Renal cortical stiffness obtained by shear wave elastography imaging is increased in patients with type 2 diabetes mellitus without diabetic nephropathy

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Abstract

Purpose It is known that patients with type 2 diabetes mellitus (DM) who develop diabetic nephropathy have increased renal cortical stiffness (CS) determined by shear wave elastography (SWE). However, there is no data in the literature to our knowledge related to CS values determined by SWE in type 2 DM patients with normal renal function. In this study, we aimed to investigate the change of renal CS obtained by SWE examination in type 2 DM patients with normal renal function compared to non DM patients.

Methods A total of 103 patients (86 males, 17 females and mean age 63.2 ± 11.8 years) with or without type 2 DM were included in the study. The eGFR value of all patients was $> 60 \text{ ml/kg/1.73}^2$. Routine history, physical examination and laboratory examinations were performed. In addition to routine renal ultrasonography (USG), renal resistive index (RRI), renal pulsatility index (RPI), accelerated time (AT), and CS were measured.

Results Fifty patients with type 2 DM and 53 patients without type 2 DM were included in the study. Patients with type 2 DM had higher blood glucose, blood urea nitrogen and HbA1c levels ($p < 0.05$ each one). Renal length and width and echogenicity were similar between two groups with conventional renal USG. Renal parenchyma thickness was higher in patients with type 2 DM. When the findings of renal Doppler USG were examined, RRI was similar between two groups. RPI and AT were higher in patients with type 2 DM. CS values obtained with renal SWE were significantly higher in patients with type 2 DM ($p < 0.05$).

Conclusion Cortical stiffness value obtained by SWE is significantly higher in type 2 DM patients with normal renal function compared to patients without DM. We recommend CS measurement as part of routine screening of nephropathy in patients with type 2 DM and normal renal function to guide management and treatment plan.

Keywords Renal cortical stiffness · Shear wave elastography · Diabetes mellitus · Nephropathy

Sommario

Obiettivo I pazienti con diabete mellito di tipo 2 (DM2) che sviluppano nefropatia diabetica hanno un' aumentata stiffness (rigidità) renale corticale (CS) all' elastografia in modalità shear wave. Tuttavia, non ci sono dati in letteratura relativi a valori di CS in pazienti diabetici con funzione renale normale. In questo studio, abbiamo voluto indagare le differenze fra la CS di pazienti diabetici rispetto ai pazienti non diabetici.

Materiali e metodi Sono stati inclusi nello studio 103 pazienti (86 maschi, 17 femmine, età media $63,2 \pm 11,8$ anni), tra cui 50 diabetici (DM2) e 53 non diabetici. Il valore di eGFR di tutti i pazienti è risultato $> 60 \text{ ml/kg/1.732}$. A tutti i pazienti sono stati effettuati: raccolta dell' anamnesi, esame obiettivo, esami di laboratorio di routine, ecografia renale (USG), indice di resistenza renale (RRI), indice di pulsilità renale (RPI), tempo di accelerazione (AT), e stiffness corticale misurata con elastografia shear wave.

Risultati Nei 50 pazienti diabetici abbiamo riscontrato aumentata glicemia, azotemia, ed HbA1c ($p < 0,05$ ciascuno). Le dimensioni, l' ecogenicità e la RRI dei reni sono risultate sovrapponibili fra i due gruppi di pazienti, mentre lo spessore parenchimale, RPI, AT e CS con SWE ($p < 0.05$) sono risultati più elevati nei pazienti diabetici.

Conclusione La stiffness corticale ottenuta mediante SWE è significativamente maggiore nei pazienti diabetici con funzione renale normale rispetto ai pazienti senza DM, pertanto il nostro suggerimento è di includere la misurazione della stiffness con elastografia nello screening della nefropatia nei pazienti diabetici per guidarne la gestione e la terapia.

Introduction

Kidney disease is a major problem in patients with long-term type 2 diabetes mellitus (DM). The early pathophysiologic changes in cortical cells occur prior to developing clinical nephropathy [1]. The earliest histologic change is thickening of basal membrane which is followed by hyalinization of afferent and efferent arterioles in the next 3–5 years. There is increase in the mesangial volume in approximately 15 years of the disease onset [1]. Early diagnosis has prognostic significance in patients with DM since 20–30% of them develop nephropathy in long term [1].

Renal ultrasonography (USG) may reveal changes in kidney size, echogenicity and thickness of cortex which are confirmed in studies. Shear wave elastography (SWE) has become a frequently used technique recently and it has been started to use in patients with DM. Shear wave elastography is a non-invasive, cost-effective USG technique with consistent results [2–4]. Cortical stiffness (CS) determined by SWE correlates with renal parenchyma disease and fibrosis and it is not effected by systemic and demographic parameters [3–8]. Increase in renal CS determined by SWE is known to occur in patients with type 2 DM [4, 6, 9]. There is no information regarding the changes in CS in patients with type 2 DM who have normal kidney function in the current literature to our knowledge. Studies revealed that changes at the cellular level occur prior to diagnosis of abnormalities associated with nephropathy [1]. We suggested CS determined by SWE may indicate early changes at the cellular level prior to onset of nephropathy in patients with type 2 DM in our hypothesis.

We studied the differences in CS value using SWE in patients with type 2 DM compared to the patients without DM when the kidney functions are still normal.

Materials and methods

Patient enrollment

We enrolled 50 patients (40 male, 10 female with average age 63.1 ± 12.0) with type 2 DM without clinical nephropathy and 53 control patients without type 2 DM and nephropathy (46 male, 7 female with average age 63.4 ± 11.8). We excluded patients with type 2 DM who have reduced

eGFR (estimated Glomerular Filtration Rate) < 60 ml/dk/1.73 m² or > 30 mg/l proteinuria. Patients with coronary artery disease or history of myocardial infarction, significant cardiac valvular disease, respiratory or heart failure, active thyroid disease, chronic liver disease, hematological disorders, renal artery stenosis, history of nephrectomy, history of malignancy, bleeding diathesis, active infection, pregnancy are excluded.

We obtained renal USG (B mode, Doppler and SWE) in addition to lab analysis. This study followed the recommendations of ethical principles published in the Declaration of Helsinki developed by World Medical Association (WMA) and approved by local ethical committee. Informed consents were explained in details to patients and patients were enrolled only after obtaining written consents.

Risk factors were obtained after the detailed physical examinations. Demographic data included age, gender, presence of hypertension (HT) and hyperlipidemia, tobacco use, duration of DM and medications. Complete blood count, lipid profile, creatinine, blood urea nitrogen (BUN) and uric acid levels were obtained from all patients enrolled into study. We obtained weight, height measurements and calculated body mass index (BMI). We calculated eGFR using Modification of Diet in Renal Disease (MDRD) formula.

Renal ultrasonography

We obtained renal USG using high-resolution USG machine (Philips EPIQ 7) and 1–5 MHz high resolution convex probe (Philips Health Care, Bothell, WA, USA). Images were obtained at minimum of 6 h of fasting and at least 20 min of rest. Images were initially obtained with grey scale B-mode USG and then quantitative Doppler parameters were obtained. Kidney size, cortical thickness and parenchyma echogenicity were assessed in grey scale. Kidney length was measured between upper and lower poles of kidney. The distance between renal hilum and renal capsule was measured in the middle pole in coronal plane. Cortical thickness was measured between pyramid base of renal medulla in the middle and renal capsule.

Peak systolic velocity (PSV) in interlobular arteries, end diastolic velocity (EDV) and acceleration time (AT) were measured when Doppler angle was 30–60° in right and left kidneys. Spectral wave form was obtained manually after the PSV and EDV measurements and renal resistive index (RRI) value was obtained automatically with PSV–EDV/

PSV formula. Renal pulsatility index (RPI) is calculated on spectral wave form based on PSV–EDV/Mean flow rate formula. AT is the measured time between the onset of increased systole and first peak point. All measurements were obtained three times from right and left kidney. The mean values of RRI, RPI and AT values from right and left kidneys were recorded.

Shear wave elastography evaluation was obtained with 5–1 MHz convex abdomen probe using elastography point quantification (ElastPQ) technique. All measurements were obtained as explained previously [6]. Renal USG was performed in right and left lateral decubitus position. The least possible compression was applied to probe during USG and probe was placed in a stable condition and patients were asked to hold their breath for a few seconds to minimize kidney movement with respiration. The measurements were taken after ROI was placed on targets on traditional renal USG images (Figs. 1 and 2). ROI was placed vertically on a renal cortex area without vessels or cysts. The main axis of ROI was adjusted to be parallel to the axis of renal pyramid (vertical to kidney surface). ROI target distance was maximum 8 cm and ROI constant box size was 1–0.5 cm. The applied compression was minimized during imaging to prevent mechanical pressure on kidneys. The contralateral kidney was imaged with the same technique. We obtained six valid measurements for each kidney and calculated the mean value. If reliability of measurement is low, the result will be seen with 0.00 kPa. Result is given as kPa value. Subjects were evaluated by a single well experienced radiology specialist for conventional, Doppler and SWE examinations. Specialist had more than 5 years of experience in SWE studies and at least 500 SWE procedures in a year. All USG examination time was approximately 25–30 min.

Fig. 1 Cortical stiffness measurement by shear wave elastography in patients with type 2 DM. Increased shear wave velocity in 15.11 ± 8.81 kPa is displayed in the lower left corner

Fig. 2 Cortical stiffness measurement by shear wave elastography in patients without type 2 DM. Normal shear wave velocity in 2.23 ± 0.42 kPa is displayed in the lower left corner

Statistical analysis

All analyses were made using SPSS 22.0 (Chicago, IL, USA) statistical software. The distribution of continuous variables was evaluated and tested for being normal by Kolmogorov–Smirnov test. Continuous variables in group data were referred as mean $\pm$ standard deviation. Categorical variables were referred as number and percentiles. Student *t* test was used to compare continuous variables in groups. The Chi-square (χ^2) test was used to compare categorical variables. Pearson correlation analysis was used for single variable correlation analysis. Linear regression analysis was used to determine markers found in single variable analysis which were independent from parameters related to CS. It was determined as statistically significant if $p < 0.05$.

Results

All demographic parameters in two patient groups with and without type 2 DM were compared. Patients with type 2 DM had significantly elevated blood glucose, HbA1c and BUN levels and low hemoglobin levels compared to group of patients without type 2 DM (Table 1). Serum creatinine and eGFR levels were similar in two groups.

Patients with type 2 DM had larger cortical thickness and kidney size in B-mode renal USG compared to patients without type 2 DM (Table 2). Patients with type 2 DM had significantly higher RPI and AT levels in Doppler studies (Table 2). Whereas RRI was similar between two groups. CS level obtained with renal SWE technique was significantly higher in patients with type 2 DM compared to the patients without type 2 DM (Table 2).

Table 1 Baseline characteristics and laboratory parameters in patients with and without type 2 DM

	Patients with type 2 DM <i>n</i> = 50	Patients without type 2 DM <i>n</i> = 53	<i>p</i>
Age (years)	63.1 ± 12.0	63.4 ± 11.8	0.893
Gender (male)	40	46	0.254
Office systolic BP (mmHg)	130.3 ± 12.2	126.5 ± 10.7	0.105
Office diastolic BP (mmHg)	85.4 ± 9.5	84.5 ± 8.2	0.573
Heart rate (beat/min)	77.9 ± 11.3	77.9 ± 10.8	0.999
BMI (kg/m ²)	30.0 ± 2.2	29.1 ± 2.12	0.022
Smoking, <i>n</i> (%)	19 (38%)	22 (41.5%)	0.436
Hypertension, <i>n</i> (%)	24 (48%)	22 (41.5%)	0.321
Hypercholesterolemia, <i>n</i> (%)	14 (28%)	13 (24.5%)	0.430
DM diagnosis time (years)	8.30 ± 3.36	–	–
Oral anti-diabetic therapy, <i>n</i> (%)	38 (72%)	–	–
Insulin therapy, <i>n</i> (%)	26 (52%)	–	–
Glucose (mg/dl)	230.3 ± 73.1	104.2 ± 12.9	< 0.001
HbA1c (%)	7.8 ± 1.7	5.6 ± 0.5	< 0.001
BUN (mg/dl)	39.3 ± 11.5	34.8 ± 9.9	0.045
Creatinine (mg/dl)	0.81 ± 0.19	0.80 ± 0.13	0.813
eGFR (ml/min/1.73 m ²)	97.0 ± 24.8	97.3 ± 20.1	0.942
Total cholesterol (mg/dl)	197.9 ± 64.4	181.5 ± 31.4	0.174
LDL cholesterol (mg/dl)	118.5 ± 43.7	112.3 ± 27.7	0.510
HDL cholesterol (mg/dl)	42.9 ± 6.8	39.8 ± 6.2	0.422
Triglyceride (mg/dl)	172.3 ± 156.4	129.4 ± 55.2	0.140
hs-CRP (mg/l)	2.81 ± 4.1	2.59 ± 4.4	0.530
White blood cell count (1000/mm ³)	11.7 ± 3.4	10.8 ± 3.2	0.102
Hemoglobin (g/dl)	12.5 ± 1.57	13.5 ± 1.7	0.001

BUN blood urea nitrogen, *BMI* body mass index, *DM* diabetes mellitus, *eGFR* estimated glomerular filtration rate, *HDL* high density lipoprotein, *hs-CRP* high sensitive C reactive protein, *LDL* low density lipoprotein

Table 2 Conventional, Doppler renal ultrasound and shear wave elastography imaging parameters in patient with and without type 2 DM

	Patients with type 2 DM <i>n</i> = 50	Patients without type 2 DM <i>n</i> = 53	<i>p</i>
Renal resistive index	0.77 ± 0.09	0.75 ± 0.08	0.237
Renal pulsatility index	2.19 ± 0.87	1.82 ± 0.49	0.008
Renal acceleration time (m/s)	93.9 ± 40.9	113.1 ± 52.4	0.043
Kidney length (mm)	103.3 ± 10.1	102.4 ± 7.8	0.623
Kidney width (mm)	49.9 ± 6.8	48.9 ± 5.3	0.408
Cortical thickness (mm)	12.2 ± 1.9	11.4 ± 2.4	0.048
Cortical echogenicity grade 0–I–II–III, <i>n</i>	27–19–4–0	32–15–6–0	0.429
Cortical stiffness (kPa)	9.86 ± 3.66	7.92 ± 1.96	0.001

DM diabetes mellitus

There was a negative correlation between CS and BUN level ($r = -0.292$, $p = 0.044$). We found positive correlations between renal CS, duration of DM ($r = 0.312$, $p = 0.028$), hs-CRP ($r = 0.338$, $p = 0.016$) and cortical thickness ($r = 0.306$, $p = 0.046$). Renal cortical thickness and duration of DM were independent determinants of CS level in linear regression analysis (Table 3, Figs. 3 and 4).

Discussion

The most important result of our study was high CS levels in SWE evaluation of patients with type 2 DM who do not have signs of diabetic nephropathy. Average CS value was 9.1 kPa in these group of patients. There were also

Table 3 A linear regression analysis for parameters significantly correlated cortical stiffness

	Cortical stiffness	
	<i>p</i>	β
Renal cortical thickness (mm)	0.007	0.362
DM diagnosis time (years)	0.004	0.385

DM diabetes mellitus

Fig. 3 There is significant correlation between renal cortical thickness and cortical stiffness **Fig. 4** There is significant correlation between Tip II DM diagnosis time and cortical stiffness

independent correlations between CS values in SWE tests and renal cortical thickness and duration of type 2 DM. This is the first study to our knowledge which revealed increased CS values in SWE evaluation of patients with the type 2 DM who did not develop any clinical signs of nephropathy.

Certain conventional renal USG findings may indicate parenchymal disease in kidney such as decreased kidney size, decreased cortical thickness, and increased echogenicity in cortex. CS values obtained in SWE tests have been more popular recently [6]. The limitations of SWE are inconsistent availability of the test in clinics, absence of standardized normal values of CS in patient group. Renal SWE findings are not documented in routine USG results and CS values are measured only in specific diseases and studies. SWE is a cost effective, reliable and non-invasive USG test which can be used to determine tissue elasticity [2]. CS values are given as kPa [2–4]. Renal parenchymal fibrosis is the most important sign of kidney disease and it causes changes in mechanical features of kidneys which can be measured objectively with SWE [6]. It has been shown that renal SWE evaluation is useful in determination of renal fibrosis, diagnosing rejection of renal allograft, staging diabetic nephropathy and in patient with chronic kidney disease (CKD) [3, 4, 6–8, 10].

Hassan et al. [6] found significant decrease in renal cortical thickness in a study including patients with diabetic nephropathy. It was documented that renal cortical thickness was smaller in grade 4 CKD compared to grade 3 CKD in the same study. We found increased cortical thickness in patients with type 2 DM and normal kidney function compared to control group in our study. This finding supports the study results by Soldo et al. in the literature [11]. There is an increase in the cortical parenchyma thickness as a result of hyper-filtration in the asymptomatic nephropathy stage and significant decrease occurs in the following stages. We also found increased cortical thickness in patients with type 2 DM without nephropathy.

The CS change obtained by SWE has begun to be used in diabetic nephropathy recently, there are conflicting results with increase and decrease in stages and there is no clear data on the limit value. Similarly, there is no clear evidence regarding CS values measured with SWE in patients with type 2 DM with and without nephropathy. Hassan et al. [6] found CS values as 30.4 ± 16.2 , 14.6 ± 8.1 and 9.02 ± 2.42 kPa in 15 patients with grade 4 CKD due to DM, 14 patients with grade 3 CKD and 23 healthy control patients, respectively. We found CS values as 9.86 ± 3.66 and 7.92 ± 1.96 kPa in 50 patients with type 2 DM and 53 patients in control group, respectively. In another study, CS values measured with SWE were 2.87, 3.14, 2.95, 2.68, 2.55 m/s in grade 1, 2, 3, 4 and 5 CKD patients, respectively and 2.35 m/s in the control group [4]. In this particular

study, CS values were found to be higher in patients with nephropathy compared to control group. However, advanced grade (grade 3–5) patients had lower CS values which were inconsistent to the results found by Hassan et al. [6]. The results are controversial and open the discussions. The relationship between increased CKD stage and fibrosis is clearly known, increased CKD stage and reduced CS in this study are debatable [4]. In a similar study to ours which included 3 group of type 2 DM patients with normal urine, microalbuminuria, macro albuminuria and fourth group as a control group revealed increased CS values correlating with microalbuminuria [9]. Yu et al. [9] compared 30 healthy control patients with 50 type 2 DM patients without albuminuria and found CS similar values in these two groups [9]. These results are not consistent with ours. In this study by Yu et al. [9] the average age in patient group was one decade lower and interestingly similar blood glucose and HbA1c levels were present in patients in the control group and the other patients with any degree of albuminuria. We found smaller kPa values in the control group patients compared to the previous study [6]. In our study, the most important reasons for achieving these different border values were due to the use of a new method point ElastPQ with a high-quality device (Philips Epiq 7) in a different patient population. Especially in point ElastPQ, which has a few data in liver elastography, lower kPa value is obtained than other elastography studies and in our study lower kPa values may be associated with this new method than the previous study [12].

The studies revealed close correlation with increased CS levels and BUN, creatinine, eGFR, urine albumin/creatinine ratio and urine micro albumin level in patients with diabetic nephropathy [4, 6, 9]. We did not find significant correlation between CS and eGFR since we excluded patients with $\text{eGFR} < 60 \text{ ml/kg/1.73}^2$ and/or microalbuminuria in the urine. We found inverse relationship between BUN and CS levels similar to previous study. There was a significant and independent correlation between duration of DM and increase in renal cortical thickness and increase in CS. Cortical stiffness increase occur as a result of nephropathy occurring in long-term DM [1]. The correlation between increase in renal cortical parenchymal thickness and CS is due to increase in CS from hyper-filtration and nephron hypertrophy.

There is no study in the literature evaluating CS values measured with SWE in patients with type 2 DM without signs of diabetic nephropathy to our knowledge. We found increased CS values measured with SWE in patients with type 2 DM and normal kidney function compared to control group without DM and normal kidney function. We could explain this due to pathophysiologic changes in kidneys prior to developing nephropathy or having reduced GFR.

One of the most important goal in DM management is preventing nephropathy due to DM. Blood glucose and

blood pressure control are mainstay of treatment to achieve this goal, however, it is still difficult to prevent this complication. Metabolic abnormalities results in increased glucose, lipid levels, glycolized lipid, reactive oxygen products which triggers increased production of inflammatory cytokines and fibrosis [13–15]. The damage occurs in mesangial, endothelial and epithelial cells and glomerulosclerosis and tubulointerstitial fibrosis occur in nephropathy. The most important characteristic feature is interstitial fibrosis in nephropathy due to DM [16]. It is important to determine changes in mesangium, endothelial and epithelial cells in early fibrosis levels prior to developing nephropathy. Early determination of microalbuminuria is important in early diagnosis of diabetic nephropathy [17, 18]. Histological examination with renal biopsy reveals the ongoing fibrosis clearly but cannot be used because being an invasive examination. For this reason, noninvasive examinations have been preferred. Detection of microalbuminuria is a strong predictor of DM-associated nephropathy and the urine microalbuminuria is important for the earliest diagnosis of CKD development [17, 18]. However, in addition to type 2 DM, microalbuminuria is affected by HT, exercise and blood glucose levels and may vary by 40–50% during the day [19]. Because of that, a more objective and stable parameter is needed for the early diagnosis of patients with CKD. SWE is a promising and non-invasive study that shows the renal elasticity or tissue stiffness objectively and can be used for this purpose, CS increase in type 2 DM without DM-associated nephropathy patients compared to the control group in our study may be associated with excessive hyper filtration at the nephron levels or fibrosis that occurs at cellular and mild interstitial level. For this reason, increased CS and early fibrosis in DM patients may be shown with a non-invasive examination, allowing closer follow-up and more aggressive treatment in this patient group.

Limitations

This study has significant limitations. The number of patients enrolled in this study was small and further studies with larger number patients are required. There are two groups of patients including patients with normal kidney function and with or without type 2 DM. We suggest having further studies including patients with DM and nephropathy as third group.

In our study, the average CS value was 9.1 kPa in type 2 DM patients without nephropathy. However, in different studies for patients with type 2 DM and controls, different limit values for renal CS are obtained with different patient groups, devices and techniques. To achieve an acceptable limit value, the number of studies done and the number of patients taken in studies should be increased and standardized. Tissue diagnosis is the gold standard in many

circumstances. However, it was unethical to obtain kidney biopsies and explore the correlation with our study results. We suggest, possible animal studies in the future to include histopathologic evaluation of kidney tissues. Another important limitation of our study is this is not a follow-up study. Especially if patients with high renal CS value were followed up in terms of nephropathy development, they could give information about the relation of high CS value to development of DM-related nephropathy in the future. This study only included patients with ROI target distance less than 8 cm and renal cortical thickness higher than 1 cm.

Conclusion

The results in this study indicated that CS values obtained with SWE were significantly higher in patients with type 2 DM compared to the patients without type 2 DM when the kidney functions are still normal. CS value increases prior to developing nephropathy in patients with type 2 DM. We recommend obtaining CS measurements with SWE and USG as part of routine screening of renal disease in patients with type 2 DM.

Compliance with ethical standards

Conflict of interest We have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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