Shear wave elastography in early diabetic kidney disease

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SUMMARY

OBJECTIVE: This study aimed to analyze the kidneys among the subjects with early stages of type 2 diabetic kidney disease by shear wave elastography quantitatively.

METHODS: A total of 108 patients with type 2 diabetic kidney disease and 17 control subjects were enrolled. According to the estimated glomerular filtration rate and urinary albumin-to-urinary creatinine ratio, patients were classified into stages 1 to 3 diabetic kidney disease. Grayscale ultrasound and shear wave elastography were performed. The sizes, depths, and shear wave elastography values were recorded. These parameters were compared between the diabetic kidney disease and the control subjects.

RESULTS: The mean shear wave elastography values were significantly higher in the diabetic kidney disease group (10.156±1.75 kPa vs. 8.241±1.4 kPa; p<0.001). We obtained statistically significantly higher shear wave elastography values in stages 2 and 3 diabetic kidney disease subjects than control subjects and in patients with stage 3 diabetic kidney disease compared to those with stage 1 diabetic kidney disease (p<0.05 for all). We obtained a cutoff value of 9.23 kPa for predicting diabetic kidney disease in early stages, with a sensitivity of 67% and a specificity of 82%.

CONCLUSION: Shear wave elastography may be used as a noninvasive, simple, and quantitative method to provide diagnostic information as a part of routine management of patients with type 2 diabetes mellitus, especially in the early stages of diabetic kidney disease.

KEYWORDS: Diabetes mellitus. Kidney. Ultrasonography. Elastography.

INTRODUCTION

Diabetic kidney disease (DKD) is the leading cause of chronic kidney disease (CKD)[1]. It can be controlled or even be reversed if timely diagnosis and treatment are provided. Serum creatinine, albuminuria, and estimated glomerular filtration rate (eGFR) were less reliable indicators in early stages[2]. Biopsy provides a definitive diagnosis, although it has life-threatening complications. Computed tomography (CT) and magnetic resonance imaging (MRI) can evaluate morphological and functional situation of the kidney. However, they have some disadvantages, such as higher costs, long appointment time, radiation exposure, contrast-induced nephropathy, or nephrogenic systemic fibrosis. Ultrasound (US) is a noninvasive, available, cheap, and frequently used method to evaluate the kidney. US findings might be helpful especially in advanced stages such as decreased renal size, parenchymal thickness, and increased parenchymal echogenicity[3]. Early stages are reversible, but the most common diagnostic problems appear in these stages. Because in the hyperfiltration stage, the size of the kidney is normal, even bigger and the parenchymal thickness and the echogenicity are usual[4]. There is a requirement of a noninvasive method for the evaluation of DKD in the early stages.

Advanced, noninvasive, and simple sonographic techniques such as shear wave elastography (SWE) have been improved to identify the development of parenchymal fibrosis quantitatively based on the stiffness. In SWE, the transducer applies a transient acoustic radiation force to deform the tissues. Deformed waves, also known as shear waves, measured in meters per second and converted into a quantitative stiffness score in kPa by using Young's modulus, radiating in a perpendicular direction to the US beam. A low speed corresponds to soft, while a high speed indicates a stiff medium. To the best of our knowledge, there is little information about renal stiffness in the early stages of DKD. This study aimed to investigate the SWE technique for the quantitative assessment of DKD in early stages.

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METHODS

This prospective study was approved by the Research and Ethics Committee of our institution (approval number: 17-KAEK-100) and written informed consent was acquired from participants. The inclusion criteria of the study group were the patients with type 2 diabetes mellitus (DM) who had stages 1–3 DKD. The control group included age- and sex-matched healthy subjects who had no CKD, DM, hypertension, and cardiovascular disease. Subjects with (1) other primary renal diseases such as cyst, stone, and hydronephrosis; (2) malignancy; (3) pregnancy and lactation; (4) mental illness; (5) obesity with a renal depth more than 8 cm from the skin surface; (6) thin renal parenchymal thickness; (7) could not hold breath according to the radiologists' instructions; (8) solitary kidney; and (9) <30 eGFR levels were excluded. Between April and November 2018, we evaluated 108 consecutive subjects (36 males, 72 females; mean age±SD=56.3±10.6 years; age range: 20–85 years) who were admitted to the Department of Endocrinology. The control group comprised 17 subjects (10 males, 7 females; mean age±SD=56.8±9.3 years; age range: 43–73 years) and were recruited from the study site.

Clinical and laboratory data

We obtained demographic features and serum creatinine, blood urea nitrogen (BUN), and spot urinary albumin-to-urinary creatinine (UA/UC) ratio, within 1 week of undergoing the SWE. The diagnosis and the classification of DKD were established based on the "A new Classification of Diabetic Nephropathy 2014: a report from Joint Committee on Diabetic Nephropathy." This classification was based on the eGFR and UA/UC ratio[5]. We calculated eGRF for the serum creatinine concentration and age, using the new abbreviated equation of Modification of Diet in Renal Disease (aMDRD) for Turkish patients as follows: eGFR = aMDRD = 186 × (serum creatinine) – 1.154 × (age) – 0.203 × 0.742 (if female). According to the UA/UC, normoalbuminuria is defined as the levels <30 mg/g, microalbuminuria is defined as the levels between 30 and 300 mg/g, and macroalbuminuria is defined the levels >300 mg/g.

Sonographic evaluation

A radiologist with 15 years of experience who were blinded to the groups performed examinations. All subjects were fasted at least for 4 h and instructed to urinate before the examination. Ultrasonography and SWE examinations were performed in the right and left lateral decubitus positions during maximum inspiration to minimize kidney movement and obtain a full-size image of each kidney by using a Logic E9 system (GE Medical Systems, Milwaukee, WI, USA) with C1-6-D XDclear 1–6 MHz broadband convex transducer. Grayscale settings were adjusted to have optimum brightness, contrast, and increased spatial and temporal resolution. Length, width, and depth of each kidney were measured. Transducer placed longitudinally with minimal compression and SWE software turned on. On grayscale, an elastographic box with a size of 10 mm×10 mm was manually positioned, and stiffness results were coded in a color-coded map (Figure 1). Nine consecutive 5-s cine clips were conducted from the upper-lower pole, and the midportion of renal cortex, excluding vessels. At postprocessing period on the same equipment, a circle-shaped region of interest (ROI) was placed into the box above mentioned, and measurements were conducted in kPa. The mean SWE value of both kidneys was recorded. On average, sonographic evaluation period was about 20 min and the postprocessing period was about 10 min.
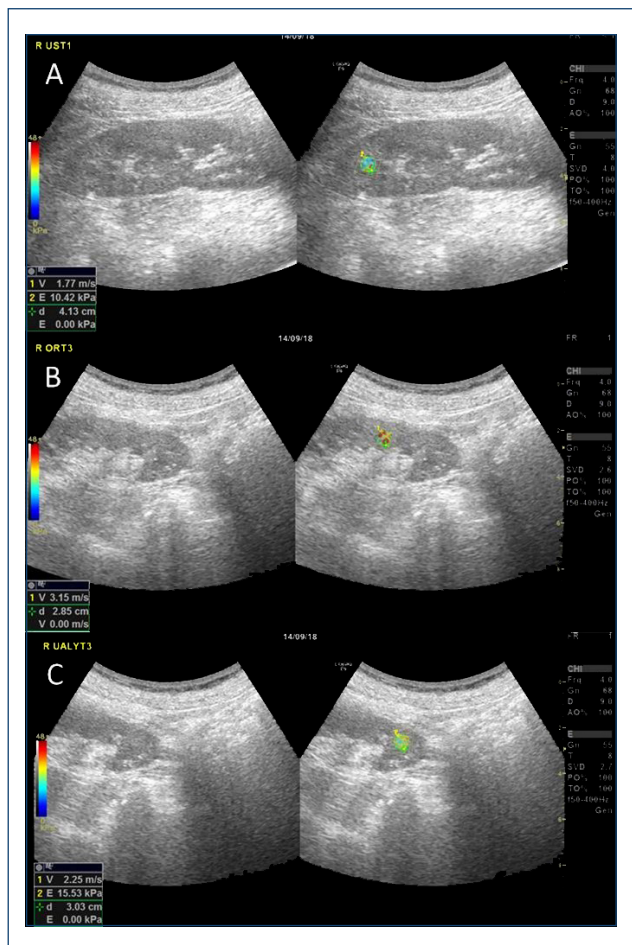

Figure 1. (A–C): Examples of shear wave elastography measurements performed from different parts of kidney on longitudinal scan in an a-73-year-old woman with type 2 diabetes mellitus and stage 3 diabetic kidney disease.

Statistical analyses

The normally distributed variables were shown as mean±standard deviation (SD), and non-normally distributed variables were stated as median [interquartile range (IQR)]. Categorical data were shown as numbers with related percentages (n, %) and compared by using the chi-square test. The differences in continuous variables were analyzed by using the Student's t-test or Mann-Whitney U test. The means of three or more samples were compared with one-way analysis of variance (ANOVA) test. The correlations between laboratory parameters, grayscale, and SWE parameters were evaluated with the Pearson's and Spearman's bivariate correlation (r) tests. Receiver operating characteristic (ROC) curves were carried out, and the areas under the curve (AUCs) were estimated in order to investigate the role of SWE values for the distinction and staging of DKD. The sensitivity, specificity, and cutoff values from the closest point to the left upper corner on the ROC curve, with 95% confidence intervals (95%CIs) were obtained. A $p < 0.05$ was considered statistically significant. All statistical analyses were performed by using SPSS (Statistical Package for the Social Sciences) statistical software package (version 11: SPSS Inc., Chicago, IL, USA).

RESULTS

There was no statistically significant difference in the age, gender, and renal length, width, depth between both groups ($p > 0.05$ for all), but the renal SWE values were significantly higher in the patient group ($p < 0.001$). ANOVA showed statistically significant increased renal SWE values in patients with stages 2 and 3 DKD compared with control subjects ($p < 0.001$ for all) and in patients with stage 3 DKD than those with stage 1 DKD ($p = 0.006$) (Table 1). Pearson's correlation coefficient revealed a weak positive correlation between albuminuria and the mean renal SWE values ($r = 0.22$, $p = 0.026$). Among the renal SWE values, the most sensitive cutoff value was 9.23 kPa between control subjects and patients with stage 3 DKD (sensitivity, 74%; specificity, 82%) (Table 2).

Table 1. Depth, length, width, and SWE values of kidneys in both groups.

	Type 2 diabetes mellitus	Control subjects	p
Depth (mm) (mean±SD)	38.7±9.48	43.2±7.33	0.064
Length (mm) (mean±SD)	103.88±12.33	101.97±9.93	0.546
Width (mm) (mean±SD)	47.44±6.74	47.92±5.72	0.781
SWE values of both kidneys (kPa) (mean±SD)	10.156±1.75	8.241±1.40	<0.001
Control subjects	8.241±1.404		
Stage 1 DKD[a]	8.948±0.799		
Stage 2 DKD[a]	10.239±1.784		
Stage 3 DKD[b]	10.572±1.804		

[a]p=0 compared with the healthy control group; [b]p=0.006 compared with DKD in stage 1. SWE: shear wave elastography; DKD: diabetic kidney disease; SD: standard deviation.

Table 2. Sensitivity, specificity, and cutoff values of SWE for predicting the presence and stage of diabetic kidney disease.

	Area under the curve	p	Cutoff value of SWE (kPa)	Sensitivity (%)	Specificity (%)
Mean value of both kidneys					
Stages 1 and 3 DKD	0.798	0	10.166	56	100
Control and stage 2 DKD	0.801	0	9.38	65	82
Control and stage 3 DKD	0.851	0	9.23	74	82
Control and DKD	0.798	0	9.23	67	82

SWE: shear wave elastography; DKD: diabetic kidney disease.

DISCUSSION

Albuminuria often indicates glomerular dysfunction, which is a characteristic of DKD in type 1 DM. However, tubulointerstitial fibrosis and vascular lesions are related to the development of DKD in type 2 DM. Some studies reported normal albuminuria levels in advanced CKD with type 2 DM[6,7]. Also, albuminuria and serum creatinine levels might be affected by diet, menstruation, muscle mass, and exercise. eGFR has a limited role in the hyperfiltration phase[8,9]. Due to the limitations of these laboratory methods in the early diagnosis of DKD, some imaging methods have been developed.

Grayscale US findings might be challenging in the early stages of DKD[3]. In early stages, due to hyperfiltration, US shows "bigger" and "better" kidney in patients with DKD compared to the kidney with the same level of chronic renal diseases[4]. It is reported that renal length, parenchymal thickness, and parenchymal echogenicity were not useful to indicate the severity of the DKD[10]. The measurement of size might be influenced by hydration. Evaluation of parenchymal echogenicity is a subjective and non-quantitative method. In recent years, new and quantitative sonographic methods such as elastography have been developed that could be helpful to demonstrate functional impairment[11-17].

We found significantly increased stiffness values in the patient group than healthy subjects (10.156±1.75 kPa vs. 8.241±1.40 kPa). Hassan et al. reported increased cortical stiffness in patients with advanced DKD compared to healthy subjects (23.72 kPa vs. 9.02 kPa) and in patients with stage 4 compared to those with stage 3 (30.4 kPa vs. 14.6 kPa)[15]. The reason for these higher values might be due to the fact that their study group consisted of patients with stages 3 and 4, in contrast to our study which included patients with stages 1–3. Lin et al. found increased parenchymal stiffness in the later stages of DKD[17]. Samir et al. obtained higher median SWE values (9.40 kPa) in patients with CKD who mostly comprised patients with DM[18]. To the best of our knowledge, there are a few studies about the diagnosis of DKD in the early stages[14,19]. Similar to our results, Liu et al. reported increased SWE values in the early (7.93 kPa) and middle stages (16.88 kPa) of patients with DKD compared to the diabetic subjects without DKD (5.51 kPa)[14]. Koc et al. reported increased stiffness in subjects with type 2 DM without diabetic nephropathy compared to healthy subjects (9.86 kPa vs. 7.92 kPa)[19]. Similar to our results, Goya et al. observed increased shear wave velocity values in DKD[16]. They obtained the highest shear wave velocity values in patients with stage 2, in contrast to our result on patients with stage 3. We found a progressive increase in the SWE values between stages 1 and 3 that might be attributed to the increase in fibrosis. However, they reported a progressive decrease in shear wave velocity values between stages 2 and 5 DKD. They stated this decrease might be related to renal function[16]. Since patients with stages 4 and 5 were not included in our study, we do not know the exact relationship of stages of DKD and SWE.

The validation of a cutoff SWE value in the investigation of early DKD might allow closer follow-up and planning of treatment. In our opinion, a cutoff value of 9.23 kPa might be considered in the diagnosis of early DKD.

Our results showed a weak positive correlation between SWE values and albuminuria. This is also accordant with previous research findings[15,16]. Some studies reported a relationship between cortical stiffness values and eGFR, BUN, and serum creatinine[12,15,16,19]. These discrepancies may conclude that eGFR is not an early marker of kidney damage, while BUN and serum creatinine levels are useful in the initial diagnosis of acute or chronic kidney disease and not monitoring of CKD[20,21].

This study has many limitations. One limitation of our study is that the analyses were performed by a single radiologist. Intra- and inter-observer agreement rates were not evaluated. The reason for this conflict is the long duration of the examinations. Another limitation is that SWE may be affected by movement artifacts, and a maximum depth of 8 cm limits the use of this method. Because of the fact that recruiting the age-matched subjects without any other chronic disease affecting kidneys and malignancies was challenging, the number of control subjects was limited. Another significant limitation is the lack of a gold standard, such as histopathological results. Performing the histopathological confirmations would increase the cost of the study and not be ethical and legal for the patients. Finally, the follow-up clinical, laboratory, and SWE results of the patients are not available.

CONCLUSIONS

Renal stiffness measured by SWE may be used as a noninvasive, simple, cost-effective, quantitative, and reliable imaging method to provide extra diagnostic information as a part of the routine sonographic investigation of patients with type 2 DM to reveal the early the changes in DKD. Despite its limitations, SWE imaging is a promising method that can be integrated with traditional laboratory methods in daily routine practice.

AUTHORS' CONTRIBUTIONS

RY: Conceptualization, Data curation, Investigation, Methodology, Writing – original draft. **FC:** Formal Analysis, Investigation, Writing – review & editing. **MY:** Formal Analysis, Methodology, Writing – review & editing. **FK:** Data curation, Resources, Writing – review & editing.

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