

Renal vascular Doppler ultrasonographic indices and carotid artery intima-media thickness in diabetic nephropathy

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Abstract

Introduction: Diabetes is one of the common causes of renal insufficiency and is responsible for about one third of cases requiring renal transplantation. Conventional sonography provides limited information regarding the severity and prognosis of disease. The present study was carried out to evaluate the renal vascular Doppler indices role in determining renal dysfunction and carotid artery atherosclerosis. **Methods:** Fifty five patients with diabetic nephropathy (albuminuria more than 300mg/24 hours) were enrolled into this cross-sectional study. Renal interlobar arterioles were studied using resistive (RI) and pulsatility (PI) indices of Doppler ultrasonography, in addition to conventional kidney length and renal parenchyma thickness. Intima-media thickness of common carotid artery (CCIMT) was also assessed just before the bifurcation. Serum creatinine (sCr), urine albumin and lipid profile were measured using standard methods. Estimated glomerular filtration rate (eGFR) was calculated by the Modification of Diet in Renal Disease formula. **Results:** The renal interlobar arterioles' RI was positively and linearly correlated with the sCr and albuminuria levels ($P<0.039$ $r=+0.320$ and $P=0.047$, $r=+0.287$). There were negative linear correlations between eGFR and the renal interlobar arterioles' RI ($P<0.001$, $r=-0.539$) and PI ($P<0.045$, $r=-0.328$). The mean CCIMT was more than 0.7 mm in 90% of the studied patients. No correlation was found between CCIMT and renal ultrasonographic and Doppler findings. **Conclusion:** Although Doppler ultrasonographic indices of renal interlobar arterioles show the severity of renal dysfunction in patients with diabetic nephropathy, these indices do not have any advantage over the simple and cost effective biochemical parameters.

Keywords: Doppler sonography, Diabetic nephropathy, Diabetes, resistive index, pulsatility index, carotid artery, intima-media thickness

Introduction

Diabetes is regarded as one of the prevalent risk factors for renal dysfunction and the main cause of renal insufficiency worldwide. About 25-41% of diabetic pa-

tients develop renal insufficiency after 25 to 30 years and this population constitutes one third of patients demanding renal transplantation [1,2].

Serum biochemistry findings such as creatinine and urea are used for screening the renal function and diagnosis of dysfunction. Despite the fact that conventional gray scale ultrasonography (US) is usually used as an initial imaging approach, ultrasonographic findings still have not found their true role in routine evaluation of diabetic patients, or studying progression of diabetic nephropathy. Although increased glomerular filtration rate leads to ultrasonographically detectable increased kidney size during the initial stages of the disease, the progress of the diseases and nephrosclerosis decrease parenchyma

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thickness and kidney length later [3]. Collectively, limited sensitivity and accuracy has been shown for these US changes which brings the value of US in determining the disease prognosis under question [4-8]. Eventually, the developing of Doppler technology has increased the probability of finding a relationship between Doppler indexes and the diseases' complications. Limited numbers of studies have reported Doppler findings of patients with diabetic nephropathy yet [9,10]. Studying changes related to diabetic nephropathy, determining disease progress and prognosis, and prediction of the complications through Doppler US can be mentioned as objectives of a recent published study [11] and are also among the objectives of this study. The present study tried to identify the possible relationship between renal interlobar arterioles flow changes and carotid artery atherosclerosis, based on studying Doppler indices of renal interlobar arterioles and determining intima-media thickness of common carotid artery.

Material and methods

Study protocol and population

In this descriptive-analytical study 55 patients with diabetic nephropathy (albuminuria > 300mg/24 hours) were evaluated during one year in the Tabriz Imam Hospital. The protocol of this study was approved by the Ethics Committee of the Tabriz University of Medical Sciences and was in compliance with the Declaration of Helsinki. Informed consent was obtained from all the participants.

To eliminate potential confounding factors, we included only patients with type 2 diabetes mellitus and albuminuria levels lower than the nephrotic range (< 3 g/dl) whose estimated glomerular filtration rate (eGFR) was higher than 30 mL/min/1.73m² (as calculated by the Modification of Diet in Renal Disease formula [11]). The fasting plasma glucose (FPG) of the participants was under the control of insulin injection and/or administration of oral sulfonylurea. Blood pressure (BP) was maintained at less than 129/79 mm Hg with treatment by angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers, with α -blockers and diuretics when needed. All of the patients were under their own regular restricted protein diet (≤ 0.8 g/kg/d), as prescribed by a nutrition consultant.

Exclusion criteria were the presence of any major changes in blood pressure, detection of stenosis in main and accessory renal arteries or coarctation of aorta, higher protein intake, recent extensive physical activity, active smoking, chronic inflammation (such as diabetic foot, hepatitis, infection, etc), active coronary artery dis-

ease in the previous one month (diagnosed by symptoms and electrocardiography), and poorly controlled diabetes mellitus (Hb-A1c > 7.5%).

Ultrasonography study

Hitachi EUB-525 Doppler US machine (Hitachi company, Japan) equipped with two types of probes was used in this study. Frequencies of the curved probes were 2.5 and 3.5 MHz, respectively and frequencies of the linear probes were 5 and 7.5 MHz, respectively. Maximum measurable Doppler shifts were 8 kHz and 10 kHz for the curved and linear probes, respectively.

The measured US parameters were: a) length of kidney and renal parenchymal thickness (mm), measured on both sides and averaged, b) renal interlobar arterioles resistance rate using resistive index (RI) and pulsatility index (PI) and also present of stenosis, and c) common carotid artery intima-media thickness (CCIMT), the mean of right and left sides (mm).

Right and left kidneys were evaluated at abdominal right and left anterolateral profile. Parenchyma thickness was preferably measured at transversal profile and pelvis level (normal range: 6-10 mm) [12]. RI was calculated using $RI=(S-D)/S$ formula where S stands for systolic speed and D demonstrates minimum diastolic speed. Numerical value of RI varies from zero to one. RI was calculated using $PI=(S-D)/M$ formula where M equals mean velocity, i.e. $M=(S+2D)/3$ (the normal value is ≈ 0.60 with 0.70 being around the upper limits of normal) [13]. Renal interlobar arterioles were evaluated using Doppler US by obtaining RI and PI through receiving the wave and drawing the related spectrum at upper, middle, and lower zones. The difference of RI rate between different parts of a kidney was about 4.8% and can be overlooked. To measure CCIMT, US of the left and right common carotid arteries was performed with a 7.5-MHz linear-array transducer 1-2 cm proximal to the bulb. The final CCA-IMT value was defined as the mean of the both sides. CCA was considered as the final CCIMT, calculated from 10 measurements on each side, CCIMT <0.80 mm was considered normal.

Biochemical Analysis

The patients were asked to fast for 12 hours. Blood samples were taken before the patients' morning breakfast and were collected in sterile tubes, centrifuged at 3,000 rpm for 10 minutes at 4°C and then stored at -79°C until final assay. Urine samples were collected for 24 hours to measure albuminuria and urine creatinine levels.

Serum levels of FPG, total cholesterol (Chol), high-density lipoprotein cholesterol (HDL), and triglyceride (TG) were determined using commercial reagents with an automated chemical analyzer (Abbott analyzer, Abbott Laboratories, Abbott Park, Chicago, Illinois,

USA). Low-density lipoprotein cholesterol (LDL) levels were calculated using the Friedewald equation [14]. Serum and urine creatinine (sCr and uCr) levels were determined by the Jaffe method [15] eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) formula [11] (normal ranges of sCr for adult males: 0.5–1.2 mg/dl, adult females: 0.4 – 1.1 mg/dl and for uCr 20-25 mg/kg/day for adult males and 15-20 mg/kg/day for adult females). Twenty-four hour urine samples were collected and Cr and albumin levels were assessed using colorimetric and immunoturbidimetric methods.

Statistical analysis

Finally, data from 55 patients with diabetic nephropathy were collected (power 0.80 and significance 0.05) and analyzed using SPSS 16 software package for windows (SPSS Inc., Chicago, USA). The data were presented as mean \pm standard deviation (SD) or frequency (%). Distribution of variables was determined by Skewness, Kurtosis and Kolmogorov-Smirnov Z tests. Pearson correlation test was used to study the linear correlation of variables. In this study, P value less than 0.05 was considered significant.

Results

Fifty-five patients were included in the study (39 male, 16 female). Their mean age, systolic and diastolic blood pressures were 58.3 \pm 8.8 years, 122.4 \pm 21.6, and 81.9 \pm 4.5 mmHg, respectively.

The results of the biochemical parameters are listed in Table I. sCr was more than 1.5mg/dl in only 11% of the patients. The US results are shown in Table II. Out of 55 studied cases, 31 ones (56%) had RI>0.7.

There was a moderately negative linear correlation between the sCr and the kidney length (P=0.023, $r=-0.306$). Also, a moderate positive linear relationship between the kidney length (P<0.001, $r=+0.366$) and eGFR was obtained. No relationship between the length of the kidney, albuminuria, lipid profile, and uric acid levels was found.

No linear correlation between the renal parenchymal thickness and sCr (P=0.170), eGFR (P=0.188), albuminuria (P=0.274), lipid profile and uric acid levels was found. There was moderate positive linear correlation between RI and sCr level with correlation coefficient of $r=+0.320$ (P<0.039). Also, a negative and strong relationship between RI and eGFR was shown (P<0.001, $r=-0.539$). RI rate was positively and linearly correlated with albuminuria level with correlation coefficient of $r=+0.287$ (P=0.047). Data analysis failed to demonstrate any relationship between RI and lipid profile including

Table I. Biochemical findings of serum and urine analysis.

	Mean \pm SD	Minimum	Maximum
FPG (mg/dl)	159.1 \pm 37.5	97	210
Cholesterol (mg/dl)	247.5 \pm 43.3	145	393
Triglyceride (mg/dl)	263.7 \pm 94.9	113	750
HDL (mg/dl)	46.0 \pm 5.3	34	69
LDL (mg/dl)	115.8 \pm 45.9	78	187
Uric acid (mg/dl)	6.9 \pm 2.7	4.8	11
sCr (mg/ml)	1.65 \pm 0.41	0.7	1.8
eGFR (ml/min)	67.4 \pm 20.5	36	102
Albuminuria (mg/day)	1358.2 \pm 572.8	650	2980

SD: Standard deviation, FPG: Fasting plasma glucose, HDL: High density lipoprotein, LDL: Low density lipoprotein, sCr: Serum creatinine

Table II. Ultrasonographic findings of the study group.

Variables	Mean \pm SD	Range	
		Min	Max
Conventional sonography			
Kidney length (mm)	113.8 \pm 2.4	87	155
Kidney cortex thickness (mm)	6.5 \pm 0.8	9.4	14
Renal Doppler			
RI	0.7 \pm 0.4	0.4	1.0
PI	1.5 \pm 0.9	0.2	2.9
Carotid sonography			
Intima-Media thickness (mm)	1.0 \pm 0.2	0.7	1.3

SD: Standard deviation, RI: Resistive index, PI: Pulsatility index .

Chol, TG, HDL and LDL, and uric acid level. Additionally, there was a reverse but weak negative linear relationship between PI and eGFR (P<0.045, $r=-0.328$), but no relationship with sCr, albuminuria, lipid profile including Chol, TG, HDL and LDL, and uric acid level. Also, we found no relationship between the length of the kidney and renal parenchymal thickness and Doppler RI and PI (P=0.656 and 0.722).

CCIMT was measured more than 0.8 in 90% of the patients and more than 1.2 in 73% of the patients. Atherosclerotic plaques were identified in 24 (43%) of patients. There was no relationship between CCIMT and sCr, eGFR, albuminuria, lipid profile and uric acid levels. Also statistical analysis could not show any relationship between CCIMT and length of kidney, renal parenchymal thickness, RI, and PI.

Discussion

The present study's results demonstrated that the Doppler indices of renal interlobar arterioles (RI and PI) are linearly related to the biochemical parameters which show the renal function in patients with diabetic nephropathy. These biochemical parameters include sCr, eGFR and albuminuria levels. No correlation was found between CCIMT and renal conventional US and Doppler findings.

Diabetes as a common cause of renal insufficiency is associated with a decrease of kidney length in advanced stages [16] which is shown by increased sCr level and decreased eGFR in the current study. The negative correlation of sCr and positive correlation of eGFR with kidney length suggest that decrease of kidney length might be an indicator of worsening the renal function based on increasing the sCr and diminishing the eGFR in patients with diabetes nephropathy. However, there was no relationship between the albuminuria rate and the kidney length. The findings are in accordance with results of previous studies [17,18].

Considering mean normal range of renal parenchymal thickness, i.e. 8 mm (normal thickness varies between 6 and 10 mm [19], a meaningful difference was found between these patients and the normal range (difference of 0.99 mm).

The renal artery stenosis is regarded as a prevalent complication in patients with diabetic nephropathy [20] and the use of RI and PI indices are important in the detection of this complication. In our study we observed that the variation range of RI was less than that of PI. These findings could correspond with the Ito et al study [21]. They demonstrated that RI efficiency in determining renal involvement severity was more than PI. The maximum median of RI in normal subjects has been reported 0.66 to 0.70. Considering 0.70 as the upper limit of reported median RI, it can be stated that the mean RI of the patients with diabetic nephropathy is 0.04 higher than the maximum reported median for normal people. In other words, RI of 56% of the studied patients was higher than the normal range in this study. Yilmaz et al [22] showed that the RI of diabetic patients with and without renal insufficiency was higher than the control group. Increase of RI is seen in patients with and without increase of sCr but the increase ratio is higher in patients with renal insufficiency. The result corresponds with the Milovanceva-Popovska et al [23] study evaluating different renal diseases. Also, in our study, by increasing of sCr level, the RI is also increased. The findings are in accordance with results of previous studies [24]. Increase of RI may be attributed to glomerular atherosclerotic

variations resulting in increasing resistivity against blood flow of the afferent vessels. Decrease of eGFR results in an increase of RI and PI. There is a high correlation with RI as such that an increase of RI correctly refers to renal dysfunction. The result is similar to the results of previous studies with correlation coefficient of -0.630 and -0.80, respectively [25, 26]. Contrary to other laboratory findings, we found a negative relationship between PI and eGFR. The relationship was weaker than RI. Therefore, RI could be regarded as the main Doppler index in evaluating renal function.

CCIMT in 90% of the patients was over the normal range (0.7 mm). However, we found no statistically significant relationship between the CCIMT and the severity of diabetic nephropathy, albuminuria, conventional and Doppler US findings. The observation is in contrast with a previous published study [27] and can be attributed to the difference in the severity of diabetic nephropathy and the presence of renal failure in the study group

As a limitation of this study, a part of the results can be attributed to the diet used by patients (generally recommended in diabetic patients) and lipid modifying medications used by patients and not recorded in our study. Increasing the sample size, studying the carotid artery thickness details using dedicated US software, and concomitant quantification of the atherosclerotic plaques would achieve more information. Also, designating a control group and considering inter-observer and intra-observer variations in Doppler studies will result in more accurate conclusions.

In conclusion, although Doppler US indices of renal interlobar arterioles showed the renal hemodynamic changes and the severity of renal dysfunction in patients with diabetic nephropathy, these indices do not have any advantage over the simple and cost effective biochemical parameters. Furthermore, changes of the renal interlobar arterioles hemodynamic seem to occur independently from the atherosclerotic process of carotid artery.

Conflict of interest: none

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