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RESEARCH

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Diagnostic utility of renal shear wave elastography and renal Doppler findings in diabetic nephropathy: a case–control study

Ahmed Abdelrahman Baz[1*], Eman Muhammad Abdeen[2], Mona Yousry Helmy[3] and Abo El-Magd Al-Bohy[1]

Abstract

Background Diabetes mellitus is a common systemic disease that affects the kidneys and could eventually develop an end-stage renal failure. Renal biopsy is considered a gold standard for histological characterization of diabetic nephropathy, of which renal fibrosis is a dominant component, affecting its stiffness. The objective of this study is to investigate a correlation between renal stiffness obtained by shear wave elastography, renal Doppler resistivity indices, laboratory findings, and the histological characterization depicted by renal biopsies (if feasible) in diabetic nephropathy patients and to compare their results with those obtained from normal population to explore the diagnostic efficacy of shear wave elastography. Shear wave elastography and color duplex US were performed in twenty-six diabetic nephropathy patients and twenty-six healthy (age and sex-matched) control subjects. The shear wave elastography-derived mean value of the renal tissue stiffness was measured (in kilopascals) as well as the resistivity indices of segmental renal arteries, and then the mean values were correlated to patients' clinical-laboratory data (serum creatinine and albumin/ creatinine ratio) and the biopsy results, if feasible.

Results A significant positive correlation was found between the mean resistivity indices and the mean renal cortical stiffness at one hand and the patients' clinical-laboratory data with statistically significant differences found between the control, early, and late stages of diabetic nephropathy.

Conclusions Shear wave elastography is a promising, non-invasive, and accurate diagnostic tool for assessment and differentiation between early and late stages of diabetic nephropathy with a significant positive correlation to the clinical-laboratory and renal Doppler findings.

Keywords Diabetic nephropathy, Resistivity indices, Kidney, Shear wave elastography, Stiffness

Background

Diabetes mellitus (DM) is considered one of the most common systemic diseases that affects multiple organs including the kidneys. It exhibits a rising incidence among general populations and is expected to affect more people in the coming future and is anticipated to influence more than 350 million people by the year 2035. At the moment, 15.6% of Egyptian people between the ages of 20 and 79 have type 2 diabetes [1].

Diabetic nephropathy (DN) is one of the most common serious microvascular complications of diabetes mellitus. DN occurs in about 20–40% of all diabetics who eventually develop end-stage renal failure, then dialysis and its complications as well as renal transplantation and its hazards. So, diagnosis of DN is of paramount importance for diabetic patients not only because of the consequences of renal disease progression but also because of the strong association with developing cardiovascular diseases [2].

*Correspondence:
Ahmed Abdelrahman Baz
ahmedbaz2012@yahoo.com
[1] Radiology Department, Faculty of Medicine, Cairo University, Giza, Egypt
[2] Faculty of Medicine, Cairo University, Giza, Egypt
[3] Internal Medicine Department, Faculty of Medicine, Cairo University, Giza, Egypt

From a clinical-laboratory aspect, DN is characterized by a progressive increase in proteinuria, a decline in glomerular filtration rate (GFR), elevated blood pressure, and a high risk of renal failure (RF). In addition, advanced DN is morphologically and histopathologically characterized by renal tissue changes that include variable degrees of parenchymal fibrosis that is reflected on the renal microcirculation [3].

The renal resistivity indices (RI) are Doppler indices of intrarenal arteries defined as peak systolic velocity (PSV)—end-diastolic velocity (EDV)/peak systolic velocity. The estimated normal range is 0.50–0.70. Elevated RI values are associated with poor prognostic outcomes in various native renal disorders and renal transplants as well. RI is measured using spectral Doppler within the intrarenal arteries, and it exhibits a value in identifying diabetic patients who are developing nephropathy and thus could be used as an additional diagnostic tool. Besides, it is well correlated with serum creatinine and albuminuria which are biochemical parameters for DN diagnosis [2].

The renal biopsy is the gold standard for the assessment of the pathological alterations of the renal parenchyma such as interstitial fibrosis and glomerular-sclerosis. However, there are concerns regarding its potential complications including bleeding and renal arterio-venous fistula [4].

Ultrasound shear wave elastography (SWE) is an ideal modality for evaluating the alterations in various organs and diagnosing malignant tumors, hence, SWE imaging may be applied as a simple non-invasive tool for judging the severity of chronic morphologic changes of renal parenchyma and for establishing categories of severity based on cortical stiffness measurements, at least in cases in which renal biopsy is contraindicated [5].

The present study aims to investigate a correlation between renal stiffness obtained by SWE, renal RI obtained by color duplex, laboratory findings, and the histological characterization depicted by renal biopsies (if feasible) in DN patients and to compare their results with those obtained from normal population to explore the diagnostic efficacy of SWE.

Methods

Subjects

The study was designed as a prospective case–control study including twenty-six diabetic patients and twenty-six control subjects who had clinical and laboratory-proven DN findings, the patients were referred to the ultrasound unit at the radiology department of our institute either from outpatient clinics or inpatient departments in the period from February 2022 to August 2022 where our study was conducted. The patients' ages were ranging from 25 to 70 years.

- *Inclusion criteria* patients with type I and type II DM and patients with DN diagnosed by the persistently high urinary albumin to creatinine ratio (A/C) ratio > 30 mg/g which ranges from microalbuminuria (A/C ratio 30–300 mg/g) to macroalbuminuria (A/C ratio greater than 300 mg/g) and/or prolonged decrease in eGFR < 60 ml/min per 1.7 m^2 were included in the study.
- *Exclusion criteria* patients with morbid obesity (patients BMI > 40), respiratory problems, renal failure, renal artery stenosis, or any renal disease other than DN were excluded.

This prospective study was performed following the ethical guidelines of the Research Ethics Committee of our institute. The reference number: Code Ms-59-2022, Date of approval; 17-7-2022 and it was approved by the local Research Ethics Committee of our institute. All of the participants were informed of the details and gave their informed consent.

All of our patients were subjected to:

1. Full history taking and clinical examination.
2. Laboratory investigations:
   (a) Serum creatinine.
   (b) 24-h urinary creatinine.
   (c) 24-h urinary albumin.
   (d) A/C ratio is then calculated.
3. Ultrasound examination:

Equipment The study was done using an ultrasound machine (TOSHIBA Aplio 500) with a (6C1) curvilinear probe for color duplex sonography and SWE examination.

Position The patient was placed in the supine, prone or lateral positions according to the best-taken image view.

Techniques

(a) *Color duplex sonography* at first, we examined the abdominal aorta and main renal arteries to exclude renal artery stenosis. Measurements of PSV, EDV, and RI in upper polar, mid, and lower polar segmental renal arteries were taken.
(b) *Supersonic shear imaging (SSI)* according to Singh et al., it was performed over the B-mode US, where the patient was seated, at first, in a supine position then the US probe was held steadily with a very light compression and the patient was trained to

hold breath in full inspiration for a few seconds to decrease the respiratory motion of the kidney. The region of interest (ROI) box of 1.0 × 0.5 cm (as predefined by the manufacturer) was located at the renal cortex excluding the renal medulla as possible with the ROI box main axis being aligned as parallel as possible to the main axis of the renal medullary pyramids. The "Update" button of the US machine was then pressed to take the shear wave values measured in kilopascals (kPa). Five valid elasticity measurements of shear wave values were elicited during separate breath holds for the examined kidney and then the mean value for this kidney was obtained. If an invalid measurement was obtained, the process was repeated for taking new valid measurements [6].

We modified the technique to measure at the upper, middle, and lower renal zones (three measurements at each renal zone instead of one) to cope with the diffuse pattern of renal affection in DN.

However, eleven patients were examined but were excluded from the final results as we found pathologies other than nephropathy (four of them had renal stones, one had renal cortical scarring, four had hydronephrosis, one had polycystic kidney disease, and one had renal artery stenosis).

Statistical analysis

Statistical analysis was conducted using SPSS 22nd edition, quantitative data were presented in mean and standard deviation, and means comparison was conducted using unpaired t test for 2 groups and ANOVA post hoc for > 2 groups. Categorical data were presented in frequency and percentages and were compared using the Chi-square (χ^2) test between study groups. Sensitivity analysis was conducted to assess the diagnostic ability of US for DN among diabetic patients compared to healthy controls, and the severity of the renal disease. Any p value < 0.05 was considered significant.

Results

A total of twenty-six diabetic patients (14 males and 12 females) (mean age ± SD = 47 ± 11.9 years) and twenty-six healthy control subjects (13 males and 13 females) (mean age ± SD = 46 ± 11.2 years) were included in the current study, we assessed each kidney separately by SWE and color Doppler to analyze the findings of 52 renal units for cases and 52 renal units for controls.

Shear wave elastography and renal Doppler findings

The comparison of RI across the renal units of the included cases showed statistically significantly higher RI compared to those of the included controls at the upper pole, mid-zone, and lower pole of the kidneys with p values < 0.001 for each. Also, the comparison of SWE across the renal units of the included cases showed statistically significant higher values in the cases compared to controls in the upper pole, mid-zone, and lower pole of kidneys with p values < 0.001 for each. Moreover, the comparison of mean Doppler findings across the whole renal units in cases showed statistically significant higher values compared to controls with p values < 0.001 (Table 1) (Fig. 1).

Severity of renal disease among cases

Among the included diabetic patients, the median Albumin/creatinine ratio was 722 ± 685, and the median creatinine level was 3.2 ± 1.3 mg/dL. DN accordingly was found to be early in 24 renal units (46.2%), while 28 units were found to be in late stages (53.8%) (Table 2).

Severity and age

By comparison of age and laboratory findings in correlation to the severity of DN, statistically significant higher creatinine levels and A/C ratios in late stages with p values 0.01, and < 0.001, respectively, were documented (Table 3).

Table 1 Comparison of SWE and renal Doppler findings between study groups

	Group				*p* value
	Cases (n = 52 renal units)		Control (n = 52 renal units)		
	Mean	SD	Mean	SD	
RI upper	0.73	0.07	0.63	0.04	< 0.001
RI mid	0.74	0.07	0.64	0.04	< 0.001
RI lower	0.75	0.06	0.63	0.04	< 0.001
Mean RI	0.74	0.06	0.63	0.03	< 0.001
SWE Upper 1	27.2	13.8	9.8	3.0	< 0.001
SWE Upper 2	24.1	9.9	9.6	2.9	< 0.001
SWE upper 3	24.0	8.5	10.0	5.5	< 0.001
SWE mid 1	25.00	13.96	8.80	2.13	< 0.001
SWE mid 2	28.2	16.1	9.3	1.9	< 0.001
SWE mid 3	29.53	18.51	9.83	2.83	< 0.001
SWE lower 1	30.40	16.99	10.37	2.58	< 0.001
SWE lower 2	24.6	11.0	8.9	2.6	< 0.001
SWE lower 3	29.0	14.0	9.5	2.4	< 0.001
Mean SWE	27	8.2	9.4	1.5	< 0.001

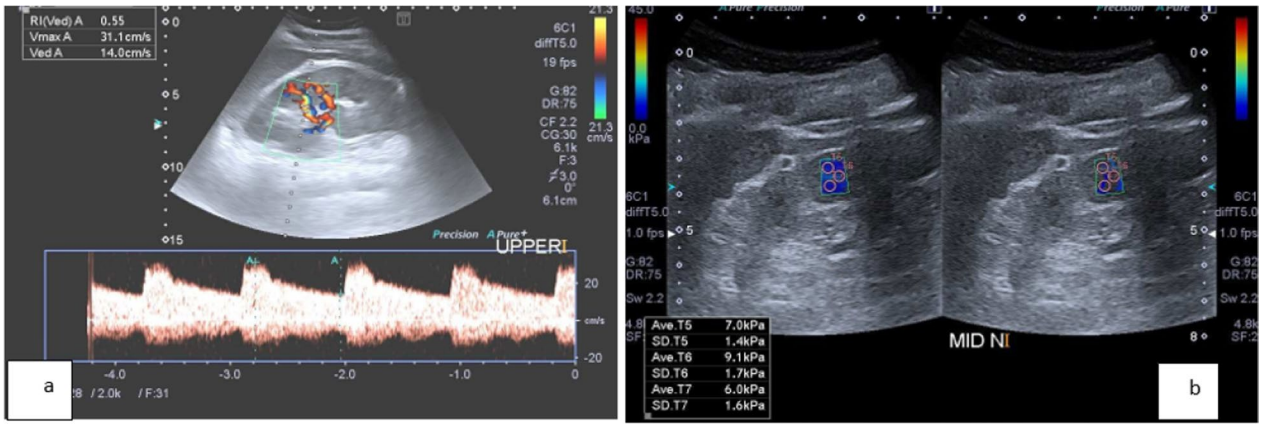

Fig. 1 **a**, **b** for a 45-year-old (healthy control) male with no history of DM and his serum creatinine was 0.7 mg/day. **a** A color duplex image showing mean RI = 0.55. **b** SWE image showing a mean stiffness value of the mid-zone of kidney was 10.27 kPa

Table 2 Laboratory findings and severity of renal disease among diabetic patients

		N = 52 renal units	
A/C ratio	Mean, SD	722	685
Creatinine (mg/dL)	Mean, SD	3.2	1.3
Stage			
Early	*N*, %	24	46.2%
Late	*N*, %	28	53.8%

Table 3 Comparison of age and laboratory findings according to severity of DN

	Groups				*p* value
	Early stage (*n* = 24 renal units)		Late stage (*n* = 28 renal units)		
Age	43.5	9	50.1	13.5	0.164
A/C ratio	182	81	1185	629	< 0.001
Creatinine (mg/dL)	2.2	0.5	4.2	1	0.010

Severity of disease, color Doppler, and elastography findings

There was a statistically significant higher RI among cases with late DN compared to the early stage across the upper pole, mid-zone, and lower pole with *p* value < 0.001 for each. There was a statistically significant higher SWE among cases with late DN compared to early stages across the upper pole, mid-zone, and lower pole with a *p* value < 0.01 for each (Table 4).

Table 4 Comparison of elastography and Doppler findings according to the severity of DN

	Groups				*p* value
	Early stage (*n* = 24 renal units)		Late stage (*n* = 28 renal units)		
R.I. upper	0.67	0.02	0.79	0.04	< 0.001
R.I. mid	0.67	0.02	0.80	0.03	< 0.001
R.I. lower	0.68	0.02	0.80	0.03	< 0.001
Mean RI	0.68	0.02	0.80	0.02	< 0.001
SWE Upper 1	19.1	5.1	34.2	15.1	< 0.001
SWE Upper 2	19.4	5.7	28.2	10.9	0.003
SWE upper 3	19.2	4.8	28.2	8.9	< 0.001
SWE mid 1	18.5	5.1	30.6	16.6	< 0.001
SWE mid 2	19.4	3.9	35.7	18.7	< 0.001
SWE mid 3	19.1	5.8	38.5	21.0	< 0.001
SWE lower 1	20.4	4.3	39.0	19.1	< 0.001
SWE lower 2	19.3	4.3	29.1	12.9	0.005
SWE lower 3	21.4	4.8	35.6	16.0	< 0.001
Mean SWE	19.5	1.2	33.4	5.9	< 0.001

Color Doppler, shear wave elastography findings and prediction of renal disease

RI of the upper pole, mid-zone, and lower pole of kidneys can significantly predict diabetic nephropathy with a *p* value < 0.001for each, using a cutoff 0.66, 0.67, and 0.69, with sensitivity of 80.8%, 71.2%, and 80.8%, and specificity of 69.2%, 73.1%, and 88.5%, finally with a diagnostic accuracy of 78.8%, 74% and 86.5%, respectively (Table 5) (Figs. 2, 3).

Furthermore, RI of the upper pole, mid-zone, and lower pole of kidneys can significantly predict late DN with a *p* value of 0.001 for each, using cutoff 0.72, 0.71, and 0.72, with sensitivity 100%, and specificity > 95%,

Table 5 Sensitivity analysis and the predictability of R.I. for diagnosis of DN

Test result variable(s)	AUC	*p* value	Cutoff	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)	Accuracy (%)	95% CI
R.I upper	0.902	< 0.001	0.66	80.8	69.2	85.7	74.2	78.8	0.84–0.95
R.I. mid	0.863	< 0.001	0.67	71.2	73.1	79.1	70.5	74	0.79–0.93
R.I lower	0.943	< 0.001	0.69	80.8	88.5	85.2	88	86.5	0.90–0.98

AUC area under the curve, *NPV* negative predictive value, *PPV* positive predictive value, *CI* confidence interval

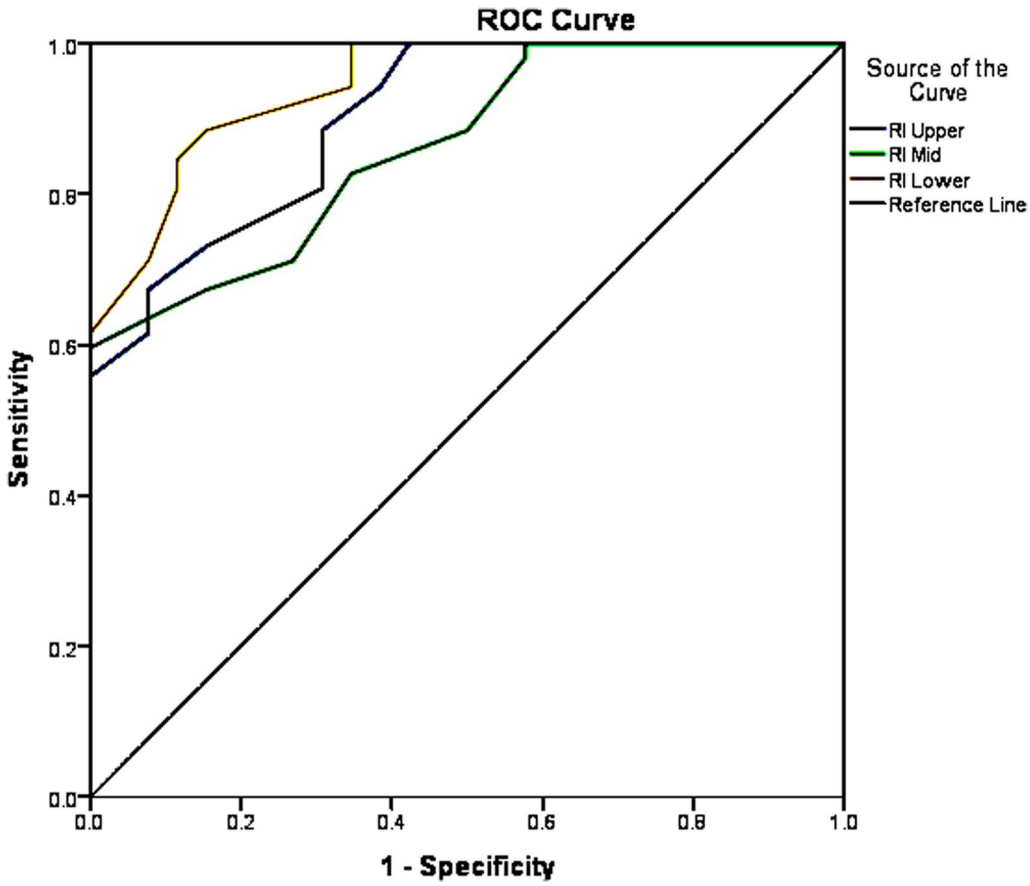

Fig. 2 ROC curve showing the ability of RI to diagnose DN

with diagnostic accuracy 98% for each (Table 6) (Figs. 4a, 5).

When comparing the RI between the study groups, there was a statistically significant difference between RI in the upper pole, mid-zone and lower pole of kidneys between the study groups mainly reported between control versus late as well as early versus late nephropathy with *p* values 0.0001 for all. The comparison of RI between early DN and controls showed no statistically significant difference between groups in RI of upper pole and mid-zones with *p* values 0.109 and 0.112, respectively (Table 7).

SWE values were significantly different among study groups according to severity, as the late stages of DN were associated with significantly higher stiffness compared to early stages and control groups with *p* values of 0.0001 for all, post hoc analysis showed that main differences were reported between the control and the late stages with *p* values < 0.001, and between control and early DN with *p* values < 0.001. Also, there was a statistically significant difference between early and late

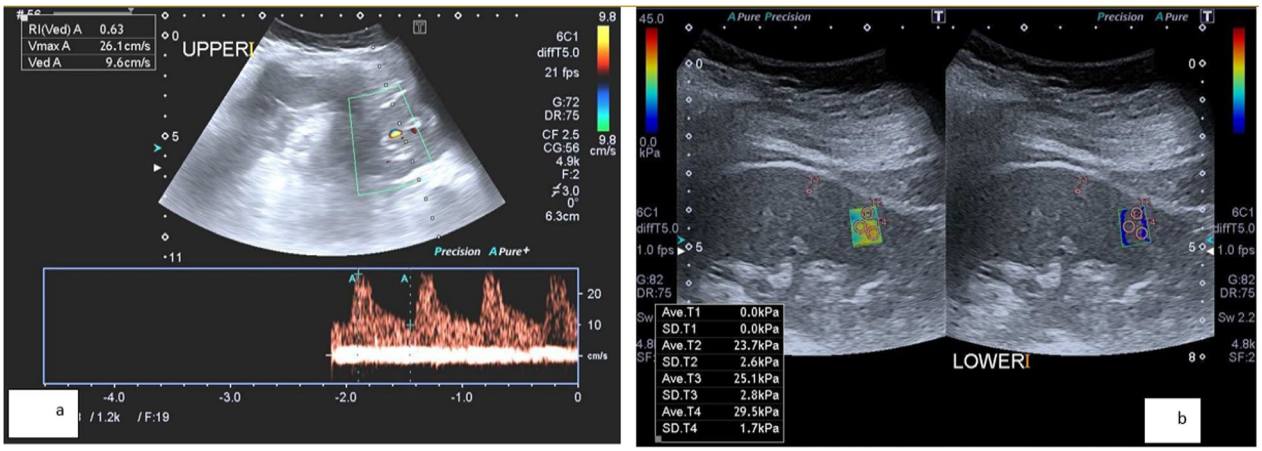

Fig. 3 **a**, **b** for a 48-year-old male patient with a history of DM for 5 years and had presented with proteinuria and his serum creatinine was 1.8 mg/dl. **a** A color duplex image showing mean RI = 0.61. **b** SWE image showing a mean stiffness value of the kidney was 20.6 kPa

Table 6 Sensitivity analysis and the predictability of R.I. for diagnosis of late DN

Test result variable(s)	AUC	*p* value	Cutoff	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)	Accuracy (%)	95% CI
R.I. upper	1.000	0.001	0.72	100	96	100	96	98	1–1
R.I. mid	1.000	0.001	0.71	100	96	100	96	98	1–1
R.I. lower	0.958	0.001	0.72	100	95.8	100	96	98	0.8701

nephropathies with p values < 0.05 for all regarding the mean elastography findings (Tables 8, 9).

SWE of the upper pole of kidneys can significantly predict late DN with p value 0.001 for each, using cutoff 18.3, with sensitivity of 92.9% and specificity of 86.8%, and diagnostic accuracy of 88%, while SWE of the mid-zone of kidneys can significantly predict late DN with p value 0.001 for each, using cutoff 19.4, with a reported sensitivity 92.9% and specificity 85.5%, finally with diagnostic accuracy of 87.5%, the SWE of the lower pole of kidneys can significantly predict late DN with p value 0.001 for each, using cutoff 20.2, with sensitivity of 92.9% and specificity of 86.8%, and diagnostic accuracy of 88.5% (Tables 10, 11, 12) (Figs. 4b–d, 5).

Discussion

Diabetic nephropathy (DN) is a clinical-laboratory condition that is characterized by chronic albuminuria on at least two occasions 3–6 months apart. It is considered one of the leading causes of end-stage kidney disease (ESKD) in both developed and developing countries; nonetheless, it is predicted that diabetic patients are seventeen times more likely to die from renal disease than nondiabetic ones [2, 7].

Diabetes mellitus (DM) often jeopardizes the entire circulation with micro and macrovascular affections where renal arteries atherosclerosis and microangiopathy of the glomerular loops are the salient pathological findings in DN, thus early detection of DN aims to hinder the progression of the disease into the late stages, additionally, it can provide an optimal glycemic control to delay or prevent other complications of DM and further progression to ESKD [8, 9].

Resistivity index (RI) is defined as the ratio of the difference between PSV and EDV flow velocities to PSV velocity as determined by spectral Doppler waveform interrogation of the intrarenal arteries. Being simple, and non-invasive, the color Doppler examination has been employed as a well-established approach for the evaluation of the renal functional and structural alterations in DN [10].

Shear wave elastography (SWE) imaging is a simple and cost-effective diagnostic tool that is based on acoustic radiation force impulse (ARFI) technology and is currently used for the assessment of tissue elasticity [5]. It measures the velocity of the transmitted shear waves through the examined tissues in meter\second (m\s), then the software

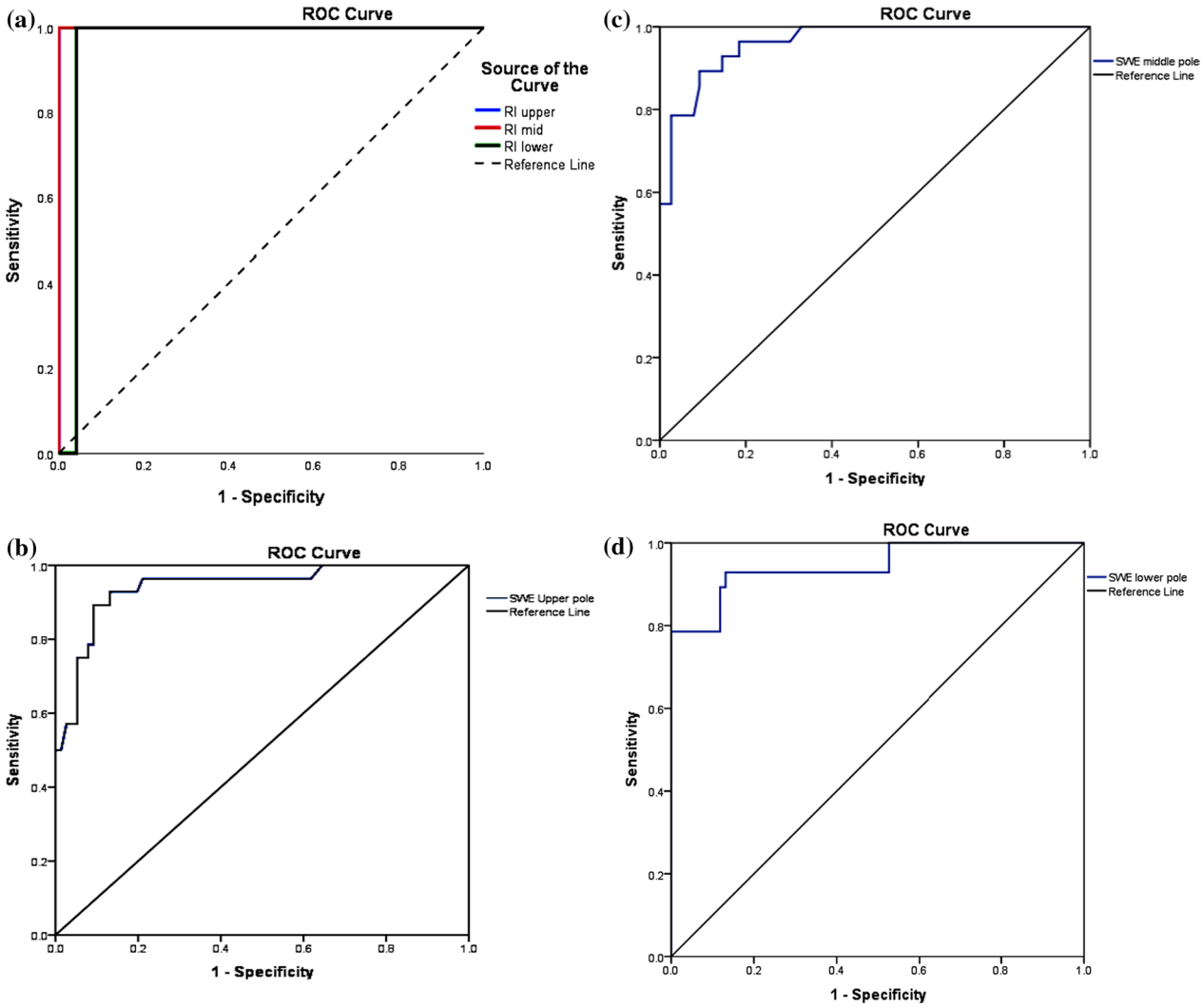

Fig. 4 **a** ROC curve showing the ability of RI to diagnose late DN. **b** ROC curve showing prediction of upper renal pole stiffness for late DN. **c** ROC curve showing prediction of mid-zone stiffness for late DN stage. **d** ROC curve showing prediction of lower renal pole stiffness for late DN stage

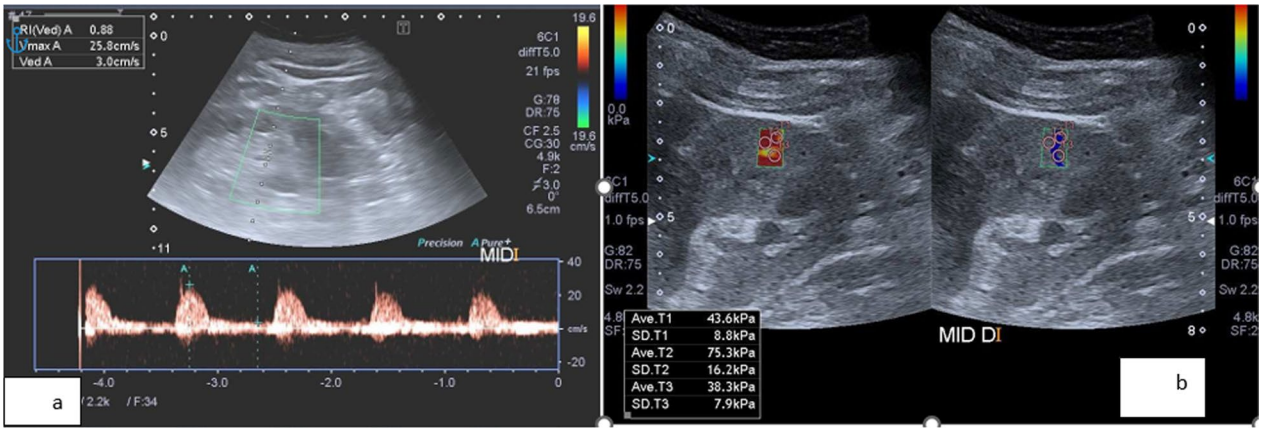

Fig. 5 **a**, **b** for a 65-year-old male patient with a history of DM for 20 years and had presented with proteinuria and his serum creatinine was 4.5 mg/dl. **a** A color duplex image showing mean RI = 0.84. **b** SWE image showing a mean stiffness value of the kidney was 43.4 kPa

Table 7 Comparison of R.I. between study groups according to the stage of DN

	Stage						*p* value	P1 (control versus early)	P2 (control versus late)	P3 (early versus late)
	Control		Early		Late					
	Mean	SD	Mean	SD	Mean	SD				
RI upper	0.63	0.04	0.67	0.02	0.79	0.04	0.0001	0.109	0.0001	0.0001
RI mid	0.64	0.04	0.67	0.02	0.80	0.03	0.0001	0.112	0.0001	0.0001
RI lower	0.63	0.04	0.68	0.02	0.80	0.03	0.0001	0.0001	0.0001	0.0001

Table 8 Comparison of SWE values among study groups according to stage of DN

	Stage						*p* value
	Control		Early		Late		
	Mean	SD	Mean	SD	Mean	SD	
SWE upper 1	9.8	3.0	19.1	5.1	34.2	15.1	0.0001
SWE upper 2	9.6	2.9	19.4	5.7	28.2	10.9	0.0001
SWE upper 3	10.0	5.5	19.2	4.8	28.2	8.9	0.0001
SWE mid 1	8.8	2.1	18.5	5.1	30.6	16.6	0.0001
SWE mid 2	9.3	1.9	19.4	3.9	35.7	18.7	0.0001
SWE mid 3	9.8	2.8	19.1	5.8	38.5	21.0	0.0001
SWE lower 1	10.4	2.6	20.4	4.3	39.0	19.1	0.0001
SWE lower 2	8.9	2.6	19.3	4.3	29.1	12.9	0.0001
SWE lower 3	9.5	2.4	21.4	4.8	35.6	16.0	0.0001
Mean	9.5	1.5	19.5	1.2	33.4	5.9	0.0001

Table 9 Post hoc analysis and pairwise comparison of renal stiffness across study groups

	P1 (control versus early)	P2 (control versus late)	P3 (early versus late)
SWE upper 1	0.0001	0.0001	0.016
SWE upper 2	0.0001	0.0001	0.014
SWE upper 3	0.0001	0.0001	0.034
SWE mid 1	0.0001	0.0001	0.041
SWE mid 2	0.0001	0.0001	0.040
SWE mid 3	0.0001	0.0001	0.025
SWE lower 1	0.0001	0.0001	0.046
SWE lower 2	0.0001	0.0001	0.007
SWE lower 3	0.0001	0.0001	0.018
Mean	0.0001	0.0001	0.001

processes the obtained data into a tissue stiffness parameter and finally is interpreted in kilopascals (kPa) [11].

Tissue elasticity could be evaluated in quantitative and qualitative patterns by using a combination of conventional and SWE imaging. Recently, the SWE has been implemented for investigating the mechanical properties of renal tissue [12].

The present study was conducted as a case–control study to assess the role of renal elastography in the early detection of DN in correlation to laboratory and renal Doppler findings. Therefore, we included a total of 26 diabetic patients and 26 healthy control subjects, and each kidney was individually assessed by SWE and color Doppler to analyze the findings of 52 renal units for cases and 52 renal units for controls.

In order to address the diffuse pattern of renal affection in DN, we modified the methodology to measure the RI and the SWE at the upper, middle, and lower renal zones (three measures at each renal zone instead of one). This

Table 10 Sensitivity analysis and prediction of upper renal pole stiffness for the late DN stage

Test result variable(s)	AUC	*p* value	Cutoff	Sensitivity	Specificity	PPV	NPV	Accuracy	95% CI
SWE upper pole	0.942	0.0001	18.3	92.9%	86.8%	72%	97%	88%	0.89–0.99

Table 11 Sensitivity analysis and prediction of mid-zone stiffness for the late DN stage

Test result variable(s)	AUC	*p* value	Cutoff	Sensitivity	Specificity	PPV	NPV	Accuracy	95% CI
SWE mid-zone	0.962	0.0001	19.4	92.9%	85.5%	70%	97%	87.5%	0.929–0.99

Table 12 Sensitivity analysis and prediction of lower renal pole stiffness for the late DN stage

Test result variable(s)	AUC	*p* value	Cutoff	Sensitivity	Specificity	PPV	NPV	Accuracy	95% CI
SWE lower pole	0.945	0.0001	20.2	92.9%	86.8%	72%	97%	88.5%	0.891–0.99

was the novel aspect of the current study using both color Doppler and the SSI.

Our statistics showed that renal Doppler RI across the renal units of DN cases was significantly higher compared to those for controls in the upper pole, mid-zone, and lower pole of kidneys with p values < 0.001 for each, moreover, there was a statistically significant higher RI among cases with late DN compared to those with early stages across renal poles with p value < 0.001 for each, nevertheless, the comparison of RI between early DN and controls showed no statistically significant difference between groups in RI across the upper and middle zones (p values 0.109 and 0.112, respectively).

Our findings agreed with those reported by Elshweehy et al. [13] who stated that the mean RI in the control group was significantly lower than the mean RI in all stages of the DN and found that progressive increase in the mean RI values was significantly associated with an increase in severity of DN (p value < 0.001).

Furthermore, a study conducted by Sistani et al. [14] showed that RI greater than or equal to 0.7 had been defined as an indicator of impaired renal functions in diabetic patients with micro or macroalbuminuria. We do believe that due to the relatively small sample size and the small number of subgroups, the difference between early DN and the control group was not statistically significant in terms of RI, however, further studies including a larger sample of diabetic patients with different stages of DN is required to assess a real and a reproducible difference in RI between early DN patients and healthy control individuals.

Our data showed that the renal RI of the upper pole, mid-zone, and lower pole of kidneys can significantly predict DN with p value < 0.001 for each, using a cutoff 0.66, 0.67, and 0.69, with sensitivity 80.8%, 71.2%, and 80.8%, specificity 69.2%, 73.1% and 88.5%, finally with diagnostic accuracy 78.8%, 74%, and 86.5%, respectively, such findings are concordant with a large retrospective study enrolling 332 DN patients and 137 non-DN patients who were included for analysis, they had reported that RI was significantly higher in the DN group compared with those in the non-DN group (0.70 versus 0.63, p value < 0.001), and they had described an optimum cutoff RI value of 0.66 for predicting DN with sensitivity (69.2%) and specificity (80.9%) [15].

Another study had defined 0.7 as a cutoff for renal RI among diabetic patients for diagnosis of DN, they stated that 77% of patients with overt nephropathy, and 90% of those with renal failure had an RI > 0.7, which indicated that RI was positively correlated with the stage of DN [16].

In the current study, the comparison of renal elastography values across the renal units of DN cases showed statistically significant higher values compared to controls in the upper pole, mid-zone, and lower pole of kidneys with p values < 0.001 for each. Also, SWE values were significantly different among study groups according to severity, as late stages of DN were associated with significantly higher stiffness compared to early DN and control groups with p values of 0.0001 for all, and post hoc analysis showed that main differences were reported between control and late stage with p values < 0.001, and between control and early DN with p values < 0.001. Nonetheless, there was a statistically significant difference between early and late nephropathies with p values < 0.05 for each and mean SWE values for the whole renal unit with a p value of 0.006.

Koc and Sumbul [17] investigated the role of SWE in assessing the cortical stiffness and renal RI among patients with type 2 diabetes versus the control group, they found that RI was similar among the study groups, while the cortical stiffness was significantly higher among the DM group even among those without DN, indicating that cellular and microvascular changes are occurring in DN even at the preclinical stage, can be significantly detected by SWE rather than the Doppler findings.

Other authors investigated the role of SWE in determining the stage of chronic kidney disease (CKD) among children, their ROC analysis revealed that the ideal cutoff points for diagnosing stage III-IV CKD in the left and

right kidneys were 11.7 kPa and 11.0 kPa, respectively, with the highest diagnostic sensitivity and specificity (left: 93.3% and 95.0%; right: 93.3% and 91.7%) [18].

In a similar case–control study, that included 29 cases of type 2 diabetes with DN and compared with 23 healthy subjects, they found that renal stiffness by SWE was 11.0 ± 4.2 Kpa for stage IIIa CKD, 15.7 ± 6.7 Kpa for stage IIIb CKD, 14.6 ± 8.1 Kpa for stage IIIc CKD, and 30.4 ± 16.2 Kpa for stage IV CKD. They had reported a statistically significant difference between stage IIIa and stage IIIb CKD, as well as, stage III and stage IV CKD [19]. However, ROC analysis was not performed and their findings were similar to those reported in our study.

Yuksekkaya et al. reported a significant difference in renal stiffness between diabetic patients versus control (10.1 ± 1.75 Kpa versus 8.2 ± 1.40 Kpa) with a p value < 0.001. They also defined 9.23 Kpa as an optimal cutoff point for diagnosing DN, and 10.1 Kpa as an optimal cutoff point for depiction of early versus late DN [20]. These cutoff points were slightly lower than those documented in our current study and this might be explained by the differences in race and ethnicity of the studied populations.

Nonetheless, Lin et al. [21] described higher parenchymal stiffness in the late stages of DN compared to the early ones. Furthermore, Samir et al. [22] revealed a higher median SWE value (9.40 kPa) in patients with CKD, however, they mostly comprised patients with DM. To the best of our knowledge, there are a few studies that have documented the diagnosis of DN in its early stages [18, 22].

Our findings were discordant with Gunduz et al. [23], who found that SWE was not significantly different between healthy controls and early DN patients, they documented that there was no significant difference between the diabetic group and healthy controls in terms of the average 2D-SWE as their obtained 2D-SWE values of the upper, middle, and lower kidney regions were similar between the study groups (all p values > 0.05) for both kidneys.

In the current study, SWE of the upper pole of kidneys can significantly predict late stages of DN (p value 0.001), using cutoff 18.3, with sensitivity 92.9% and specificity 86.8%, finally with diagnostic accuracy 88%, while SWE of the mid-zone of kidneys can significantly predict late DN (p value 0.001), using cutoff 19.4, with sensitivity 92.9% and specificity 85.5%, with diagnostic accuracy 87.5%, and the SWE of lower pole of kidneys can significantly predict late DN (p value 0.001), using cutoff 20.2, with sensitivity 92.9%, specificity 86.8%, and diagnostic accuracy 88.5%.

A cross-sectional study enrolled 126 patients and 22 healthy controls who were screened by SWE, they assessed 8.5 kPa as a cutoff point for diagnosing patients with DN compared to controls with a sensitivity of 65.2%, specificity of 60.4%, and AUC of 0.708 [24]. These findings were inconsistent with ours as we reported higher cutoff points and higher diagnostic indices, however, the different results could be attributed to the different sample sizes.

Although the renal stiffness changes obtained by SWE have recently begun to be employed in DN, there are conflicting outcomes with no definite standard data on the cutoff values [17].

Measurement of the renal tissue stiffness by US is more difficult due to the deep position of the kidneys in the abdomen. Due to compartmentalization and the inhomogeneous nature of the examined tissues, only US-guided procedures appear to be more appropriate. Many factors could enhance measurement variability including the different transducer pressures applied on the abdominal wall, as well as the tissue anisotropy, thus, additional experience in preclinical models and patient cohorts with correlation to the pathological results is mandated to better investigate the physical and the histological reasons of variations in tissue elasticity [25].

Zaffanello et al. [5] stated that the disadvantages of SWE may be due to the exam's uneven availability in clinics and insufficient standard cutoff values in different patient populations.

We had met some limitations in our study including a relatively small sample size, lack of standard cutoff values for normal and abnormal renal stiffness, and lack of standardization of SWE examination protocol. Moreover, this was a single institution study, so its results cannot be generalized over the whole region. Consequently, larger multicentered studies should be managed to define an optimal cutoff point for diagnosis of preclinical, early, and late stages of DN.

Conclusions

In our final analysis, we came to the conclusion that SWE is a very promising diagnostic tool that is highly sensitive, specific, and accurate for comparing the early DN group to the control group and differentiating between the early and late phases of DN. As integrated and complemented by laboratory and Doppler findings, it is regarded as a useful tool that can further improve the sensitivity and specificity of early DN diagnosis as compared to the renal Doppler's diagnostic value when used alone.

Abbreviations

A/C	Albumin to creatinine ratio
ARFI	Acoustic radiation force impulse
BMI	Body mass index
CKD	Chronic kidney disease
DM	Diabetes mellitus

DN	Diabetic nephropathy
EDV	End diastolic velocity
ESKD	End-stage kidney disease
GFR	Glomerular filtration rate
PSV	Peak systolic velocity
RF	Renal failure
RI	Resistivity indices
SSI	Supersonic shear imaging
SWE	Shear wave elastography
US	Ultrasound

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Author contributions
AAB: the corresponding author contributed by supervising the ultrasound examinations and in the final editing and submission of the manuscript, EMA did the ultrasound examinations for the patients and shared in the manuscript editing and reference collection, MYH had done the clinical and laboratory assessment of the patients, AEA: introduced the idea of the current study and helped in the image selection and revised the final version of the submitted manuscript. All authors have read and approved the manuscript.

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Availability of data and materials
All data are available on a software system owned by each of the authors, and the corresponding author has the authority to respond if there is any query.

Declarations

Ethics approval and consent to participate
The protocol was reviewed and approved by the local ethics committee of the radiology department, at Kasr Alainy Hospital, Cairo University. The reference number: Code Ms-59-2022, Date of approval 17-7-2022. All patients had given their written consent to participate in this work.

Consent for publication
All patients had given their written consent for publication of this work.

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