UNIVERSITI PUTRA MALAYSIA

COMPARISON OF RENAL STIFFNESS BETWEEN DIABETIC PATIENTS AND HEALTHY CONTROLS USING SHEAR WAVE ELASTOGRAPHY

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By

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Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Master of Science

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COMPARISON OF RENAL STIFFNESS BETWEEN DIABETIC PATIENTS AND HEALTHY CONTROLS USING SHEAR WAVE ELASTOGRAPHY

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June 2022

Chairman : Suzana Ab Hamid
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Type Ⅱ diabetes Mellitus（T2DM）is a relatively common chronic disease. The most common complication of T2DM is diabetic kidney disease (DKD). This complication has a high mortality rate, and patients have a poor prognosis and health status. Therefore, diagnosis and treatment at an early stage of DKD are particularly important. The most common clinical screening methods for kidney disease are computed tomography (CT), ultrasound (US), magnetic resonance imaging (MRI), and biochemical studies. However, these methods are not specific for early detection of DKD disease. According to diabetes guidelines, the gold standard for chronic kidney disease (CKD) is tissue biopsy. This is an invasive and expensive test that is rarely used in clinical practice. The prognosis and survival of patients with DKD have become a public health issue. Early detection of the onset of DKD and timely treatment can help patients improve their prognosis and quality of life.

The Second Affiliated Hospital of XinXiang Medical University was used to recruit 62 volunteers for this study. Based on their glucose metabolism, they were divided into 3 groups: Normal Glucose Metabolism (NGM), Pre-Diabetes Mellitus (Pre- DM) and T2DM. Each patient's medical history, baseline demographic data, laboratory data, and ultrasound data were systematically recorded. Renal cortical stiffness (CS) values were measured by shear wave elastography (SWE) technique of conventional 2D ultrasound. The three sets of data obtained in the experiment were compared to clarify differences between and within groups. Possible early signs of DKD were detected and identified by examining the functional curve characteristics of the participants.

With the exception of heart rate and blood pressure, all demographic data were identical in the three groups. When laboratory data were analyzed, all laboratory values differed between the groups, with the exception of uric acid. Blood glucose, lipid, and blood urea nitrogen levels were significantly higher in T2DM than in the other groups. Pre- DM and T2DM had higher LDL, creatinine, and microalbumin than NGM. In US examinations, all ultrasound parameters were the same in Pre- DM and T2DM.

Kidney length, kidney width, and cortical stiffness were higher in pre- DM and T2DM than in the NGM group. The CS value of patients with abnormal glucose metabolism was higher than that of NGM. Renal length and cortical thickness were independently correlated with renal stiffness ($r = 0.335$ and $r = 0.411$, respectively). Kidney thickness was an independent determinant of CS level. In the ROC analysis, with a renal CS level of 8.5 Kpa, the specificity and sensitivity of CS for predicting the occurrence of nephropathy were 66.7% and 66.9%, respectively.

The CS values of subjects with impaired glucose metabolism were significantly higher in this study based on their glucose metabolism. The performance of the SWE as a non-invasive tool for diagnosing DKD is better than traditional examination, and it is expected to detect and diagnose DKD early. CS Values assessed by SWE should be used as a standard test for screening early nephropathy in Pre-DM and newly diagnosed T2DM. According to the results, it should be widely used in medical care.

Key words: cortical stiffness，Pre-diabetic，Shear-wave Elastography，kidney disease， mellitus

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Master Sains

PERBANDINGAN KEKAKUAN BUAH PINGGANG ANTARA PESAKIT DIABETES DAN KAWALAN SIHAT DENGAN MENGGUNAKAN ELASTOGRAFI GELOMBANG RICIH

Oleh

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Diabetes jenis II Mellitus（T2DM）adalah penyakit kronik yang agak kerap dikenalpasti. Komplikasi T2DM yang paling biasa ialah penyakit buah pinggang diabetik (DKD). Komplikasi ini mempunyai kadar kematian yang tinggi dan pesakit mempunyai prognosis dan status kesihatan yang buruk. Oleh itu, diagnosis dan terapi pada peringkat awal DKD amat penting. Kaedah saringan klinikal yang lebih biasa untuk penyakit buah pinggang ialah tomografi berkomputer (CT), ultrasound (AS), pengimejan resonans magnetik (MRI) dan penilaian biokimia. Teknik tersebut, bagaimanapun, tidak khusus untuk pengesanan awal penyakit DKD. Menurut garis panduan diabetes, standard emas untuk penyakit buah pinggang kronik (CKD) adalah biopsi tisu. Ia adalah ujian invasif dan mahal yang jarang digunakan dalam amalan klinikal. Prognosis dan kualiti kehidupan pesakit DKD telah menjadi isu kesihatan awam. Pengenalpastian awal permulaan DKD dan rawatan tepat pada masanya boleh membantu pesakit meningkatkan prognosis dan kualiti kehidupan mereka.

Hospital Gabungan Kedua Universiti Perubatan XinXiang telah digunakan untuk mengambil 62 sukarelawan untuk kajian ini. Berdasarkan metabolisma glukosa mereka, mereka dibahagikan kepada 3 kumpulan, metabolisma glukosa normal (NGM), Pra-Diabetes Mellitus (Pra-DM), dan T2DM. Sejarah perubatan, data demografi asas, data makmal, dan data ultrasound setiap pesakit dikumpulkan secara sistematik. Nilai kekakuan kortikal buah pinggang (CS) diukur menggunakan teknik elastografi gelombang ricih (SWE) ultrasound 2D konvensional. Tiga set data yang diperolehi dalam eksperimen telah dibandingkan untuk menjelaskan perbezaan antara dan dalam kumpulan. Petunjuk awal yang berpotensi DKD telah diwujudkan dan dikenal pasti dengan meneliti ciri-ciri keluk fungsian peserta.

Kecuali kadar jantung dan tekanan darah, semua demografi dalam tiga kumpulan adalah sama. Dalam analisis data makmal, semua nilai makmal berbeza antara kumpulan kecuali asid urik. glukosa darah, lipid, dan paras nitrogen urea darah adalah lebih tinggi dalam T2DM berbanding kumpulan lain. Pra-DM dan T2DM mempunyai lebih banyak LDL, kreatinin, dan mikroalbumin daripada NGM. Semua parameter ultrasound adalah sama dalam Pra-DM dan T2DM dalam peperiksaan AS.

Panjang buah pinggang, lebar buah pinggang, dan kekakuan kortikal pra-DM dan T2DM adalah lebih tinggi daripada kumpulan NGM. Nilai CS pesakit dengan metabolisme glukosa yang tidak normal adalah lebih tinggi daripada NGM. Panjang buah pinggang dan ketebalan kortikal dikaitkan secara bebas dengan kekakuan buah pinggang ($r = 0.335$, $r = 0.411$, masing-masing). Ketebalan buah pinggang adalah penentu bebas tahap CS. Dalam analisis ROC, dengan tahap CS buah pinggang 8.5 kpa, kekhususan dan kepekaan CS untuk meramalkan kejadian nefropati adalah 66.7% dan 66.9%, masing-masing.

Nilai CS bagi individu yang mengalami metabolisme glukosa terjejas dalam kajian ini adalah lebih tinggi berdasarkan metabolisme glukosa mereka. Prestasinya sebagai alat bukan invasif untuk mendiagnosis DKD adalah lebih baik daripada pemeriksaan tradisional, dan ia dijangka dapat mengesan dan mendiagnosis DKD lebih awal. Nilai CS yang dinilai oleh SWE harus digunakan sebagai ujian standard untuk pemeriksaan nefropati awal dalam Pra-DM dan T2DM yang baru didiagnosis. Menurut penemuan, ia harus kerap digunakan dalam penjagaan perubatan.

Kata kunci: kekakuan kortikal，Pra-diabetes，Elastografi gelombang ricih，penyakit buah pinggang， mellitus

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At that time, the outdoor area was full of flowers. People are also looking for a new balance in COVID -19 and in their lives. In these extraordinary two years, I have gained a lot, but I have also learned a lot. To survive in adversity and to be grateful in happiness. The future learning path is still long. I should encourage myself to persevere and adapt to my effort so that I will have no regrets!
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This thesis was submitted to the Senate of the Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Master of Science. The members of the Supervisory Committee were as follows:

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Declaration by Members of Supervisory Committee

This is to confirm that:

- the research conducted and the writing of this thesis was under our supervision;
- supervision responsibilities as stated in the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2012-2013) are adhered to.

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LIST OF ABBREVIATIONS

NGM	Normal glucose metabolism
T2DM	TypeⅡdiabetes mellitus
CKD	Chronic kidney disease
DKD	Diabetic kidney disease
GFR	Glomerular filtration rate
CRF	Chronic renal failure
CEUS	Contrast-enhanced ultrasound examination
RIF	Renal interstitial fibrosis
GS	Glomerulo sclerosis
CIF	Cost, Insurance and Freight
DM	Diabetes mellitus
CT	Computed tomography
MRI	Magnetic resonance imaging
EGFR	Estimated glomerular filtration rate
GBM	Glomerular basement membrane
SCR	Serum creatinine rate
SWE	Shear wave elastography
SWV	Shear wave velocity
TE	Transient elastography
PSWE	Point shear wave elastography
ROI	Region of interest
MSWE	Multidimensional shear wave elastography imaging
YM	Young's modulus

DK	Diabetic kidney
US	Ultrasound scanning
E	Elastic modulus
ARFI	Acoustic radiation force impulse
DMA	Dynamic mechanical analysis
BMI	Body mass index
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
NGM	Normal glucose metabolism
Pre-DM	Pre-diabetic patients
DM	Type 2 diabetes
OGTT	Oral glucose tolerance test
PSV	Peak systolic velocity
EDV	End diastolic velocity
EDTA	Ethylene diamine tetraacetic acid
FBG	Fasting blood glucose
FPG	Fasting plasma glucose
AT	Acceleration time
RPI	Renal pulse index
ANOVA	Analysis of variance
AUC	Area under the curve
CI	Confidence intervals
CS	Cortical stiffness
CT	Cortical thickness

ICC	Intra-class correlation coefficient
LDL	Low-density lipoprotein
HDL	High-density lipoprotein
BUN	Blood urea nitrogen

LIST OF SYMBOLS

cm	centimeter
kg	kilogram
mg/kg	milligram per kilogram
MHz	meter hertz
mins	minutes
mm	millimeter
n	sample size
P	level of significance
r	correlation coefficient
r^2	coefficient of determination
SD	standard deviation

CHAPTER 1

INTRODUCTION

This chapter introduces the basic aspects of this study. It discusses the background of the research and the problem statement. Furthermore, the aim and problem for this study are clarified，and the significance of the study is indicated.

1.1 Background of the Study

The chronic kidney disease (CKD) is a global disease. The main characteristics of this disease are high incidence, long course, poor prognosis, and low cure rate. Diabetic kidney disease (DKD) is a very significant challenge to the health of a country and society. Data suggest that, so far, about 8-16% of the world's population has been affected by chronic kidney disease (Koresh J et al., 2005). And disease development of end-stage chronic kidney disease (CKD), the result is almost always accompanied by cardio vascular disease (CVD), and patients have increased risk of death. According to the current global medical standard, there are no better medical methods to slow down and suppress the progression of CKD than renal dialysis and kidney transplantation (Lozano R et al, 2005). Some research data suggest that the global prevalence of CKD reaches 11% to 13% (American Diabetes Association, 2015). In developed countries, the prevalence of chronic kidney disease (CKD) is also increasing. The number of deaths due to CKD has doubled in the last 20 years (Cores J et al., 2017). According to the International Organization of Nephrology, chronic kidney disease (CKD) is defined as chronic structural and functional damage to the kidneys caused by various causes with a disease duration greater than 3 months. The main pathological findings are impairment of glomerular filtration rate (GFR) and urine composition or abnormal blood indexes. And the abnormal morphology is also evident in the imaging examination. Clinically unexplained GFR decline (GFR < 60ml /min) and the clinical course of disease was more than 3 months. (American Diabetes Association, 2018). Many of the presentations of chronic kidney disease (CKD) are more insidious. Most kidney damage is not evident in the early clinical stage. However, as the disease progresses, clinical manifestations gradually become apparent, such as proteinuria, hematuria, edema, elevated creatinine, and hypertension (American Diabetes Association, 2015). In the study of CKD, many causes of pathogenesis have been suggested, including primary and secondary glomerulonephritis, diabetic nephropathy, hypertension, atherosclerosis, renal tubular disease, renal vascular disease, hereditary nephropathy, and renal transplantation. And they can led to chronic renal failure (CRF). Studies have shown that many risk factors, both physical and chemical, increase the incidence. Including hypertension, hyperlipidemia, hyperglycemia, smoking, acute kidney injury, nephrotoxic drugs, and so on（Grenier，N et al., 2012). These risk factors can increase or

contribute to the progression. As CKD progresses, especially in the uremic stage, serious complications such as severe anemia, cardiovascular abnormalities, electrolyte disturbances, and central nervous system disorders will occur. Therefore, a major challenge in improving the prognosis of CKD patients is the inability to identify CKD patients at an early subclinical stage. Many cases of CKD go undetected in time for clinical diagnosis and treatment. With the increase in related research in recent years, the underlying pathophysiological mechanisms involved in the disease process of CKD have gradually become clear. The main pathological change of CKD is the fibrotic changes in the renal parenchyma, which leads to the gradual irreversible changes in renal function (Vistisen, D et al., 2018). Renal fibrosis is a manifestation of pathological changes in renal tissue. Its pathological changes are chronic deposition of extracellular matrix in the glomeruli and tubulointerstitium (tubulointerstitial fibrosis). In different stages of renal disease, renal interstitial fibrosis (RIF) and glomerulosclerosis (GS) have different adaptations to the renal parenchyma and changes in the elasticity of renal tissue (Jha V et al. 2013). At present, effective clinical treatment mainly depends on the early detection of this disease. Therefore, timely detection of changes in renal parenchymal stiffness and accurate assessment are necessary.

Type II diabetes Mellitus (T2DM) is a chronic metabolic disease，which is caused by defective or impaired insulin secretion（Maralescu, F.at，al., 2022). Long-term persistent hyperglycemia and metabolic disorders can cause damage to multiple systems, such as eye, kidney, cardiovascular, and neurological function (American Diabetes Association, 2018) (Kidney Disease Improving Global Outcomes-KDIGO, 2012, 2013). Among the known risk factors for CKD globally, T2DM is considered to be the cause of 40% of new cases in the United States (Jha V et al. 2013). In other developed countries, kidney disease associated with T2DM accounts for 50% of patients with end-stage renal disease (Vistisen, D et al. 2018). The kidneys are one of the more severely affected organs in type 2 diabetes. The main reasons for this lie in two aspects. First, the kidneys rely primarily on hemodynamics. Second, it is the main metabolic pathway in the human body. More data suggest that T2DM is the leading cause of end-stage renal disease in most countries. Renal involvement also directly or indirectly increases involvement of other organs. At the same time, it also increases the mortality and morbidity of diabetic patients. Studies have shown that even with optimal treatment of first-episode diabetes, a large proportion of patients develop diabetic nephropathy (DKD) (Melsom T, Fuskevag OM, Mathisen UD, et al., 2013).

CKD caused by diabetes is clinically called DKD. (American Diabetes Association 2015). A large number of sociological data show that diabetes is the main cause of CKD and end-stage renal disease. (Koresh J, Selvin E, Stevens La et al. 2017). Some studies suggest that 20% - 40% of people with diabetes have DKD (Vistisen et al, 2018). In China, the prevalence of T2DM has always been high due to the large population base, dietary habits and factors such as geography, environment, and climate. Therefore, the prevalence of DKD has

been increasing year by year (Lee, H.Y., et al, 2017). According to research, in 2019, the prevalence of DKD in Chinese T2DM patients was as high as 10% - 40% (Guo et al., 2019).

The research and evaluation of kidney disease are mainly based on several common clinical examination methods. Such as magnetic resonance imaging (MRI), ordinary two-dimensional ultrasound, computed tomography (CT), biochemical analysis, etc. Monitoring the progress of DKD relies mainly on biochemical tests. Such as the amount of urine protein and serum creatinine level. However, serum tests such as serum creatinine are slightly less sensitive. Kidney biopsy is a commonly used and effective method for identifying kidney disease. It is widely used in the diagnosis of renal fibrosis and is also the gold standard for renal disease. A kidney biopsy is an invasive test. During the procedure, the patient is at risk of bleeding. This test has certain limitations. Although accurate, it is expensive and requires a skilled clinician to reduce the risk of some complications. Among imaging techniques, magnetic resonance imaging (MRI) is one of the common diagnostic methods used in clinical practice to evaluate chronic renal parenchymal disease (ET al, 2010). However, it is contraindicated in patients who are claustrophobic or have pacemakers. MRI testing is also more expensive. In addition, if contrast-enhanced MRI is required, this procedure may also increase the risk of renal fibrosis in patients with advanced DKD. Computed tomography (CT) is also a method of diagnostic kidney imaging. It is characterized by convenience and effectiveness. However, exposure of patients to ionizing radiation poses a radiation risk. The population of CT examination also has certain limitations, and it is not suitable for children and pregnant women. Traditional ultrasonography mainly relies on grayscale imaging to visualize the morphological features of organs. It can assess kidney size, cortical thickness, and echogenicity. Spectral Doppler ultrasonography of the renal arteries allows assessment of renal hemodynamics in relation to changes in renal parenchyma and renal function (Hallan SI, Dahl K, Oien CM et al., 2016). Shear wave elastography (SWE) is one of the sub-ultrasound examination methods developed in recent years. It mainly includes elastic strain imaging and shear wave elastography. It also belongs to an imaging technology. It has the advantage of being able to assess the biomechanical properties of tissue in relation to histopathological changes. such as interstitial fibrosis. In recent years, many studies have found that there is a correlation between renal cortical lesions and renal function (Chen QK, he f, Feng XR, et al., 2014).

1.2 Problem Statement

DKD is characterized by a sustained increase in urinary albumin excretion. This manifestation is mainly in the first stage. The second stage is characterized by a decrease in estimated glomerular filtration rate (EGFR) and a decrease in kidney volume as renal fibrosis increases (Gross et al., 2018). Under normal conditions, protein is rarely found in the urine of healthy individuals due to glomerular filtration and tubular reabsorption. When various pathological injuries occur, such as primary and secondary injuries acting on the kidney, this leads to

local microcirculatory disorders in the injured kidney. Kidney tissues become ischemic and hypoxic, further damaging the glomerular capillary endothelial cells. Inflammatory cells will infiltrate in the blood circulation and release some pathogenic inflammatory mediators (e.g. IL-1, TNF-a). At the same time, a series of changes occur in the glomerular basement membrane (GBM) (Samir et al, 2015). Proteinuria, as one of the typical symptoms of CKD, was considered as a response to glomerular injury only (Samir et al., 2015). However, recent studies have shown that glomerular filtration protein can cause tubular epithelial cell injury, which is closely associated with the development and progression of tubular interstitial fibrosis (Samir et al., 2015). The production of proteinuria accelerates the progression of renal disease to end-stage renal failure, which is supported by a growing number of experimental and clinical studies (Guo, H. Y.,et al., 2021).

Proteinuria is both an independent factor contributing to the progression of kidney disease and as an aid to clinicians in determining the prognosis of the disease. Glomerular filtration rate (GFR), is an important indicator to evaluate renal function. It is also a key indicator of clinical staging and diagnostic prognosis. Chronic kidney disease (CKD) is mainly classified into 5 stages according to the guidelines set by the American Kidney Foundation. Stage 1: GFR > 90 ml/min and normal glomerular filtration rate (GFR), but should focus on treating the primary disease to slow the progression of kidney disease and reduce the risk of cardiovascular disease. Stage 2: GFR of 60 to 89 ml/min and mildly decreased glomerular filtration rate, when the progression of renal disease is expected and intervention should be administered. Stage III: GFR of 30 to 59 ml/min, a moderate decrease in glomerular filtration rate, possible corresponding clinical symptoms, and complications requiring active treatment. Stage IV: GFR of 15 to 29 ml/min, severe decrease in glomerular filtration rate, preparation for renal replacement therapy (Koc, Ayse Selcan, 2019). Stage V: known as the chronic renal failure stage with GFR < 15 ml/min. This stage should be treated clinically with renal replacement therapy (Levey as, Atkins R, cores J, et al, 2007). Although renal transplantation therapy prolongs the life of many patients, it remains a heavy financial burden for families and society due to its complications and substantial medical costs. Serum creatinine rate (SCR) is the most applied laboratory index for clinical evaluation of GFR. It has a certain sensitivity and accuracy.

The molecular weight of blood creatinine is very small. It is not bound to proteins in the blood. It can be filtered through the glomerulus and very rarely can be reabsorbed in the renal tubules（Stegall，M.D., et al，2011）. Almost all creatinine in the body is excreted in the urine and is less affected by the volume of urine. levels, but because the decrease in glomerular filtration rate (GFR) and serum creatinine rate (SCR) is a nonlinear relationship, and because the kidney is highly compensatory, some loss of function due to a glomerular injury can be compensated by other units（Tang，A.,et al，2015). Therefore, the serum creatinine rate (SCR) increases only when the degree of renal injury is >50%. It has been shown that biochemical tests are not very sensitive for early mild renal

injury (Whitman IR, Feldman Hi, Deo R, 2012). Based on pathological studies, a progressive decline in renal function is associated with interstitial fibrosis and tubular atrophy (if/TA) Wansapuea，J.P.,et al., 2010). CKD is a process in which the normal kidney is heavily replaced by fibroblasts and myofibroblasts, which in turn leads to glomerulosclerosis and tubular interstitial fibrosis, resulting in the production of renal fibrosis (Jayasumana C, Gunnislake s, Siribaddana s, 2015). Thus, the pathological changes of renal fibrosis are a gradual process from mild to severe.

The main clinical applications of renal ultrasound include the elimination of urinary obstruction and the identification of irreversible chronic kidney disease (CKD). It is non-invasive, non-ionizing radiation and widely available. Renal ultrasound can monitor the changes of renal morphology and renal echo. Ultrasound elastography can provide elastic information of tissue, which is a basic mechanical property. It can indirectly reflect the pathophysiology of the tissue. SWE technology is the latest elastography technology, which continuously focuses tissue at different depths at ultra-high speed, producing the "Mach cone" phenomenon (Figure 1.1). Since renal parenchymal fibrosis is the most important sign of renal disease, it can cause changes in renal mechanical properties. SWE can objectively measure the changes of renal mechanical properties. However, renal SWE results are not commonly used in routine USG testing because CS values are primarily for quantitative assessment of specific diseases and studies. Renal SWE evaluation has been shown to be useful in determining renal fibrosis, diagnosing allograft rejection, staging of diabetic nephropathy, and patients with chronic kidney disease (CKD). In recent years, non-invasive imaging techniques, for organ function and structure, have been increasingly investigated with the aim of minimizing invasive methods in the diagnostic and screening setting.

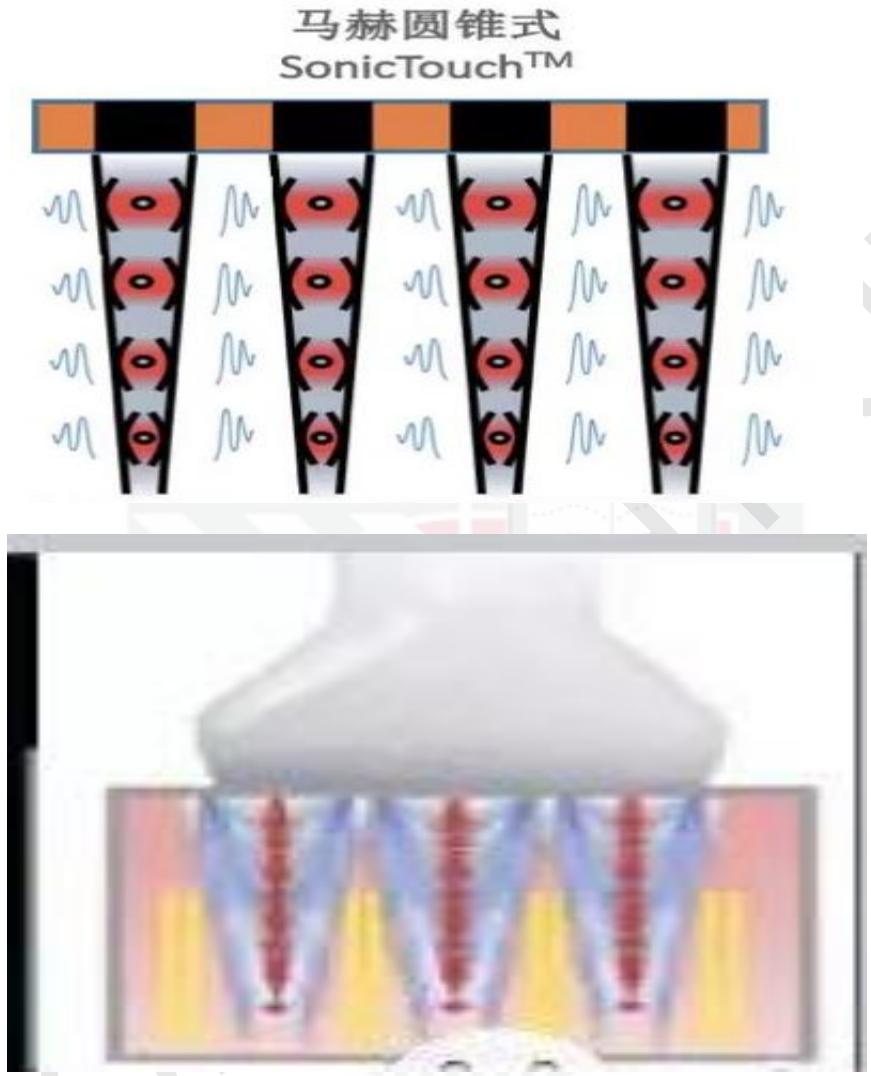

Figure 1.1 : The "Mach Cone" Phenomenon

Renal disease caused by diabetes accounts for nearly 50% of end-stage renal disease in developed countries (Jha V et al., 2013). Once diabetes is diagnosed and given the best treatment, a significant proportion of patients will also develop chronic kidney disease (CKD). Several studies have reported that up to 1/3 of newly diagnosed diabetic patients develop kidney damage (Serón D, 2007). This suggests that the development of CKD may already exist in the early stages of the disease. the natural history of T2DM is characterized by a long history of mildly elevated blood glucose and abnormal glucose metabolism. This metabolic instability increases cardiovascular risk and major vascular complications (Vistisen et al, 2018). Several studies have shown that the prevalence of pre-

diabetes is 14%. the risk of developing pre-diabetes in volunteers over 45 years of age is 48.7%. The risk of Pre-diabetes and then developing diabetes is 74% (Lithrat et al, 2016). There has been a large body of research literature demonstrating the correlation between diabetes and DKD. However, little literature has reported the association between DKD and pre-diabetes (De Nicola et al. 2016). The long-term effects of pre-diabetes, which is associated with the kidney, are not known. Therefore, considering the high prevalence of pre-diabetes in the population and the favorable impact on DKD interventions. Whether pre-diabetes has a certain effect on the kidneys remains to be explored. If diabetes has already occurred before screening for CKD is performed. Then, many patients may miss the window of opportunity for early treatment. Therefore, individual screening and early CKD intervention in the early stages of diabetes (pre-diabetes) will reduce the damage to renal function. In the early stages of the disease, when kidney damage is still reversible, creating good opportunities for patients is beneficial to both patients and society.

Currently, the clinical diagnosis of DKD consists of (1) Laboratory tests such as urine and serology. It includes urine protein, blood creatinine level, cystatin C, urine red blood cells, urine white blood cells, etc. However, in the early stages of chronic kidney disease (CKD), the sensitivity and specificity of these laboratory indicators are not high. This is because there may be some factors that have an impact on the laboratory data. (2) Routine ultrasonography. This test is simple to perform, accurate and reproducible in real-time. It has gradually become the preferred clinical examination modality for CKD. Conventional two-dimensional ultrasound can measure the long diameter of the kidney and the parenchymal thickness of the kidney. It can also observe the echogenic and morphological changes of the kidney. Color Doppler ultrasound can provide detection in terms of blood flow direction, flow velocity, and blood resistance. Changes in kidney length and parenchymal thickness are the main features of CKD. Also, an increase in the interrenal artery resistance index can suggest abnormal changes in the kidney, and this finding is consistent with changes in renal parenchymal echo and blood flow (Zhang,Q, & Rothenbacher.,2008） However, these abnormal manifestations of CKD are usually evident in the middle and late stages of the disease. Therefore, its sensitivity for early diagnosis is not high. For CKD, renal tissue biopsy is its gold standard. In clinic, it is helpful to clarify pathological classification, but this kind of examination is risky. During the invasive sampling process, it may lead to some complications. Such as hematoma, macrohematuria, static and dynamic pulses, and infection (Zaffanello M, Piacentini G, Bruno C, et al, 2015). Therefore, it has become particularly important to find a non-invasive and reproducible examination technique.

Shear wave elastography (SWE) is a new ultrasound technique that has been developed relatively quickly in recent years. It is based on the principle of generating a wave in a relatively short period of time. It is perpendicular to the direction of wave propagation and is called a transverse wave. When propagating to the target tissue, the tissue is pushed in the direction of

propagation, at which point the tissue undergoes temporary deformation and displacement (Tang, A.,et al., 2015). This wave generates a velocity that becomes the shear wave velocity (SWV). It is approximately 1-10 M/s in soft tissues. It allows the shear modulus to vary considerably between tissues and is suitable for the measurement of different tissue contrasts (Zaffanello et al, 2021). Currently, three main types of shear wave techniques are included. Transient elastography (TE), single point shear wave elastography (PSWE), and multidimensional shear wave E imaging (2D-SWE, 3D-SWE) (Marticorena Garcia et al. 2017). Transient elastography (TE) entered clinical use earlier because it does not use ultrasound probes as traditionally conceptualized and therefore cannot observe the anatomical structure of grayscale tissues. It lacks the guidance of 2D images during data measurement. Single point shear wave elastography (PSWE) is based on the principle of applying an acoustic radiation force within a certain depth of the tissue, resulting in a shear wave (Sporea，I.,et al., 2013). It forms an asymmetric cylinder along the axis of the focused thrust pulse and propagates outward. The shear wave is strongest at the depth level of focus. Although it does not produce an elastic map, ultrasound image guidance can be used to place the region of interest (ROI), relatively avoiding blind measurements（Sigrist，R.M.S.,et al., 2017). With the development of technology, multidimensional shear wave elastography imaging (MSWE) has been extended based on PSWE. It focuses on the continuous excitation of acoustic radiation force from multiple points within a large region of interest. Then, the arrival time of each focal excitation shear wave is detected. Within this region, a shear wave image is formed. It also detects the arrival time of shear waves at multiple points within the entire region of interest (Sporea，I.,et al., 2013). A real-time 2D shear wave tissue stiffness map is generated. Such images, in the form of red and blue color coding, are displayed overlaid or side-by-side with gray-scale images (Tang et al, 2015; Zaffanello et al, 2015; Samir et al, 2015; Sarvazyan et al, 1998; Goya et al. 2015). The magnitude of shear wave elasticity is expressed as Young's modulus (YM) in Pa or kPa. SWE has been widely used in clinical practice for the diagnosis of liver diseases, such as liver fibrosis screening. It has high sensitivity and specificity. With the continuous improvement of technology, shear wave elastography (SWE) has been increasingly used in other fields, such as thyroid, breast, musculoskeletal, and prostate. For the kidneys, studies have focused on the quantitative assessment of morphological changes and the graded diagnosis of CKD. Fewer studies have applied the SWE technique approach to populations with pre-diabetes and diabetes. In clinical practice, there are also no systematic studies conducted to evaluate the effectiveness of SWE as a routine screening method. When pre-diabetes is present and tissue fibrosis has occurred, it is worthwhile to explore studies to determine and monitor changes in kidney stiffness by a non-invasive and effective means.

The main objective of this study was to predict changes in tissue stiffness (fibrosis) by obtaining YM measurements for T2DM and YM measurements for NGM (shear wave elasticity values). SWE technology can predict the occurrence or development of DKD by observing the change of elasticity value. At the same time, this study evaluates the feasibility of SWE as a routine ultrasound

screening tool in regular follow-up of high-risk populations. This is the main content of this research.

1.3 Objectives

1.3.1 General objective

To evaluate the feasibility of SWE as a screening method for early diabetic kidney disease (DKD).

1.3.2 Specific Objectives

1) To compare the demographic characteristics by NGM、Pre-DM and T2DM.
2) To compare the laboratory indicators by NGM、Pre-DM and T2DM.
3) To compare the imaging indicators (renal thickness, kidney length, kidney width, Cortical stiffness Emean) by NGM、Pre-DM and T2DM.
4) To compare the differences in ultrasound indexes between the two sonographers.
5) To correlate renal stiffness with demographic characteristics, laboratory indicators, and ultrasound indicators.
6) To compare the NGM and Pre - DM stiffness value of renal, determine the cut-off value of early kidney disease.

1.4 Hypothesis

Differences in renal stiffness between diabetic patients and healthy controls

1.5 Significance of the Study

Shear wave elastography is a noninvasive, cost-effective, and safe imaging modality. SWE can be used diagnostically in routine examinations and disease screening in Pre- DM, and T2DM. In the early stages of diabetes, when fibrosis has already occurred, changes in renal stiffness can be visually measured and accurately recorded using a noninvasive technique. Therefore, this technique can be used as a tool for routine and periodic monitoring to detect the early onset of chronic kidney disease in diabetes based on changes in shear wave velocity.

In addition, it is widely used as a screening method to prevent the onset or progression of DKD in both the general population and high-risk groups. This one technical tool could also become a method of assessment for many healthcare professionals involved in the treatment of patients.

1.6 Thesis Organization

There are five chapters in this thesis. The first chapter discusses the research's sociological and medical background, and the study's purpose and problems. At the same time, this chapter also expounds the scope and significance of the research. In chapter 2, the relationship between SWE and CKD was reviewed from the aspects of imaging, pathology and physiology. The classification of kidney diseases and their respective characteristics are elaborated in detail. The principles and scope of adaptation of shear wave techniques are also presented. This chapter summarizes the analysis of their correlation by previous authors and discusses the aspects and contents of future studies. Chapter 3 focuses on the experimental content and statistical methods of this study. The population included in the experiment, the technical approach, contraindications, and how to obtain the experimental data. A detailed description of the experimental data statistical methods is also presented. Chapter 4 categorizes and analyzes the results of the experimental data. Each statistical method is discussed, and supporting images and tables are given. This chapter also discusses the commonalities and differences between this study and previous case studies. Finally, Chapter 5 gives the conclusions of the overall study. And some suggestions and directions for future research are given.

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