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PhD THESIS
NOVEL KIDNEY ELASTOGRAPHY METHODS IN EVALUATING CHRONIC KIDNEY DISEASE

A B S T R A C T

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GENERAL PART

1. CHRONIC KIDNEY DISEASE

1.1. DEFINITION, EPIDEMIOLOGY, AND PROGNOSIS

Chronic kidney disease (CKD) is a significant threat to public health since it is connected with an increase in morbidity and mortality. CKD has become one of the leading causes of mortality and suffering in the twenty-first century. The prevalence of CKD patients has also been rising, impacting an estimated 843.6 million people globally in 2017.

CKD gradually evolves to end-stage renal disease, a stage when renal replacement methods are necessary, and therefore it is very important to quantify the progression of CKD. Initially, numerous individuals are symptomless or have clinical manifestations such as tiredness, itching, or decreased appetite. As CKD advances and kidney function deteriorates, numerous compounds termed uremic residual substances build in the body, with the ones that exert harmful biological effects being referred to as uremic toxins.

Because the disease is mainly asymptomatic, especially in the initial stages, the development of a quick and non-invasive image screening technique would be crucial.

1.2. IMAGING EXAMINATIONS OF THE KIDNEYS

It is essential to identify CKD sooner and properly track the course of the illness using indicators like imaging. Conventional ultrasonography is used to examine the kidneys but this technique only provides limited quantitative information.

1.3. KIDNEY ELASTOGRAPHY

In recent years, elastography has emerged as a non-invasive procedure for diagnosing widespread renal diseases. For nephrologists, the approach's primary purpose would be to detect CKD early and to track how the illness progresses over time.

1.4. THE NEW PARADIGM IN KIDNEY ELASTOGRAPHY: 2D SWE PLUS AND VI PLUS

A recent study published by Richard Barr in 2020 shows that, up until now, elastographic investigations conducted on the kidneys are likely incorrect and new software is needed to gather correct shear wave displacements in the kidney. Hologic SuperSonic Imagine has integrated a novel algorithm, which might reduce artifacts that are observed while measuring the kidneys' rigidity and it offers real-time qualitative and quantitative evaluations of tissue elasticity by monitoring the velocity of shear waves and tissue viscosity by measuring tissue shear wave dispersion.

SPECIFIC PART

2. GENERAL OBJECTIVES

We performed four studies regarding kidney elastography.

The first one entitled "Are the Currently Available Elastography Methods Useful in the Assessment of Chronic Kidney Disease? A Systematic Review and a Meta-Analysis" considered and gathered all English-language research (full-length articles) that performed kidney elastography between the years of 2010 and 2021.

The second one "Non-Invasive Evaluation of Kidney Elasticity and Viscosity in a Healthy Cohort" aimed to be the first study to assess the normal range values for kidney stiffness and viscosity using the new technology 2D SWE PLUS and Vi PLUS in normal renal function subjects and to investigate the factors that impact them.

The third one "Assessment of Renal Allograft Stiffness and Viscosity Using 2D SWE PLUS and Vi PLUS Measures—A Pilot Study" aimed to evaluate the feasibility and the performance of the new ultrasound-based technique for the non-invasive assessment of renal allograft fibrosis and viscosity.

The fourth one "Relationship between Novel Elastography Techniques and Renal Fibrosis—Preliminary Experience in Patients with Chronic Glomerulonephritis" investigated whether these elastography techniques could reveal renal tissue fibrosis in patients with chronic glomerulonephritis.

3. RESEARCH I
ARE THE CURRENTLY AVAILABLE ELASTOGRAPHY METHODS USEFUL IN THE ASSESSMENT OF CHRONIC KIDNEY DISEASE? A SYSTEMATIC REVIEW AND A META-ANALYSIS

3.1. INTRODUCTION

Whether or not renal elastography has a place in clinical practice, it is vital to understand the factors that impact the results that are obtained. In order to evaluate CKD in a more comprehensive manner, we decided to perform a systematic review and a meta-analysis comparing the various findings acquired through renal elastography.

3.2. MATERIALS AND METHODS

We considered all English-language research (full-length articles) that conducted kidney elastography between the years of 2010 and 2021 and included the following keywords when searching databases: renal elastography, ARFI, Virtual touch tissue quantification, kidney stiffness, and kidney fibrosis.

3.2.1. STUDY SELECTION AND DATA EXTRACTION

We extracted the country of origin, the year the publication, the type of patients, the etiology of CKD, the technical failures, if the renal biopsy that was used for the evaluation of fibrosis in CKD, the quality of specimen that was obtained in renal biopsy, the correlation coefficient between kidney shear wave speed (KSWS) and eGFR, the area under the curve (AUC) (if it was provided), and the cut-off values for predicting CKD.

Only 21 of the 37 titles that were identified during the first search employed point shear wave elastography (the Virtual Touch Quantification-VTQ system). We were mainly interested in finding a statistically significant correlation coefficient between eGFR and kidney stiffness, as well as an area under the curve (AUC) and a cut-off value

of KSWS that could potentially be helpful for the diagnosis of CKD. In the end, 11 research (11 full-length publications) containing a total of 1214 CKD patients and 781 healthy controls that analyzed renal stiffness using VTQ were reviewed.

3.3. RESULTS

Patients who suffer from CKD have a KSWS that is much lower than healthy controls. Shear wave velocity, as measured by VTQ, was found to be much greater in healthy volunteers than it was in CKD patients, and this difference was connected to eGFR. It also demonstrates an enhanced heterogeneity index (I^2 = 98.12%) between studies as it was anticipated.

We found a strong relationship in six studies that looked at the correlation coefficient between eGFR and KSWS. Despite this, heterogeneity was still high among them with an I^2 value of 93.1%.

In addition, a pooled area under the ROC curve of 0.831 was discovered in order to predict CKD but again with high heterogeneity between studies with an I^2 of 78.82%.

3.4. DISCUSSION

In the variety of investigations that used VTQ, the correlation between kidney SWS and renal disease was shown to be extremely distinct. Even though there is a general trend for kidney SWS to lessen as the CKD stage increases, no statistically significant similarities have been found in the research that has looked into the relationship between CKD stages and KSWS and it would be plausible to draw the conclusion that elastography, or at least VTQ, is not appropriate for distinguishing between the various phases of CKD.

It is unclear whether or not there is a clear relationship between KSWS and eGFR because only 13 of our 37 studies showed any statistically significant correlation between the variables. Various studies suggested cut-off ranges for renal stiffness to indicate advanced stages of CKD, but again with high heterogeneity between them.

While there are some benefits to using elastography in the evaluation of the kidneys, for instance, the fact that the image can be obtained in real-time without the need for the subjects to undergo any kind of special preparation beforehand and without the procedure leading to any complications, utilizing elastography in the evaluation of the kidneys is more challenging than using it in the evaluation of other organs.

3.5. CONCLUSIONS

Even though renal elastography could become an appealing tool for monitoring the progression of CKD studies up to date show an increased heterogeneity and as a result, this method is not compelling enough to be implemented into routine clinical practice.

4. RESEARCH II
NON-INVASIVE EVALUATION OF KIDNEY ELASTICITY AND VISCOSITY IN A HEALTHY COHORT

4.1. INTRODUCTION

There is currently insufficient published evidence on the elasticity and viscosity of the kidneys. Noninvasive approaches, such as two-dimensional shear-wave elastography (2D-SWE PLUS) and viscosity plane-wave ultrasound (Vi PLUS), have emerged as new investigative techniques, which are anticipated to enhance renal stiffness and viscosity measures owing to efficient processing software.

This study's objective was to evaluate the practicability and efficacy of these new ultrasound-based procedures. To differentiate between normal and pathologic cases, it is first required to establish normal kidney elasticity and viscosity values in order to identify the variables that impact them and their variability in healthy individuals.

4.2. MATERIALS AND METHODS

4.2.1. STUDY POPULATION

In a tertiary nephrology clinic over the course of seven months (March 2022 to September 2022), cross-sectional, monocentric research was undertaken. Pursuing confirmation of informed permission, fifty healthy participants were included in the study.

4.2.2. ELASTOGRAPHY USING 2D-SWE PLUS AND VI PLUS

Utilizing a convex C6-1X probe and Hologic Aixplorer Mach 30 ultrasound software, the 2D-SWE PLUS and Vi PLUS data were evaluated.

4.2.3. STATISTICAL ANALYSIS

MedCalc software Version 19.4 (MedCalc Software Corp., Brunswick, ME, USA) and Excel from Microsoft Office 2020 for Windows were utilized for the statistical analysis.

4.3. RESULTS

Our research comprised 29 women and 21 men with the average kidney elasticity being 31.88± 2.89 kPa and the average viscosity 2.44± 0.57 Pa.s at a measuring depth of 4.58± 1.02cm. Both 2D-SWE PLUS (r = 0.6101, p< 0.0001) and Vi Plus (r = 0.4057, p = 0.0038) values appeared to be influenced by eGFR. In addition, we discovered a negative association between age and eGFR (r = 0.8521, p< 0.0001). The mean kidney stiffness values in males were 32.03± 2.84 kPa, somewhat higher than those in women at 31.08± 2.5 kPa (p = 0.2185), whereas the mean viscosity values in men were 2.49± 0.47 Pa.s, slightly lower than those in women at 2.52± 0.79 Pa.s (p = 0.8964).

Age appeared to affect both renal stiffnesses (r = 0.7047, p< 0.0001) and viscosity (r= 0.4251, p = 0.0021) although BMI had no link with renal stiffness (r = 0.2150, p = 0.1338) but solely with viscosity (r= 0.3676, p = 0.0086).

Good intra-operator repeatability was seen for the 2D- SWE PLUS measures, with an ICC of 0.8365 and a 95% CI of 0.7512 to 0.8990, and for the Vi PLUS readings, with an ICC of 0.9 and a 95% CI of 0.8515 to 0.9397.

4.4. DISCUSSION

In actuality, identifying tissue mechanical characteristics is difficult, but to truly understand these new US-based measures, it is essential to evaluate baseline data from healthy renal individuals of varying ages and sexes and to explore the elements that influence them. To the best of our knowledge, however, no previous clinical investigation has focused on finding the reference values of kidney stiffness and viscosity in healthy renal participants using these novel, noninvasive approaches.

The average stiffness of the kidneys was 31.88± 2.89 kPa, and the average viscosity was 2.44± 0.56 Pa.s. Consequently, a 2D-SWE PLUS reading of around 31.88 kPa and a Vi PLUS value of approximately 2.44 Pa.s are suggestive of a kidney that is devoid of fibrosis and inflammation.

4.5. CONCLUSIONS

Screening for renal stiffness and viscosity may become a cost-effective and efficient method for collecting additional diagnostic information from CKD patients. The results reveal that these noninvasive approaches are extremely practicable and gender-independent and that their values correlate with renal function and diminish with age.

5. RESEARCH III
ASSESSMENT OF RENAL ALLOGRAFT STIFFNESS AND VISCOSITY USING 2D SWE PLUS AND VI PLUS MEASURES – A PILOT STUDY

5.1. INTRODUCTION

Renal allograft biopsy is the "gold standard" for identifying chronic allograft injury or acute rejection. It is crucial to recognize an early reduction in eGFR and follow the progression of the disease using a range of indicators (biomarkers, histology, imaging). The easiest answer to this problem would be a noninvasive way of assessing the advancement of progressive fibrosis following transplantation and ideally be accurate for fibrosis grading, easy to use, reliable, inexpensive, and enabling for long-term monitoring of the patients.

This study sought to determine the practicability and effectiveness of this new ultrasound-based technique (ShearWave Elastography and Viscosity Plane-wave UltraSound) embedded in the new Hologic Aixplorer Mach 30 system (Aixplorer, Supersonic Imagine, Aix-en-Provence, France) for the non-invasive evaluation of renal allograft fibrosis and viscosity.

5.2. MATERIALS AND METHODS

5.2.1. STUDY POPULATION

A monocentric cross-sectional study was conducted in a tertiary nephrology department for three months (March 2022 to May 2022). Following obtaining informed permission, fifty kidney transplant recipients (16 women and 34 men, with a mean age of 47.5 ±12.5, a mean eGFR of 52.19 ±22.6 mL/min/1.73 m2, and a mean time after transplant of 10.09 ±5 years) were recruited.

5.3. RESULTS

The mean value for 2D SWE PLUS measures was 25.95 kPa, and for Vi PLUS 2.82 Pa.s. We discovered a positive correlation between eGFR and the median measure of renal cortical stiffness (r = 0.5699, p<0.0001), between eGFR and the median measure of viscosity (r = 0.3335, p = 0.0180), between the median depth of measures and renal cortical stiffness (r = 0.2795, p = 0.0493), and between median depth of measures and BMI (r = 0.6574, p<0.0001).

Our work demonstrates excellent intra-operator agreement for 2D SWE PLUS measures with an intraclass correlation coefficient of 0.9548 and for Vi PLUS with an intraclass correlation coefficient of 0.8323.

Our research demonstrates a marked drop in mean 2D SWE PLUS measurements as CKD progresses. We obtained a cut-off value of renal cortical stiffness of <27.3kPa for the detection of estimated glomerular filtration rate(eGFR)<60ml/min/1.73m2 with 80% sensitivity and 85% specificity (AUC=0.811, P<0.0001), a cut-off value of <26.9kPa for detection of eGFR<45ml/min/1.73m2 with 82.6% sensitivity and 74% specificity (AUC=0.789, P<0.0001) and a cut-off value of <23kPa for detection of eGFR<30ml/min/1.73m2 with 88.8% sensitivity and 75.6% specificity (AUC=0.852, P<0.0001).

5.4. DISCUSSIONS

Previous elastography systems were unable to give reliable stiffness estimations, but with the release of revised software for the new Supersonic Image Mach 30, this issue may be rectified. eGFR was positively correlated with median values of renal cortical stiffness expressed in kPa.

Even though the primary intent of the 2D SWE technique was to identify liver fibrosis and the present work reveals that this method may also be used to evaluate renal transplant parenchymal stiffness, which, based on our findings, appropriately represents CKD stages. Our work also demonstrates a favorable association between eGFR and median Vi PLUS measurements, as well as median Vi PLUS and 2D SWE PLUS measurements.

Non-invasive techniques such as 2D SWE PLUS and Vi PLUS will never be able to compete with the diagnostic power of the gold standard, which is renal allograft biopsy, and are unlikely to replace histopathology for evaluating fibrosis and loss of renal function after transplantation. However, the most exciting and attractive application would be the ability to track changes in allograft parenchymal structure over time.

5.5. CONCLUSIONS

Evaluation of renal allograft stiffness and viscosity may be an efficient tool for detecting individuals with chronic allograft injury, as well as a cost-effective strategy for providing extra diagnostic information in kidney-transplanted patients.

6. RESEARCH IV
RELATIONSHIP BETWEEN NOVEL ELASTOGRAPHY TECHNIQUES AND RENAL FIBROSIS -PRELIMINARY EXPERIENCE IN PATIENTS WITH CHRONIC GLOMERULONEPHRITIS

6.1. INTRODUCTION

Damage to the kidney parenchyma and tissue scarring leads to a reduction in renal function and the only way to diagnose fibrosis is by a kidney biopsy, with histopathology remaining the most important diagnostic and prognostic tool.

Thus, the goal of this study was to evaluate the efficacy of these new ultrasonic-based procedures and compare the outcomes to the "gold standard" represented by kidney biopsy in patients with chronic glomerulonephritis.

6.2. MATERIALS AND METHODS

6.2.1. PATIENT SELECTION

A cross-sectional, monocentric study was conducted in a tertiary nephrology department during a ten-month period (March 2022 to December 2022). We included 40 patients with chronic glomerulonephritis who underwent renal biopsies and elastography evaluation.

6.2.2. ELASTOGRAPHY

After voiding the bladder, the patient was placed in dorsal decubitus while five successive measurements were made in the central region of the renal parenchyma, directly underneath the subcapsular cortex.

6.2.3. RENAL BIOPSY AND HISTOPATHOLOGY

Based on the severity of interstitial fibrosis, the patients were divided into four categories: no/minimal fibrosis (0–10%), mild fibrosis (10–30%), moderate fibrosis (30–50%), and severe fibrosis (>50%).

6.3. RESULTS

A total of 26 men and 14 women with a mean age of 52.35 ± 15.54 years, a mean body mass index (BMI) of 26.71 ± 4.65, a mean kidney length of 104.33 ± 20.19 mm, a mean estimated glomerular filtration rate (eGFR) of 53.8 ± 35.49 mL/min/1.73 m2, and mean proteinuria of 6.39 ± 7.42 g/24h underwent elastography then renal biopsy procedures.

The mean 2D-SWE PLUS value for the whole group was 23.8±7.45 kPa and the mean Vi PLUS value was 2.39±0.73 Pa.s at a mean depth of measures of 6.22±1.43cm. eGFR correlate with both 2D-SWE PLUS measures (r=0.7065, P<0.0001) and Vi PLUS measures (r=0.3637, P=0.0211).

Predicting between the fibrosis (over 10%) and no-fibrosis group (0–10%), we found a cut-off value of <20.77 kPa for detecting the presence of fibrosis with the area under the curve (AUC) of 0.860, p < 0.001 with 88.89% sensitivity, and a 75% specificity for the 2D SWE PLUS measures and a cut-off value of <2.8 Pa.s for detecting the presence of fibrosis with an AUC of 0.792, p < 0.001 with 94% sensitivity, and a 60% specificity for the Vi PLUS measures.

6.4. DISCUSSION

The most practical and appealing use of this technique would be to monitor alterations in the parenchymal structure over time, with a steady decline in parenchymal stiffness and viscosity across successive 2D SWE PLUS and Vi PLUS measures would give nephrologists a better understanding of the development of fibrosis in the kidneys, even if serum creatinine levels remained unchanged.

Because of the uncommon but potential complications that might arise from a kidney biopsy, patients occasionally choose not to perform one. On the other hand, 2D SWE PLUS and Vi PLUS are quick, non-invasive methods with great patient acceptance, excellent reproducibility, and prompt results for assessing the natural presence of fibrosis and inflammation in the kidney.

6.5. CONCLUSIONS

Our results show that these upgraded elastography techniques can differentiate among people with various stages of renal fibrosis, correlate with renal function and inflammation, are simple to use, repeatable, and have a high patient approval rate.

FINAL CONCLUSIONS

Although there are some advantages to using elastography in the evaluation of the kidneys, such as the fact that the image is obtained in real-time without the need for special preparation of the subjects and without procedure complications, using elastography in the evaluation of the kidneys is more challenging than in other organs.

Our findings indicate that these novel elastography methods can distinguish between individuals with different stages of renal fibrosis, correlate with renal function and inflammation (in chronic glomerular patients), and are easy to use and reproducible.

Together with previously published research, the current thesis demonstrates that it is possible to accurately identify stiffness and viscosity changes in connection to eGFR in healthy participants, kidney-transplanted patients, and also in patients with chronic glomerulonephritis. Therefore, screening for renal stiffness and viscosity may become a cost-effective and efficient method for collecting additional diagnostic information from CKD patients. Even though the results reveal that these noninvasive approaches were heterogenous up until now, with this new improved renal software they can become extremely practicable and useful and their values can guide nephrologists for a better understanding and follow-up of CKD patients, but more research is needed for them to be routinely employed into clinical practice.