient with CKD stage-1 with average YM measurement of 4.81 kPa

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ANNEXURES

PROFORMA

Serial number :
Hospital number:
Consent taken : Yes / No

SUBJECT EVALUATION

Date: **Time:**

Demographic Variables

Age :
Sex :
Occupation:

Disease Details

Hypertension ☐ Diabetes mellitus ☐
Duration of disease :
Not a case of acute kidney injury: ☐

Physical Parameters

BMI :
Blood pressure:

Conventional Ultrasound Features

Right kidney ☐ Left kidney ☐
Size :

Cortical thickness :
Parenchymal changes:
PSV, EDV and RI of main renal artery:

Shear Wave Elastography

ROI size:
ROI location:
Elastography values: / / / /
Average reading:

Biochemical Parameters

Blood urea :
Serum creatinine:
Urine protein :
HbA1c :

Stage of Diabetic Kidney Disease: Stage G1 / G2 / G3 / G4 / G5

INFORMED CONSENT FORM

I Miss/Mrs. _____ have been explained in my own understandable language, that I will be included in a study which " **ROLE OF ELASTOGRAPHY AND ULTRASONOGRAPHY IN RENAL PARENCHYMAL DISEASE IN DIABETIC AND HYPERTENSIVE PATIENT**S **"**

I have been explained that my clinical findings, investigations, will be assessed and documented for study purpose.

I have been explained my participation in this study is entirely voluntary, and I can withdraw from the study any time and this will not affect my relation with my doctor or the treatment for my ailment.

I have been explained about the interventions needed possible benefits and adversities due to interventions, in my own understandable language.

I have understood that all my details found during the study are kept confidential and while publishing or sharing of the findings, my details will be masked.

I have principal investigator mobile number for enquiries.

I in my sound mind give full consent to be added in the part of this study.

Signature of the patient:

Name:

Signature of the witness:

Name:

Relation to patient:

Date:

Place:

PATIENT INFORMATION SHEET

STUDY TITLE: ROLE OF ELASTOGRAPHY AND ULTRASONOGRAPHY IN RENAL PARENCHYMAL DISEASE IN DIABETIC AND HYPERTENSIVE PATIENTS

STUDY SITE: R.L Jalappa Hospital and Research Centre, Tamaka, Kolar.

This is to inform you that,

We are conducting this study to assess CKD and its correlation with eGFR. If you are willing you will be enrolled in this study and we will do Elastography and other relevant investigations needed to diagnose CKD.

This will facilitate identifying CKD with the help of Elastography indices and treating it. It will also benefit other patients with CKD undergoing medical therapy in the future. You are free to opt-out of the study at anytime if you are not satisfied or apprehensive to be a part of the study. Your treatment and care will not be compromised if you refuse to be a part of the study. The study will not add any risk or financial burden to you if you are part of the study

Your identity and clinical details will be confidential. You will not receive any financial benefit for being part of the study. You are free to contact Dr. Arun Rajkumar or any other member of the above research team for any doubt or clarification you have.

Dr. Arun Rajkumar
Mobile no: 8668134330
E-mail id: drarunrajkumar1994@gmail.com

CONTROLS

UHID	Age	Range	Gender	Group	Disease	Length	SWE-Avg	BMI
619254	24	18-29	MALE	NORMAL	NONE	8.9	2.11	29.8
628320	34	30-39	MALE	NORMAL	NONE	9.1	2.37	24.6
604049	40	30-39	MALE	NORMAL	NONE	10.1	2.79	31.2
655768	54	50-59	MALE	NORMAL	NONE	8.9	0.9	22.7
643355	37	30-39	MALE	NORMAL	NONE	9.4	1.1	26.5
568371	64	60-69	FEMALE	NORMAL	NONE	828	3.7	23.6
610956	70	70-79	MALE	NORMAL	NONE	9.8	1.12	19
667351	31	30-39	MALE	NORMAL	NONE	8.4	3	21
588181	38	30-39	FEMALE	NORMAL	NONE	9.6	2.11	27.1
609282	46	40-49	MALE	NORMAL	NONE	10.2	2.6	25.1
606800	30	30-39	FEMALE	NORMAL	NONE	11.1	1.877	22.6
642454	20	20-29	MALE	NORMAL	NONE	9	2.33	21.2
576337	25	20-29	FEMALE	NORMAL	NONE	9.8	3.64	22.9
626769	28	20-29	MALE	NORMAL	NONE	8.9	1.49	22.2
620301	27	20-29	MALE	NORMAL	NONE	9.5	1.1	21.5
592611	24	20-29	MALE	NORMAL	NONE	9.8	3.02	20.3
623041	39	30-39	FEMALE	NORMAL	NONE	10.2	1.63	19.4
578305	25	20-29	MALE	NORMAL	NONE	10.9	2.27	23.3
659129	50	50-59	FEMALE	NORMAL	NONE	8.25	1.49	19.9
617787	38	30-39	MALE	NORMAL	NONE	11.1	3.54	23.9
678775	64	60-69	FEMALE	NORMAL	NONE	8.8	3.79	31
625537	47	40-49	FEMALE	NORMAL	NONE	10.4	2.656	21
656200	63	60-69	MALE	NORMAL	NONE	9.4	2.647	26.8
573556	32	30-39	MALE	NORMAL	NONE	8.1	2.91	24.4
647852	74	70-79	MALE	NORMAL	NONE	9	4.96	22.1
605670	43	40-49	MALE	NORMAL	NONE	9.1	2.44	23
666082	22	20-29	FEMALE	NORMAL	NONE	8.3	2.23	22
625145	54	50-59	MALE	NORMAL	NONE	8.74	3.13	21.7
644746	57	50-59	FEMALE	NORMAL	NONE	10.1	3.98	19.2
667523	25	20-29	MALE	NORMAL	NONE	9.4	6.56	23.6
616272	24	20-29	FEMALE	NORMAL	NONE	9.2	4.91	24.5
607439	60	60-69	MALE	NORMAL	NONE	9.9	9.11	20.9
583783	62	60-69	FEMALE	NORMAL	NONE	8.5	3.21	18.7
674414	55	50-59	MALE	NORMAL	NONE	9.7	3.91	26.8
585299	64	60-69	FEMALE	NORMAL	NONE	8.3	5.92	27.8
622429	59	50-59	FEMALE	NORMAL	NONE	8.9	3.56	23
598473	64	60-69	MALE	NORMAL	NONE	10.2	2.5	24.31
594578	28	20-29	MALE	NORMAL	NONE	9.4	4.08	25.36
615378	25	20-29	MALE	NORMAL	NONE	8.2	1.08	24.98
577131	30	30-39	MALE	NORMAL	NONE	7.9	3.99	19
628166	24	20-29	MALE	NORMAL	NONE	10.4	3.2	24.5
647993	66	60-69	MALE	NORMAL	NONE	12	4.73	17
665226	42	40-49	MALE	NORMAL	NONE	8.1	7.77	19.7
632739	58	50-59	FEMALE	NORMAL	NONE	9.4	4.5	15
608418	55	50-59	FEMALE	NORMAL	NONE	10.2	4.17	19.8
622983	52	50-59	MALE	NORMAL	NONE	9.5	3	24.7
610636	74	70-79	FEMALE	NORMAL	NONE	8.1	4.71	17.5
672375	58	50-59	MALE	NORMAL	NONE	9.3	2.97	2.6
578531	24	20-29	FEMALE	NORMAL	NONE	9.1	4.69	22.7

606825	20	20-29	FEMALE	NORMAL	NONE	10	4.9	24.2
627081	28	20-29	FEMALE	NORMAL	NONE	10.9	4.08	25.6
637081	35	30-39	MALE	NORMAL	NONE	11.4	3.73	24.5
614909	62	60-69	MALE	NORMAL	NONE	9.3	4.57	23.7
588356	48	40-49	MALE	NORMAL	NONE	8.9	6.29	19.8
628217	72	70-79	MALE	NORMAL	NONE	8.7	6.21	22.1
623407	65	60-69	MALE	NORMAL	NONE	9.02	4.98	23
618003	32	30-39	MALE	NORMAL	NONE	8.2	3.5	24.7
609853	22	20-29	MALE	NORMAL	NONE	8.6	5.55	23.6
585080	65	60-69	FEMALE	NORMAL	NONE	8.9	2.99	27.4
604479	38	30-39	MALE	NORMAL	NONE	9.4	3.33	21.4
642144	27	20-29	MALE	NORMAL	NONE	9.1	4.39	22.3
664842	58	50-59	MALE	NORMAL	NONE	10	1.89	25.6
570419	51	50-59	MALE	NORMAL	NONE	8.9	2.64	21.4
674137	30	30-39	MALE	NORMAL	NONE	9.3	3.8	23.4
643430	62	60-69	MALE	NORMAL	NONE	8.2	4.11	22.4
594836	78	70-79	FEMALE	NORMAL	NONE	9.1	3.49	32.4
621512	50	50-59	MALE	NORMAL	NONE	10.3	4.03	23.5
602642	68	60-69	FEMALE	NORMAL	NONE	8.8	2.26	21.1
604960	79	70-79	MALE	NORMAL	NONE	8.5	3.73	27.2
570929	81	80-89	MALE	NORMAL	NONE	9.2	4.01	33

CASES

UHID	Age	Age range	Gender	Group	Disease	Length	STAGE	e GFR	SWE-Avg
616340	47	40-49	MALE	CKD	DIABETES	8.2	2	65	5.9
619069	64	60-69	MALE	CKD	HTN	8.9	5	11	13.2
599550	61	60-69	MALE	CKD	DIABETES	7.1	4	24	9.8
568457	65	60-69	MALE	CKD	DIABETES	8.7	2	76	6.2
577079	60	60-69	MALE	CKD	DIABETES	9.2	5	9	10.7
618627	58	50-59	FEMALE	CKD	DIABETES	10.1	3	32	7.3
586172	65	60-69	MALE	CKD	DIABETES	8.1	4	26	8.2
641955	62	60-69	MALE	CKD	HTN	8.6	2	82	6.8
572778	86	80-89	FEMALE	CKD	BOTH	9.5	5	8	9.3
625734	51	50-59	MALE	CKD	HTN	9.2	5	13	4.2
575282	83	80-89	MALE	CKD	BOTH	7.1	4	26	8.4
585098	61	60-69	MALE	CKD	BOTH	6	2	87	7
643406	54	50-59	FEMALE	CKD	BOTH	7.5	4	21	8.5
659273	63	60-69	MALE	CKD	BOTH	8.1	5	14	11.7
609488	61	60-69	MALE	CKD	HTN	0.2	2	74	7.2
577390	52	50-59	MALE	CKD	BOTH	9.1	3	41	8.1
634282	77	70-79	FEMALE	CKD	HTN	7.8	4	20	8.9
577710	64	60-69	MALE	CKD	DIABETES	8.2	2	78	5.6
594022	78	70-79	FEMALE	CKD	DIABETES	7.32	1	93	3.98
603350	61	60-69	MALE	CKD	BOTH	7.3	5	15	10.2
617624	79	70-79	FEMALE	CKD	HTN	9.1	3	54	6.2
570387	50	50-59	MALE	CKD	HTN	8.8	2	61	5.5
625665	58	50-59	FEMALE	CKD	HTN	7.4	3	34	7.4
574311	51	50-59	MALE	CKD	BOTH	9.2	2	68	5.7
583133	67	60-69	FEMALE	CKD	HTN	8.6	4	18	11.4
592561	60	60-69	FEMALE	CKD	BOTH	6.74	3	52	8.4
610479	39	30-39	MALE	CKD	DIABETES	7.2	1	107	4.3
607432	50	50-59	MALE	CKD	DIABETES	6.4	5	14	6.1
644921	58	50-59	MALE	CKD	DIABETES	9.5	2	76	6.6
647523	61	60-69	MALE	CKD	HTN	11.1	3	47	7.6
596074	47	40-49	MALE	CKD	BOTH	8.1	2	71	10
569825	62	60-69	MALE	CKD	BOTH	9.1	5	13	9.8
570842	75	70-79	MALE	CKD	BOTH	5.2	5	11	9.2
593715	20	20-29	FEMALE	CKD	BOTH	8.6	2	75	5.4
571988	48	40-49	MALE	CKD	HTN	4.3	3	48	6.9
621742	27	20-29	MALE	CKD	DIABETES	11.2	4	17	8.2
600253	42	40-49	FEMALE	CKD	BOTH	9	2	63	4.9
572038	48	40-49	MALE	CKD	DIABETES	7.2	4	25	6.4
579995	60	60-69	FEMALE	CKD	HTN	7.8	3	56	7.9
598804	67	60-69	MALE	CKD	BOTH	8.4	5	14	4.5
627603	47	40-49	FEMALE	CKD	DIABETES	8.1	4	27	12.1
597329	60	60-69	MALE	CKD	HTN	10	3	59	8.1
577019	71	70-79	FEMALE	CKD	HTN	9.2	5	11	14.3
610897	80	80-89	MALE	CKD	DIABETES	7	4	28	8.4
595059	59	50-59	FEMALE	CKD	BOTH	9.2	5	9	9.9
612630	80	80-89	FEMALE	CKD	BOTH	10.3	3	39	10.1
652210	64	60-69	MALE	CKD	HTN	7.8	5	3	10.3
576548	38	30-39	MALE	CKD	DIABETES	8.9	5	5	10.4
632834	27	20-29	MALE	CKD	BOTH	10.5	2	61	5.9
601155	59	50-59	MALE	CKD	BOTH	8.2	3	41	4.2
571753	70	70-79	FEMALE	CKD	DIABETES	10.6	4	20	9.8
618451	31	30-39	FEMALE	CKD	HTN	10.1	4	24	7.9

571074	39	30-39	MALE	CKD	BOTH	9.6	4	26	8.4
655098	38	30-39	MALE	CKD	BOTH	11.2	3	57	8.6
665027	48	40-49	FEMALE	CKD	DIABETES	9.8	5	9	8.6
640851	40	40-49	MALE	CKD	HTN	11.1	1	114	3.5
595577	70	70-79	FEMALE	CKD	BOTH	10.5	4	17	7.3
602459	42	40-49	MALE	CKD	HTN	9.3	3	58	7.5
624848	64	60-69	MALE	CKD	HTN	10.41	5	10	9.9
580457	29	20-29	FEMALE	CKD	BOTH	5.8	1	91	3.7
625595	51	50-59	MALE	CKD	BOTH	11.1	4	19	12.7
603084	58	50-59	FEMALE	CKD	HTN	9.8	3	38	6.9
638083	31	30-39	MALE	CKD	HTN	10.2	1	97	3.8
640297	61	60-69	FEMALE	CKD	HTN	6.4	5	11	10.9
628890	28	20-29	FEMALE	CKD	BOTH	9.9	5	14	11.6
657702	26	20-29	FEMALE	CKD	BOTH	10.2	4	18	6.5
575979	52	50-59	FEMALE	CKD	DIABETES	7.1	3	50	8.6
657607	65	60-69	MALE	CKD	DIABETES	5.9	4	17	7.6
584784	58	50-59	FEMALE	CKD	DIABETES	9.7	3	32	7.6
617887	73	70-79	MALE	CKD	DIABETES	8.1	4	16	8.9
570901	72	70-79	FEMALE	CKD	HTN	7.8	3	49	7.8