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Remember Diabetes Mellitus When Assessing Renal Blood Flow in Hypertensive Patients: A Renal Frame Count Study

Hipertansif Hastalarda Renal Kan Akışını Değerlendirirken Diabetes Mellitus Unutulmamalıdır: Bir Renal Çerçeve Sayım Çalışması

ORIGINAL ARTICLE
KLİNİK ÇALIŞMA

ABSTRACT

Objective: Diabetes mellitus (DM) progresses with dynamic changes in renal blood flow and glomerular filtration. Renal frame count (RFC) is a cineangiographical parameter that is capable of presenting microvascular and macrovascular changes in the renal blood flow. We aimed to show the changes, which may be caused by DM in the perfusion, by using RFC.

Methods: A total of 110 hypertensive subjects consisting of 55 DM patients and 55 non-DM patients, as a control group who underwent renal angiography, were retrospectively enrolled in the study. The RFC values of all subjects were calculated and compared to each other.

Results: There were no significant differences between the two groups in terms of basal demographic characteristics and antihypertensive medications. The RFC value measured from the left renal artery was significantly lower in the DM group compared to the control group (11.33 ± 2.55, 13.49 ± 3.24, respectively; *P* <0.001). The RFC value measured in the right renal artery was detected to be significantly lower in the DM group than in the control group (11.07 ± 2.43, 13.33 ± 3.07, respectively; *P* <0.001). The mean RFC value was also significantly lower in the DM group compared to the control group (11.20 ± 2.18, 13.41 ± 2.84, respectively; *P* <0.001). In the multivariable linear regression analysis conducted to determine the variables which may affect mean RFC, it was determined that only the HbA1C level had a relation with the mean RFC value.

Conclusion: To the best of our knowledge, this is the first study to show the influence of DM on RFC. The RFC seems to decrease in DM subjects.

Keywords: Diabetes mellitus, renal blood flow, renal frame count

ÖZET

Amaç: Diabetes mellitus (DM), renal kan akışında ve glomerüler filtrasyonda dinamik değişikliklerle ilerler. Renal çerçeve sayısı (RFC), renal kan akışındaki mikrovasküler ve makrovasküler değişiklikleri gösterebilen sineanjiyografik bir parametredir. Bu çalışmada biz DM'nin renal perfüzyonda neden olabileceği değişiklikleri RFC kullanarak göstermeyi amaçladık.

Yöntemler: Çalışmaya renal anjiyografi yapılan 55 DM hastası ve 55 DM olmayan hasta olmak üzere toplam 110 hipertansif olgu retrospektif olarak alındı. Tüm deneklerin RFC değerleri hesaplandı ve birbirleriyle karşılaştırıldı.

Bulgular: Bazal demografik özellikler ve antihipertansif ilaçlar açısından iki grup arasında anlamlı fark yoktu. Sol renal arterden ölçülen RFC değeri DM grubunda kontrol grubuna göre anlamlı derecede düşüktü. (sırasıyla 11,33 ± 2,55, 13,49 ± 3,24; *P* <0,001). Sağ renal arterden ölçülen RFC değeri DM grubunda kontrol grubuna göre anlamlı derecede düşük saptandı (sırasıyla 11,07 ± 2,43, 13,33 ± 3,07; *P* <0,001). Ortalama RFC değeri de DM grubunda kontrol grubuna göre anlamlı olarak daha düşüktü (sırasıyla 11,20 ± 2,18, 13,41 ± 2,84, *P* <0,001). Ortalama RFC'yi etkileyebilecek değişkenleri belirlemek için yapılan çok değişkenli lineer regres-

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yon analizinde, ortalama RFC değeri ile sadece HbA1C düzeyinin ilişkisi olduğu belirlendi.

Sonuç: Bildiğimiz kadarıyla bu çalışma DM ile RFC arasındaki ilişkiyi araştıran ilk çalışmadır. DM hastalarında renal kan akımındaki artışa paralel olarak RFC azalmaktadır. RFC'nin klinik kullanımında bu ilişki dikkate alınmalıdır.

Anahtar Kelimeler: Diabetes mellitus, renal çerçeve sayısı, renal kan akımı

Diabetes mellitus (DM) leads to microvascular and macrovascular complications and affects almost the entire vascular system in the human body. The pathological changes associated with diabetic nephropathy (DN) in kidneys may occur associated with the atherosclerotic lesions of intrarenal and extrarenal arteries or associated with microangiopathic changes in glomerular capillaries, afferent arterioles, and efferent arterioles. Therefore, DN is a well-known microvascular complication of diabetes.[1]

Renal blood flow changes are variable depending on the stage of DN and even while the DN phase is not clinically begun (hyperfiltration), it may evaluate with various modalities. For this purpose, nuclear scintigraphy,[2] computerized tomography (CT),[3] positron emission tomography (PET),[4] magnetic resonance imaging (MRI),[5] and Doppler ultrasonography have been used to assess renal blood flow.[6] The most frequently used among these imaging modalities is the resistive index measurement with Doppler ultrasonography, and this presents conflicting results in many studies.[7]

ABBREVIATIONS

ACEi	Angiotensin-converting enzyme inhibitors
ARB	Angiotensin receptor blocker
BMI	Body mass index
BUN	Blood urea nitrogen
CCB	Calcium channel blocker
CI	Confidence interval
CT	Computerized tomography
DBP	Diastolic blood pressure
DM	Diabetes mellitus
DN	Diabetic nephropathy
EF	Ejection fraction
eGFR	Estimated glomerular filtration rate
GFR	Glomerular filtration
HDL	High-density lipoprotein
HT	Hypertension
LDL	Low-density lipoprotein
MRI	Magnetic resonance imaging
OR	Odds ratio
PET	Positron emission tomography
RFC	Renal frame count
RRI	Renal resistive index
SBP	Systolic blood pressure
TIMI	Thrombolysis in myocardial infarction
TTE	Transthoracic echocardiography

Invasive angiographical imaging is still the gold standard for the evaluation of vascular structures. In the evaluation of the perfusion, the methods which do not require additional costs to angiographic imaging were considered, and Thrombolysis in Myocardial Infarction (TIMI) frame count is one of them.[8] The evaluation of renal blood flow with a method similar to the one used in coronaries had been a subject of research recently. This method, which is called renal frame count (RFC), is considered a good perfusion marker in patients who had percutaneous intervention in the renal artery.[9] It was shown that this flow variation in the renal artery may be affected by the plaque composition leading to obstruction[10] and the hypertensive condition of the patients.[11] Various cut-off values have been proposed by researchers for successful revascularization and good renal perfusion.[10,12] However, the effect of renal perfusion changes on RFC in DM patients is unclear. The DM status was ignored in these interpretations and may be an important confounder in the results obtained.

In this study, we aimed to determine the association between DM and RFC by measuring RFC in diabetes patients without renal insufficiency or obstruction in the renal artery.

Methods

Study Population

In this study, the patients diagnosed with uncontrolled hypertension and evaluated with renal angiogram in our university hospital between 2015 and 2019 were screened retrospectively. Patients with more than 30% stenosis in the renal artery, chronic kidney failure (glomerular filtration rate [GFR] <60 ml/min/m^2), previous renal artery disease, history of a renal stent, or renal artery anomalies were excluded from the study. Fifty-five DM patients from the remaining population that were suitable for the study were enrolled in the study and then 55 age and sex-matched non-diabetic patients were enrolled in the study as a control group (Figure 1).

Local ethics committee approval was obtained for the retrospective study (CUTF: 2020-06/09). Consent from the participants was obtained through telephonic interaction.

Angiography

All angiographic imaging was performed with the Philips Allura Xper Percutaneous Coronary Intervention system. Renal

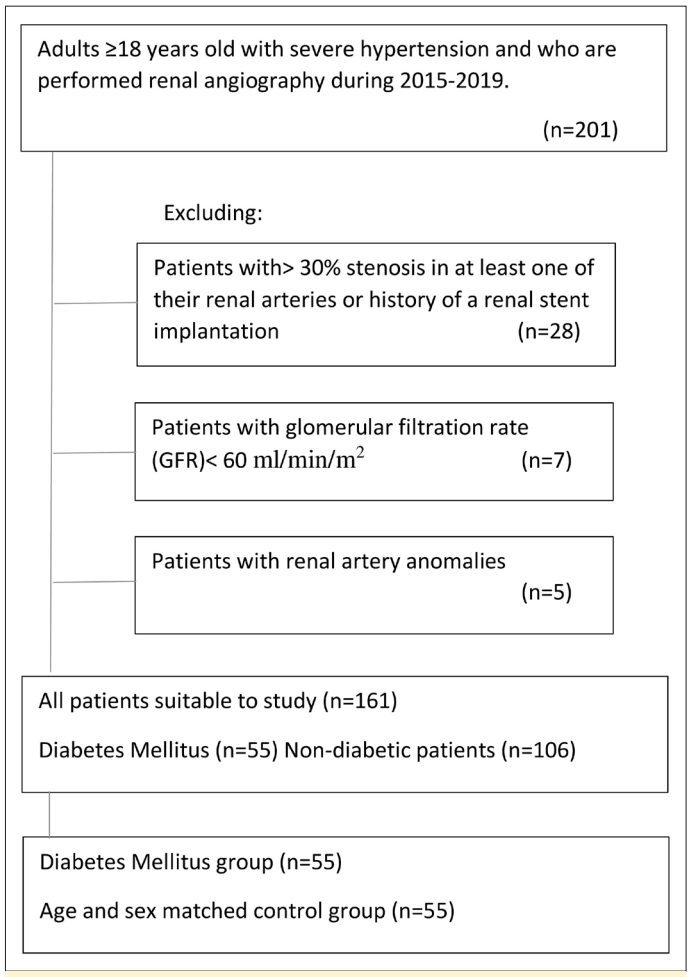


Figure 1. Patient flow diagram.

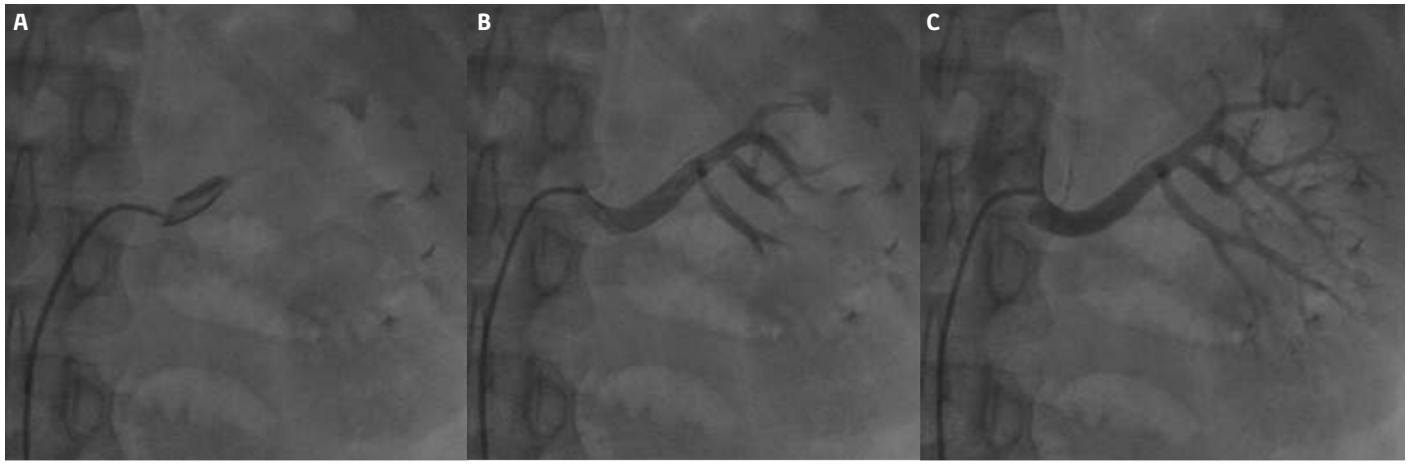
angiography was performed by 6F Right Judkins catheters at 15 frames/sec for both the left and right renal arteries and an iso-osmolar contrast media was used. The RFC was measured according to the method described by Mulumudi et al.[13] The number of cine frames required for the contrast to reach the smallest visible distal branch in the renal parenchyma was measured. The first frame approved for the RFC is the frame in which the contrast first dyes the renal artery. The column of contrast must extend the entire width of the artery, touching both borders at the origin of the renal artery, and there must be antegrade flow. The final frame was considered when the renal artery dyes the smallest visible branch in the distal renal parenchyma by contrast media (Figure 2). Radiopaque was administered to the renal artery manually by a cardiologist who is blind to patients' DM status. All RFC measurements were performed by another cardiologist who is blind to patients' DM status. Systolic blood pressure and diastolic blood pressure were invasively recorded before renal angiography.

Basic Tests

Basic blood test parameters at the time of admission for renal angiography were recorded for all patients. All measurements were performed within 30 minutes after blood collection. An automatic blood cell counter (Beckman, California) was used for complete blood count measurement. Fasting blood glucose, HbA1c, serum electrolytes, blood urea nitrogen (BUN), creatinine levels, and lipid panel of all patients were recorded. The estimated glomerular filtration rate (eGFR) calculation was made according to the Cockroft–Gault formula. Transthoracic echocardiography (TTE) was performed on all patients with Vivid E7 (GE Vingmed Ultrasound) echocardiography device and MS5 (1.5–4.5 MHz) ultrasound probe by an echocardiographer who is blind to patients' DM status. Left ventricular ejection fraction was measured by the Simpson method.

Statistical Analysis

The suitability of the data to normal distribution was evaluated by the histogram, q-q graphs, and Shapiro-Wilk test. To evaluate variance homogeneity, the Levene test was



a: 1st frame b:6th frame c:11th frame

Figure 2. (A-C) Renal frame count measurement.

used. To test the difference in the continuous variables between the groups, the Student T-test was used when there was a normal distribution, and the Mann-Whitney U-test was used when there was a non-normal distribution. A Chi-square analysis was used to compare categorical variables. The relationship between continuous variables was evaluated by Spearman's correlation analysis. Linear regression analyses (with stepwise and enter methods) were performed to determine the factors affecting the mean renal frame counts. The analysis of the data was performed with the help of TURCOSA (Turcosa Analytics Ltd Co, Turkey, www.turcosa.com.tr) statistical software. A *P*-value of <0.05 was accepted as statistically significant.

Results

A total of 110 hypertensive subjects who underwent renal angiography consisting of 55 subjects in DM and 55 subjects in the control group were enrolled in the study. The mean age of the subjects enrolled in the study was approximately 60 years, and almost half of the subjects were women. The invasively measured systolic and diastolic blood pressure values of the participants were high in both groups, but there was no significant difference between the DM group and the control group (164 ± 20, 167 ± 26, *P* = 0.449; 97 ± 10, 98 ± 10, respectively, *P* = 0.910). Body mass index (BMI) was significantly higher in the DM group compared to the control group (30.76 ± 5.19, 28.44 ± 5.03, respectively; *P* = 0.043). There were no significant differences between the two groups in terms of basal demographic characteristics and antihypertensive medications (Table 1).

When the laboratory characteristics of the patients enrolled in the study were compared, hemoglobin level was slightly lower in the DM group compared to the control group, but this was determined to be statistically significant (14.1 ± 1.30, 14.60 ± 1.60, respectively; *P* = 0.047). Hematocrit level was detected as significantly lower in the DM group compared to the control group (42.20 ± 4.11, 43.88 ± 4.34, respectively; *P* = 0.040). Fasting plasma glucose was detected as significantly higher in the DM group compared to the control group (138.0 [109.0–176.0], 96.0 [87.0–114.0], respectively; *P* <0.001). Sodium values were significantly lower in the DM group compared to the control group (138.0 [135.0–140.0], 140.0 [138.0–142.0], respectively; *P* = 0.001). The BUN values were detected significantly higher in the DM group compared to the control group (17.0 [12.9–21.0], 14.0 [12.0–17.0], respectively; *P* = 0.023). There were no significant differences between the two groups in terms of other laboratory characteristics (Table 2).

No significant difference was observed regarding the presence of atherosclerotic plaque in the left and right renal arteries of subjects in the DM group compared to the control

Table 1. Comparison of demographic characteristics between groups

Variables	DM group (n = 55)	Control group (n = 55)	*P*
Age (years)	60.00 ± 8.00	60.00 ± 10.00	0.896
Female n (%)	31 (56.4)	28 (50.9)	0.566
SBP (mmHg)	164.00 ± 20.00	167.00 ± 26.00	0.449
DBP (mmHg)	97.00 ± 10.00	98.00 ± 10.00	0.910
BMI (kg/m^2)	30.76 ± 5.19	28.44 ± 5.03	**0.043**
Smoking n (%)	4 (7.3)	7 (21.2)	0.093
Coronary artery disease n (%)	24 (43.6)	22 (40.0)	0.847
Antihypertensive treatment			
ACEi/ARB n (%)	30 (54.5)	33 (60.0)	0.700
Beta-blocker n (%)	24 (43.6)	24 (43.6)	0.999
Thiazides n (%)	15 (27.3)	18 (32.7)	0.677
CCB n (%)	20 (36.4)	14 (25.5)	0.302
Anti-diabetic treatment			
Biguanides n (%)	49 (89)		
Sulfonylureas n (%)	8 (14.5)		
Glitazones n (%)	1 (1.8)		
DPP-4 inh n (%)	15 (27.2)		
Combination of OAD n (%)	18 (32.7)		
Insulin n (%)	16 (21.8)		

ACEi: Angiotensin-converting enzyme inhibitors; ARB: Angiotensin receptor blocker; BMI: Body mass index; CCB: Calcium channel blocker; DBP: Diastolic blood pressure; SBP: Systolic blood pressure. Data are expressed as mean ± standard deviation.

Table 2. Comparison of laboratory properties between groups

Variables	DM group (n = 55)	Control group (n = 55)	*P*
Hemoglobin (g/dL)	14.10 ± 1.30	14.60 ± 1.60	**0.047**
Hematocrit (%)	42.20 ± 4.11	43.88 ± 4.34	**0.040**
Sodium (mEq/L)	138.0 (135.0-140.0)	140.0 (138.0-142.0)	**0.001**
Potassium (mEq/L)	4.40 ± 0.50	4.40 ± 0.30	0.640
Uric acid (mg/dL)	5.06 ± 1.10	4.75 ± 1.03	0.129
BUN (mg/dL)	17.0 (12.9-21.0)	14.0 (12.0-17.0)	**0.023**
Creatinin (mg/dL)	0.9 (0.7-1.0)	0.8 (0.7-1.0)	0.624
eGFR (ml/min/m^2)	83.0 (68.0-99.0)	90.0 (62.0-98.0)	0.597
Glucose (mg/dL)	138.0 (109.0-176.0)	96.0 (87.0-114.0)	**<0.001**
HbA1c (%)	7.1 (7.0-7.2)	5.3 (5.1-5.6)	**<0.001**
Osmolality (mOsm/kg)	290.8 (285.3-293.8)	291.9 (287.5-294.1)	0.473
Triglycerides (mg/dL)	144.0 (118.0-215.0)	141.0 (103.0-188.0)	0.225
HDL (mg/dL)	42.41 ± 12.29	45.09 ± 10.08	0.214
LDL (mg/dL)	123.93 ± 38.03	124.69 ± 32.66	0.910
EF (%)	55.0 (53.0-55.0)	55.0 (55.0-58.0)	0.101

BUN: Blood urea nitrogen; EF: Ejection fraction; eGFR: estimated Glomerular filtration rate; HDL: High-density lipoprotein; LDL: Low-density lipoprotein. Data are expressed as mean ± standard deviation and median (25th–75th quarter).

Table 3. Comparison of renal angiography features between groups

Variables	DM group (n = 55)	Control group (n = 55)	*P*
Atherosclerotic plaque in renal artery n (%)	23 (41.8)	26 (47.3)	0.701
Left RFC (frame/sec)	11.33 ± 2.55	13.49 ± 3.24	<0.001
Right RFC (frame/sec)	11.07 ± 2.43	13.33 ± 3.07	<0.001
Mean RFC (frame/sec)			

RFC: Renal frame count. Data are expressed as mean ± standard deviation.

Table 4. Multivariable linear regression analysis (Enter) to determine the parameters affecting Mean RFC

Variables	OR	95% CI	*P*
BMI	-0.027	(-0.137 - 0.082)	0.619
Hemoglobin	0.436	(-0.697 - 1.568)	0.446
Hematocrit	-0.112	(-0.499 - 0.276)	0.568
Sodium	-0.027	(-0.209 - 0.156)	0.771
BUN	-0.009	(-0.113 - 0.096)	0.868
HbA1C	-1.348	(-2.069 - -0.626)	**<0.001**
Glucose	0.007	(-0.005 - 0.018)	0.263

BMI: Body mass index; BUN: Blood urea nitrogen; CI: Confidence interval; OR: Odds ratio.

group. The RFC value measured in the left renal artery was significantly low in the DM group compared to the control group (11.33 ± 2.55, 13.49 ± 3.24, respectively; *P* <0.001). Besides, the RFC value measured in the right renal artery was detected to be significantly lower in the DM group than in the control group (11.07 ± 2.43, 13.33 ± 3.07, respectively; *P* <0.001). In the meantime, the mean RFC value calculated was significantly lower in the DM group than in the control group (11.20 ± 2.18, 13.41 ± 2.84, respectively; *P* <0.001; Table 3). The median follow-up period of subjects is 6.0 (4.0–11.0) years in terms of DM duration. Eight of the DM subjects had type 1 DM and 47 subjects had type 2 DM. There was no significant correlation between RFC and DM duration and glucose levels (*P* = 0.43, *P* = 0.35, respectively).

Multivariable linear regression (stepwise) was performed between Mean RFC with parameters (BMI, hemoglobin, hematoctitis, sodium, BUN, HbA1C, and plasma glucose) in which a marginally significant or significant difference (*P* <0.1) was found between the two groups. Analyses showed that the only statistically significant model was the HbA1C model (Odds ratio [OR]: −1.24 [−0.63 – −1.85], *P* <0.001). In the linear regression, performed with the "Enter" method and the same parameters, it was determined that the only parameter related to RFC was HbA1C (OR: 1.34 [−0.62 – −2.06], *P* <0.001; Table 4).

Discussion

The results of this study indicate that RFC is lower in DM

patients with preserved renal functions, and DM is an independent factor affecting the RFC results. Based on the findings of the study, we believe that parameters capable of affecting the vascular bed and flow dynamics, such as DM, should be taken into account when commenting on the RFC results.

Commonly used methods to demonstrate kidney damage in hypertensive and diabetic patients are the evaluation of markers, such as GFR and urinary albumin excretion;[14] however, different methods are required to demonstrate microvascular complications and to recognize renal dysfunction in the preclinical stage. The most common method for this purpose is the measurement of the renal resistive index (RRI) in ultrasonography. Although some studies conducted with RRI show a relation with renal functions, age, diabetes duration, and HbA1c, other studies failed to detect any relation.[7] The cause of this heterogeneity in the findings of the studies may be the study design, differences in patient populations evaluated, renal artery segment evaluated, poor images, and many different operators. These limitations have led to conducting of research for more objective markers of renal perfusion in selected patient groups.

The TIMI frame count was defined for the quantitative evaluation of coronary perfusion;[8] it was considered a predictor of functional recovery in revascularized patients after acute myocardial infarction[15] and as a predictor of perfusion at the tissue level by also indicating the relation with the width of infarct.[16] For the first time, Mulumudi et al.[13] defined the usability of frame count in renal arteries by comparing normal renal angiograms with fibromuscular dysplasia patients. This method allows the objective evaluation of renal perfusion, and this value evaluates the blood flow in the main renal artery and segmental arteries, besides it is influenced by the microvascular resistance in the cortex and the medulla.[13] In a study by Prasad et al.,[10] intravascular ultrasound (IVUS) was performed before stenting in 17 patients with renal artery stenosis, and IVUS images were compared with RFC measurements before and after the procedure. A high amount of necrotic core in atherosclerotic plaque was associated with a lack of improvement in RFC after stenting. The investigators concluded that this result originated from distal embolization and thus, microvascular dysfunction. In a study conducted by Paul et al.,[17] to evaluate the effectiveness of embolic protection devices, pre- and post-procedure RFC values were compared considering the success of RFC in evaluating perfusion in the distal vascular bed. In this study, in which 30 patients had renal stent implantation, a higher improvement in RFC was found after renal stenting in patients using an embolism protection device. When these studies are evaluated together, we conclude that RFC is a parameter that is affected by flow changes in both proximal renal artery pathologies and distal vascular bed. The pathologies in the microvascular bed caused by DM, which begin in the early period and lead to complications in the future, may also cause changes in flow dynamics and this can theoretically be demonstrated by RFC.

The RFC increases in the presence of renal artery stenosis.[13] In a study by Mahmud et al.,[9] the change in RFC after renal artery stenting procedure in patients with hypertension and renal artery stenosis was investigated. A decrease in RFC (>4 frames/sec) following renal artery stenting was found to correlate with the clinical response, and the systolic blood pressure (SBP) decreased by >15 mmHg during the 6-month follow-up in this patient group. In another study conducted by Naghi et al.[12] on 121 subjects with hypertension and renal artery stenosis, a significant decrease was observed in RFC following renal stenting. Another finding of this study was that the treatment response was significantly higher in subjects with renal artery stenosis and with onset, RFC >30 frames/sec, compared to those with RFC value, ≤30 frames/sec. However, our study revealed an independent relationship between RFC value and DM, so probably different cut-off values would predict treatment response in the DM patient group. It can be thought that lower values instead of >30 frames/sec in DM patients with preserved renal functions may have a role in predicting the response to treatment in patients undergoing renal stenting.

Glomerular hyperfiltration starting with the onset of nephron loss at the early stages of DN was reported up to 73%.[18] Changes in tubular creatinine secretion in obesity, hyperglycemia, and hyperfiltration media may be the cause of this condition.[19] The majority of the DM subjects evaluated in our study were overweight, and the BMI was significantly higher compared to the control group. Although the calculated eGFR was not different between the groups, the eGFR in the DM subject group may not reflect the accurate status. The lower RFC we found in DM patients with preserved renal function may be due to glomerular hyperfiltration and increased renal blood flow.

Another parameter that may affect renal blood flow is hypertension. The cases where renal endothelial dysfunction is detected were found to be associated with hypertension.[20] In a study conducted by Gocer et al.[11] on 100 subjects, of which 50 subjects had stage 1 hypertension and 50 subjects had stage 2 hypertension, it was detected that there was a significant increase in RFC parallel to the increased severity of hypertension. Besides, a significantly positive correlation was detected between hypertension and RFC. The investigators associated these findings with the endothelium dysfunction increasing with the severity of hypertension. As in this study, our patient group consists of hypertensive patients, and the renal blood flow is probably affected by

hypertension. However, there was no difference in the invasively measured blood pressures of the participants in the two groups, and the effect of hypertension, which could veil the effects of DM, was eliminated.

It was shown that dyslipidemia and the associated inflammatory process were effective in the progression of renal disease.[21] In a study by Ipek et al.[22] where 116 subjects were evaluated, a significantly high value was detected in RFC in the subject group with LDL >130 compared to the group with LDL <130 mg/dL. Besides, in this study, a significantly positive correlation was detected between LDL cholesterol level, total cholesterol level, smoking package year, and RFC, and a significantly negative correlation between GFR and RFC.

The RFC is the sum of the main renal artery and segmental branches as well as microvascular functions. To make it more effective in clinical use and particularly to determine a cut-off for invasive procedures to be performed, it is necessary to clarify the parameters that influence RFC. In previous studies, the plaque composition in the renal artery, dyslipidemia, and hypertensive condition were proved to influence RFC. To the best of our knowledge, our study is the first study to evaluate the impact of DM on RFC. According to our findings, increased renal blood flow causes a decrease in RFC value in DM patients with normal renal function, and a negative independent relationship was found between RFC value and HbA1C. In patients with lower GFR and end-stage renal failure patients with DM, the change in RFC value is still unclear and we think that this should be evaluated in different studies.

Study Limitations

Our study has several limitations. The major limitation of this study is that it is a retrospective study. The second limitation of the current study is the relatively small sample size. Another limitation, the contrast agent was administered to the renal artery manually, not with the help of an automatic injector. Also, RFC results are half of the results in the literature since the image records which were taken at 15 frames/sec are examined. Lastly, although the predictive effect of RFC on renal blood flow has been validated in previous studies, resistive index measurement with ultrasound or renal blood flow measurement with Doppler wire was not available in the data we evaluated. There are missing data in terms of DM and HT durations of the participants. Our study did not provide information regarding any relationship between disease duration and renal blood flow.

Conclusion

To the best of our knowledge, this is the first study conducted to show the impact of DM on RFC. Our findings showed that RFC decreases in DM subjects with preserved renal functions independently from other factors. We think that the effect of DM on renal blood flow should be considered if RFC is used to make clinical judgments.

Ethics Committee Approval: Local ethics committee approval was obtained (CUTF: 2020-06/09).

Informed Consent: Written informed consent was obtained from the participants of this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - I.B.C.; Design - I.B.C.; Supervision - M.B.Y; Resources - F.D., M.B.Y; Materials - F.D.; Data Collection and/or Processing - F.D.; Analysis and/or Interpretation - I.B.C., M.B.Y.; Literature Search - I.B.C., F.D.; Writing Manuscript - I.B.C.; Critical Review - M.B.Y.

Declaration of Interests: The authors declare that they have no competing interest.

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