The evaluation of renal hemodynamics changes in Familial Mediterranean fever with color Doppler sonography

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ABSTRACT

Background: Renal resistive index (RRI) scanned through renal Doppler is a practical marker employed in measuring blood flow in renal and intrarenal arteries and in noninvasive evaluation of renal vascular resistance. We aimed to investigate the renal hemodynamic variations in patients with Familial Mediterranean Fever (FMF).

Material and methods: Seventy-nine FMF patients and 51 healthy subjects suitable for age and sex were included. Patients were divided into two groups according to their urinary albumin excretion. Fifty-two patients with 0–29 mg/day albuminuria were included in the normoalbuminuric group while 27 patients with 30–299 mg/day albuminuria were included in the microalbuminuric group.

Results: RRI values were higher in patients with FMF compared to the healthy subjects (p < 0.0001). Additionally, RRI values were found to be higher in the microalbuminuric patients group compared to the normoalbuminuric patients group, and RRI values were also higher in normoalbuminuric patients group compared to the control group (p = 0.002, p < 0.0001). The ROC curve analysis suggested that the optimum RRI cutoff value for microalbuminuria in patients was 0.63, sensitivity of 66%, specificity of 60%, and p = 0.013.

Conclusion: RRI may be a marker that may be used in assessing resistance to renal blood flow, early renal damage, and progression of renal damage in FMF patients.

Introduction

Familial Mediterranean Fever (FMF) disease is a common autosomal recessive disease frequently in communities of Mediterranean descent such as Turks, Arabs, Armenians, and non-Ashkenazi Jewish. The usual progression of FMF is characterized by attacks accompanied by potential fever, and the involvement of serosal and synovial membranes and skin. FMF may be observed in the form of attacks. Attacks usually last 12–72 h and are self-restrictive. Mediterranean fever (MEFV) gene mutation is responsible for the pathogenesis of FMF disease. This mutation may a key role of inflammation in FMF patients. Inflammatory processes in the FMF disease can be controlled through the treatment of colchicine. The most important complication of FMF disease is amyloidosis developing secondary to chronic inflammation, and renal involvement occurs frequently.

Gray scale ultrasonography (US) and renal color Doppler US are the most preferred imaging methods in the evaluation of pathologies and hemodynamic variations due to the renal parenchymal involvement. In gray scale US, renal size, parenchymal thicknesses, and parenchymal echogenicity are evaluated to have an idea about the chronic phase of the disease. It is not useful in the differential diagnosis and follow-up of the disease. In Doppler US where renal hemodynamic variations are evaluated, the renal resistive index (RRI), pulsatility index (PI), systolic–diastolic ratio (S/D), peak systolic velocity (PSV), and end diastolic velocity (EDV) are the key parameters explored. Among them, RRI is the most commonly used parameter in clinical practice.
RRI evaluated under Doppler US is an easily applicable, affordable, and noninvasive method where renal parenchymal damage and variations in renal blood flow secondary to inflammation can be explored.8–10

Our study is the first one to examine renal hemodynamic variations in FMF patients. The aim of this study is to explore renal hemodynamic variations caused by chronic inflammation and renal parenchymal damage in FMF patients, and their clinical usability.

**Patients and methods**

Our study was conducted at the Gastroenterology and Radiology Clinic of the Cumhuriyet University’s Faculty of Medicine. Seventy-nine FMF patients who had been diagnosed in accordance with Tel-Hashomer criteria1 and in attack-free period and 51 healthy subjects suitable for age and gender were included. Files and archive records were examined and clinical features of the control group, laboratory data, and renal hemodynamic properties revealed by the Doppler ultrasound were recorded. Subjects with systemic diseases such as hypertension (HT), coronary artery disease, chronic obstructive pulmonary disease and diabetes mellitus, acute and chronic renal diseases, acute/chronic infections, and subjects with a history of medication except for colchicine (such as antihypertensives, nonsteroidal anti-inflammatory drugs) were excluded. Ethics committee approval required for our study was acquired from the ethics committee of the Cumhuriyet University’s Faculty of Medicine.

All US examinations of patient and control groups were performed by the same radiologist using a Logiq 9 device (GE Healthcare, Milwaukee, WI) and a 3.5–5.0 MHz convex probe. Examinations were conducted after a hunger period of minimum 12 h. Kidney size and parenchymal thicknesses were measured by B-mode US. Kidneys were thoroughly scanned for renal pathology. Cases where no corticomedullary distinction could be made on imaging and cases with severe parenchymal echogenicity were excluded.

Interlobar arteries with color Doppler examination of the duplex modes were coded in the color code. After identifying the artery trace, it was preceded with spectral analysis in the triplex Doppler mode. Waveforms for measurement were optimized based on settings for lowest PRP avoiding aliasing, highest gain not shutting the background noise, and lowest wall filter. After setting a suitable window width, samples were taken at a Doppler angle of 30–60 degrees. In all cases, measurements were made on both kidneys from the upper, middle and lower pole, and average values were obtained. Sampling was performed from levels where the interlobar artery is visible along the minimum length of 1 cm. Measurements were recorded when minimum 3 consecutive uniform waveforms were obtained. Measurements were repeated for three times and arithmetic average of these readings was recorded. RRI, PI, systolic velocity, diastolic velocity, and S/D ratio values obtained from the interlobar artery level by means of system software. While RRI, PSV, EDV values were calculated by means of PSV values, PI was calculated by means of systolic velocity, diastolic speed/average speed values.

Routine operational lab data of patient and control groups were scanned. Renal function tests and albumin excretion volume in urine were recorded. Daily albumin excretion volumes in urine were calculated with the urinary albumin in spot urine/creatinine ratio. Patients were divided into 2 groups according to their urinary albumin excretion. Fifty-two patients with 0–29 mg/day albuminuria were included in the normoalbuminuric group while 27 patients with 30–299 mg/day albuminuria were included in the microalbuminuria (MAU) group. The evaluation was based on the average of right and left renal parenchyma and renal artery RRA values revealed by USG and Doppler.

**Statistical analysis**

The analysis of our study was performed using the SPSS 14.0 statistical software (Chicago, IL). Parametric variables were stated with average ± standard deviation, and categorical variables were stated with numbers and percentages (%). Parametric variables were evaluated in independent groups by means of the t-test and the ANOVA post hoc Tukey’s test while categorical variables were evaluated by means of the appropriate chi-square test. Relationships between variables were tested using Pearson’s correlation analysis. Receiver-operating characteristic (ROC) curves were constructed to determine the optimum cutoff for tests. The area under the curve (AUC) was calculated to quantify sensitivity and specificity. p Values of less than 0.05 were regarded as significant.

**Results**

Twenty-six FMF patients (32.9%) were male and 53 (67.9%) were female. Age average was 28.8 ± 9.2 years. On the other hand, 23 subjects of the control group (45.1%) were male and 28 (54.9%) were female. Age average was 31.2 ± 9.4 years. No significant difference was found between FMF patients and the control group in terms of age and gender distribution (p = 0.165, p = 0.163, respectively). The patients’ average age at
diagnosis, disease duration, use of colchicine doses, number of family households with FMF, and clinical findings during the attack are summarized in Table 1.

Among FMF patients, gray scale US revealed grade 1 echogenicity increase in both kidneys in 8 patients (10.1%). Clinical, demographic, and laboratory characteristics, renal sizes of the patients and control group, and comparison of flow parameters on the renal Doppler are summarized in Table 2.

Age, gender, and flow parameters on renal Doppler for the all of the study groups are presented in Table 3. RRI was found higher in the microalbuminuric patients group compared with normoalbuminuric (p = 0.008)

Table 1. Baseline characteristics of patients with FMF.

| Characteristics          | FMF patients (n = 79) | p Values |
|--------------------------|-----------------------|----------|
| Age at diagnosis (years)*| 22.4 ± 9.2            | 0.165    |
| Duration of illness (years)*| 4.95 ± 6.12          | 0.163    |
| Dose of colchicine (mg/day)*| 1.24 ± 0.47          | 0.094    |
| Family history of FMF, n (%)| 40 (50.6)            | 0.570    |
| Fever, n (%)             | 72 (91.1)             | 0.532    |
| Peritonitis, n (%)       | 70 (88.6)             | 0.163    |
| Pleuritis, n (%)         | 58 (73.4)             | 0.581    |
| Pericarditis, n (%)      | 4 (5)                 | 0.532    |
| Arthritis/arthralgia, n (%)| 23 (29.1)            | 0.581    |
| Skin lesion, n (%)       | 15 (19.8)             | 0.581    |

FMF: Familial Mediterranean Fever.

*Mean ± SD.

Table 2. Comparison of baseline clinical and demographical characteristics of two study groups.

| Characteristics          | FMF patients (n = 79) | Controls (n = 52) | p Values |
|--------------------------|-----------------------|-------------------|----------|
| Age, years               | 28.8 ± 9.2            | 31.2 ± 9.4        | 0.165    |
| Male/female, n (%)       | 26 (32) / 53 (68)     | 23 (45) / 28 (55) | 0.163    |
| Serum urea nitrogen, mg/dL| 11.16 ± 3.97         | 10.79 ± 3.36      | 0.581    |
| Serum creatinine, mg/dL  | 0.72 ± 0.18           | 0.64 ± 0.20       | 0.029    |
| Serum albumin, g/dL      | 4.36 ± 0.67           | 4.50 ± 0.33       | 0.126    |
| ACR, mg/day              | 38.55 ± 54.42         | 44.8 ± 3.14       | <0.0001  |

Renal dimensions

| Characteristics          | FMF patients (n = 79) | Controls (n = 52) | p Values |
|--------------------------|-----------------------|-------------------|----------|
| Long axis, mm            | 10.51 ± 1.01          | 10.35 ± 0.95      | 0.349    |
| Short axis, mm           | 3.71 ± 0.49           | 3.65 ± 0.52       | 0.532    |
| Parenchymal thickness, mm| 1.35 ± 0.26           | 1.35 ± 0.23       | 0.570    |

Renal Doppler indices

| Characteristics          | FMF patients (n = 79) | Controls (n = 52) | p Values |
|--------------------------|-----------------------|-------------------|----------|
| PSFV, cm/s               | 32.53 ± 8.34          | 29.84 ± 9.19      | 0.094    |
| EDFV, cm/s               | 11.66 ± 3.43          | 12.46 ± 3.99      | 0.244    |
| S/D ratio                | 2.90 ± 0.61           | 2.42 ± 0.23       | <0.0001  |
| Pulsatile index          | 1.26 ± 0.38           | 1.22 ± 0.09       | 0.794    |
| Renal resistive index    | 0.64 ± 0.06           | 0.58 ± 0.03       | <0.0001  |

All data: mean ± SD; PSFV: peak systolic flow velocity; EDFV: end diastolic flow velocity; ACR: urinary albumin to creatinine ratio.

Table 3. Comparison of RMI patients with microalbuminuria, FMF patients with normoalbuminuria, and controls in terms of renal hemodynamic values and demographic characteristics.

| Characteristics          | Microalbuminuria       | Normoalbuminuria      | Controls (n = 52) | p Values |
|--------------------------|------------------------|----------------------|-------------------|----------|
| Age, years               | 29.6 ± 10.3            | 28.4 ± 8.6           | 31.2 ± 9.4        | 0.328    |
| Male/female, n (%)       | 11 (39.3) / 17 (60.7)  | 15 (29.4) / 36 (44.4)| 23 (45) / 28 (55) | 0.114    |
| PSFV, cm/s               | 33.05 ± 8.81           | 32.27 ± 8.16         | 29.84 ± 9.19      | 0.216    |
| EDFV, cm/s               | 11.12 ± 3.69           | 11.94 ± 3.30         | 12.46 ± 3.99      | 0.312    |
| S/D ratio                | 3.13 ± 0.76            | 2.77 ± 0.48          | 2.42 ± 0.23       | <0.0001  |
| Pulsatile index          | 1.43 ± 0.55            | 1.17 ± 0.20          | 1.22 ± 0.09       | 0.235    |
| Renal resistive index    | 0.66 ± 0.06            | 0.62 ± 0.05          | 0.58 ± 0.03       | <0.0001  |

All data: mean ± SD; PSFV: peak systolic flow velocity; EDFV: end diastolic flow velocity.

Discussion

In the present study, we have demonstrated that RRI values were higher in patients with FMF compared to the healthy subjects (p < 0.0001). Additionally, RRI values were found to be higher in the microalbuminuric patients group compared to the normoalbuminuric patients group.

In FMF patients, secondary amyloidosis development is the most critical complication of the disease decisive in the prognosis. In the development of amyloidosis, chronic high levels of amyloid A and accumulation of insoluble amyloid fibrils in tissues resulting from the defect occurring during the breakdown have a key role. In amyloidosis, symptoms and findings vary by the involvement site. A multisystemic involvement affecting many organs, particularly liver, spleen, intestine, heart, and kidneys. Renal involvement may manifest itself with asymptomatic MAU, macroalbuminuria, uremia, and end-stage renal failure.11,14,15

Amyloid fibrils impair the morphological integrity of the tissue and organ through renovascular structures and parenchymal involvement. Vascular involvement can be either in renal arteries and arterioles as well as in glomerular and tubulointerstitial areas of the parenchyma.16–18

RRI scanned through renal Doppler allows measuring blood flow in renal and intra-renal arteries, and making a noninvasive evaluation of renal vascular resistance. Arterial compliance, pulsatility, and peripheral resistance are complex compounds effecting RRI.8 RRI renal compression may be effected by breath...
Figure 1. Differences of renal resistive index among three groups.

Figure 2. Receiver-operating characteristic curve of renal resistive index for predicting microalbuminuria in patients with FMF.
holding and arrhythmias during the Valsalva maneuver. It has a critical role in evaluating blood flow in renal artery and vein pathology (such as stenosis, thrombosis, and trauma), acute and chronic renal inflammation, and parenchymal pathology.8,19 RRI-based studies on patients with systemic lupus erythematosus (SLE),20,21 scleroderma patients,22,23 diabetic patients,24–26 and hypertensive patients27,28 are available in the literature.

SLE is another autoimmune connective tissue disease that may cause kidney involvement. Although clinical findings in SLE reveal heterogeneity, renal involvement is observed in almost half of the patients. Kidney involvement is characterized by the accumulation of immune complexes in vascular, glomerular, and tubular structures.20,21 In their study on patients with SLE, Gao et al.20 reported higher levels of RRI in patients with mild cortical fibrosis compared to patients with light cortical fibrosis. In another study, Platt et al.21 reported correlation between RRI and the chronicity index and the tubulointerstitial damage.

Systemic sclerosis (SSc) is an autoimmune connective tissue disease that may cause renal involvement. SSc pathogenesis involves vascular damage, fibrosis, and immune activation. Histopathological changes in the kidney include glomerulonephritis and vascular structures.22,23 In their study, Habeeb et al.22 reported that RRI was higher in patients with SSc compared to the control group. In another study, Rosato et al.23 found higher levels of RRI in patients with SSc compared to the control group.

Most important long-term complications in patients with diabetes include diabetic nephropathy. DM nephropathy is characterized by decline in glomerular filtration rate secondary to the involvement of glomerular and renovascular structures, and proteinuria.29 Glomerular involvement is characterized by diffuse or nodular glomerulosclerosis while vascular involvement is characterized by afferent and efferent arteriolar damage.24–26 In the studies, RRI variations accompanying DM nephropathy were observed. In their study, Bruno et al.24 reported significantly higher levels of RRI in newly diagnosed diabetic patients compared to the healthy control group. In their study on diabetic patients, Hamano et al.25 reported higher levels of RRI in the microalbuminuric patients group compared to the non-albuminuric patients group. In their study, Afsar et al.26 showed higher levels of RRI in diabetic patients with albumin excretion and reduced creatinine clearance.

Uncontrolled HT and/or prolonged high levels may result in nephrosclerosis, decreased renal blood flow, and an increase in RRI. In hypertensive patients, RRI was found to be associated with renal artery atherosclerosis and tubulointerstitial damage. In HT patients, involvement of glomerular vascular structures is characterized by albumin excretion.27,28 In their study, Özelsancak et al.27 reported higher levels of RRI in non-treated hypertensive patients compared to the control group. Again in the same study, a positive correlation between RRI and urinary albumin excretion, and a negative correlation between RRI and creatinine clearance was reported. In another study, Berni et al.28 reported potential intrarenal tubulointerstitial area associated with RRI systemic low-grade inflammation and arteriolar damage.

While vascular involvement occurs in the medial layer of early-stage arteries in FMF patients, glomerular involvement may be observed in the capillary ball and mesangium, and tubulointerstitial involvement may result in tubular atrophy and fibrosis. In parenchymal and vascular structures, renal hemodynamic variations due to involvement may be observed.11,14,30 In our study, higher levels of RRI in the microalbuminuric patients group compared to the normoalbuminuric patients group, and in the normoalbuminuric patients group compared to the control group suggested that MAU may be evaluated with RRI in FMF patients, and also renal parenchymal and vascular variations in FMF patients may be evaluated with RRI.

To the best of our knowledge, our study is the first to examine renal hemodynamic variations in FMF patients. Our study has certain limitations. These include retrospective nature of the study, small number of patients, lack of an analysis of renal histopathology in patients with MAU, and non-consideration of correlation between RRI.

In conclusion, in FMF patients, RRI may be a non-invasive, affordable and easy method that may be used in evaluating resistance to renal blood flow, early renal damage and progression of renal damage. More studies evaluating renal histopathology and exploring correlation with RRI are needed.

Disclosure statement

The authors report no conflict of interest.

References

1. Orbach H, Ben-Chetrit E. Familial Mediterranean fever – A review and update. Minerva Med. 2001;92:421–430.
2. Lidar M, Livneh A. Familial Mediterranean Fever: Clinical, molecular and management advancements. Neth J Med. 2007;65:318–324.
3. Uslu AU, Aydin B, Inal S, et al. The relationship between red cell distribution width and homozygous M694V mutation in familial Mediterranean fever patients. Ann Saudi Med. 2015;35:151–156.
4. Lidar M, Kedem RON, Berkun Y, Langevitz P, Livneh AVI. Familial Mediterranean Fever in Ashkenazi Jews: The mild end of the clinical spectrum. J Rheumatol. 2010;37:422–425.

5. Uslu AU, Deveci K, Korkmaz S, et al. Is neutrophil/Lymphocyte ratio associated with subclinical inflammation and amyloidosis in patients with Familial Mediterranean Fever? Biomed Res Int. 2013;2013:185317.

6. Livneh A. Amyloidosis of Familial Mediterranean Fever (FMF) – Insights to FMF phenotype II. Harefuah. 2006;145:743–745, 782.

7. Duzova A, Bakkaloglu A, Besbas N, et al. Role of A-SAA in monitoring subclinical inflammation and in colchicine dosage in Familial Mediterranean Fever. Clin Exp Rheumatol. 2003;21:509–514.

8. Quaia E, Bertolotto M. Renal parenchymal diseases: Is characterization feasible with ultrasound? Eur Radiol. 2002;12:2006–2020.

9. Tublin ME, Bude RO, Platt JF. Review. The resistive index in renal Doppler sonography: Where do we stand? AJR Am J Roentgenol. 2003;180:885–892.

10. Kohler TR, Zierler RE, Martin RL, et al. Noninvasive diagnosis of renal artery stenosis by ultrasonic duplex scanning. J Vasc Surg. 1986;4:450–456.

11. Bilginer Y, Akpolat T, Ozen S. Renal amyloidosis in children. Pediatr Nephrol. 2011;26:1215–1227.

12. Berkun Y, Padeh S, Reichman B, et al. A single testing of serum amyloid A levels as a tool for diagnosis and treatment dilemmas in Familial Mediterranean Fever. Semin Arthritis Rheum. 2007;37:182–188.

13. Uslu AU, Aydin B, Icagasioglu IS, et al. The relationship among the level of serum amyloid A, high-density lipoprotein and microalbuminuria in patients with Familial Mediterranean Fever. J Clin Lab Anal. 2016;4:9.

14. Deveci K, Korkmaz S, Senel S, et al. Do neutrophil gelatinase-associated lipocalin and interleukin-18 predict renal dysfunction in patients with Familial Mediterranean Fever and amyloidosis? Ren Fail. 2014;36:339–344.

15. Deveci K, Gokakin AK, Senel S, et al. Cystatin C in serum as an early marker of renal involvement in Familial Mediterranean Fever patients. Eur Rev Med Pharmacol Sci. 2013;17:253–260.

16. Dember LM. Amyloidosis-associated kidney disease. J Am Soc Nephrol. 2006;17:3458–3471.

17. Falk RH, Skinner M. The systemic amyloidoses: An overview. Adv Intern Med. 2000;45:107–137.

18. Kyle RA, Gertz MA. Primary systemic amyloidosis: Clinical and laboratory features in 474 cases. Semin Hematol. 1995;32:45–59.

19. Krumme B. Renal Doppler sonography – Update in clinical nephrology. Nephron Clin Pract. 2006;103:c24–c28.

20. Gao J, Chevalier J, Auh YH, et al. Correlation between Doppler parameters and renal cortical fibrosis in lupus nephritis: A preliminary observation. Ultrasound Med Biol. 2013;39:275–282.

21. Platt JF, Rubin JM, Ellis JH. Lupus nephritis: Predictive value of conventional and Doppler US and comparison with serologic and biopsy parameters. Radiology. 1997;203:82–86.

22. Habeeb RA, Mansour HE, Abdeldayem AM, et al. Anti-annexin V antibodies: Association with vascular involvement and disease outcome in patients with Systemic sclerosis. Clin Med Insights Arthritis Musculoskelet Disord. 2010;3:15–23.

23. Rosato E, Gigante A, Barbano B, et al. Intrarenal hemodynamic parameters correlate with glomerular filtration rate and digital microvascular damage in patients with systemic sclerosis. Semin Arthritis Rheum. 2012;41:815–821.

24. Bruno RM, et al. Dynamic evaluation of renal resistive index in normoalbuminuric patients with newly diagnosed hypertension or type 2 diabetes. Diabetologia. 2011;54:2430–2439.

25. Hamano K, Nitta A, Ohtake T, Kobayashi S. Associations of renal vascular resistance with albuminuria and other macroangiopathy in type 2 diabetic patients. Diabetes Care. 2008;31:1853–1857.

26. Afsar B, Elsurer R. Comparison of renal resistive index among patients with Type 2 diabetes with different levels of creatinine clearance and urinary albumin excretion. Diabet Med. 2012;29:1043–1046.

27. Özelşancak R, Torun D, Koc Z, Sezer S, Ozdemir FN, Niron EA. Relationship between renal resistive index and inflammation in untreated hypertensive patients. Int Heart J. 2009;50:753–761.

28. Berni A, Ciani E, Bennett M, et al. Renal resistive index and low-grade inflammation in patients with essential hypertension. J Hum Hypertens. 2012;26:723–730.

29. Gonzalez Suarez ML, Thomas DB, Barisoni L, Fornoni A. Diabetic nephropathy: Is it time yet for routine kidney biopsy? World J Diabetes. 2013;4:245–255.

30. Markowitz GS. Dysproteinemia and the kidney. Adv Anat Pathol. 2004;11:49–63.