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Original Investigation

Relationship between endothelial dysfunction and microalbuminuria in familial Mediterranean fever

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Abstract

Objective: The aim of our study is to investigate the relationship between microalbuminuria and flow-mediated dilatation in familial Mediterranean fever (FMF) patients.

Material and Methods: In our study, there were two groups consisting of 54 patients who were out of the attack period (43 of whom had no microalbuminuria and 11 of whom had microalbuminuria) and 40 healthy controls (M/F: 12/28).

Results: There was no statistically difference between patient and control groups'age (25.06±8.07, 22.89±6.00 years, respectively). Flow-mediated dilatation (FMD) percentages were significantly different between the three groups (p=0.01). It was observed that there was a correlation between microalbuminuria and FMD percentage.

Conclusion: Endothelial dysfunction and renal damage occurred as a result of low-grade chronic inflammation. Microalbuminuria, which is the indicator of renal damage and endothelial dysfunction, and FMD show that endothelial functions can be used in the following of early detection of renal damage and endothelial functions in FMF patients.

Keywords: Familial Mediterranean fever, flow-mediated dilatation, microalbuminuria

Introduction

Familial Mediterranean fever (FMF) is an autosomal recessive disease characterized by recurrent attacks of fever and polyserositis. Episodes of fever resolve between 1 and 4 days accompanied by elevated white blood cell count and elevation of inflammatory markers, such as sedimentation rate and amyloid proteins (1). Colchicine therapy can reduce attacks and complications of FMF (2, 3). There are two mechanisms that can explain renal–vascular damage in FMF. The first mechanism involves the development of amyloidosis and progression to renal failure, which are the most important factors determining the prognosis of FMF (4). Amyloidosis develops due to the increased production of the serum amyloid A protein by the liver (5). Increased concentration and decreased elimination of the serum amyloid A cause its accumulation in extracellular areas (6). Typical manifestation of amyloidosis in a formerly known FMF patient is proteinuria, progressing to nephrotic syndrome and uremia, due to the deposition of the insoluble protein in kidneys (7). In the second mechanism, the ongoing (chronic) inflammation causes endothelial dysfunction. It is known that the endothelial dysfunction may have a substantial role in the development of atherosclerosis and glomerulosclerosis. Increased vascular permeability and nitric oxide (NO) synthesis because of proinflammatory cytokines may result in albuminuria. Tumor necrosis factor, monocytes, and macrophages may directly damage the glomeruli. Endothelial dysfunction is linked to the defect in endothelium-dependent vasodilation mediated by NO. The endothelium-dependent vasodilation may be assessed by flow-mediated dilation (FMD) test. Endothelial dysfunction is considered a substantial factor in the development of atherosclerosis and hypertension. Over the past decade, a noninvasive technique has been developed to assess FMD in the brachial artery (8-11). It discharges the endothelium to release nitric oxide (NO) with consequent vasodilation that can be imaged as an indicator of vasomotor function. The aim of our study was to investigate the relationship between microalbuminuria and FMD in FMF patients.

Material and Methods

Our study was performed at the internal medicine clinic and cardiology clinic Cumhuriyet. The study was approved by the ethics committee of Cumhuriyet University School of Medicine, and informed consent was obtained. The study consisted of 54 patients with FMF diagnosed as per the Tel Hashomer criteria (4), who were on attack-free periods from 1 April 2012 to 1 April 2013. All patients were done FMD. Briefly, the technique of FMD is as follows: patients were placed in a supine position with the left arm immobilized; FMD was then measured using a Vivid 7 (General Electrics; Munich, Germany) ultrasound platform equipped with a 14-MHz matrix probe and a micrometric probe holder. FMD corresponded to the maximal dilation observed in the 5 min following deflation of the cuff. FMD test was performed in all patients with

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FMF. Attack-free periods were defined as periods with normal physical examination and normal level of inflammatory markers, such as WBC count, erythrocyte sedimentation rate, C-reactive protein. Patients taking antihypertensive drugs, antioxidants such as vitamin C, oily food; those doing intense exercise; those with a history of cigarette smoking, those who drank/ate anything 4 hours before the test, and/or those with other chronic diseases were excluded from the study. Control group included 40 healthy people not under any medication.

All statistical analyses were performed using SPSS, version 14.0 (SPSS Inc.; Chicago, IL, USA) and a p value less than 0.05 was considered statistically significant. Continuous variables are stated as mean±SD, by used the Kolmogorov–Smirnov test. Differences between patients and control participants were analyzed using the two-sample t- and Mann–Whitney U tests (nonparametric statistics) as suitable. Categorical variables were controlled using Pearson Chi-square and Fisher's exact tests.

Results

The study included 54 patients with FMF taking colchicine regularly who were in attack-free periods. Demographic and clinical data are presented in Table 1. FMD percentages in patients and control group were 13.8±2.2 and 20.9±2.6, respectively (p=0.001). There was a significant difference in the level of microalbuminuria between the two groups (p=0.001). Laboratory data are presented in Table 2. If patients are divided into two groups as patients with microalbuminuria (n=11) and patients with normoalbuminuria (n=43), FMD levels are 12.3±1.01 and 14.2±2.12, respectively (p=0.008). Demographic and clinical data are presented in Table 3. FMD percentages in FMF patients with microalbuminuria, in FMF patients with normoalbuminuria, and in the control group are shown in Figure 1. There were no statistically significant differences in age, age at first diagnosis, duration of disease, dose of colchicine, and lipid profile between FMF patients and control groups, as shown in Table 4. We observed a negative correlation between FMD and microalbuminuria (Table 4).

Table 1. Baseline demographic and clinical data

	Patients group (n=54)	Control group (n=40)	p
Age (years)	26.06±8.07	22.89±6.00	0.523
Sex (Male/Female) (n, %)	16 (29.6)/38 (70.4)	14 (31.1)/31 (68.9)	
Age at diagnosis (years)	19.5±8.9		
Duration of disease (years)	5.4±7.8		
Dose of colchicine (mg/day)	1.2±0.4		

Table 2. Comparison of laboratory data between patients and control group

	Patient group (n=54)	Control group (n=40)	p
FMD	13.8±2.2	20.9±2.6	0.001
HDL (mg/dL)	40.7±10.3	46.8±17.2	0.191
LDL (mg/dL)	91.0±29.4	99.6±39.0	0.070
TG (mg/dL)	128.0±70.7	130.7±65.2	0.194
TC (mg/dL)	153.7±30.7	171.3±49.9	0.232
WBC (10^3/mm^3)	7.4±3.0	6.7±1.4	0.089
ESR (mm/h)	7.2±8.3	6.5±4.3	0.088
CRP (mg/L)	4.5±2.5	3.2±2.6	0.819
Microalbuminuria (mg/day)	12.00 (3.00–238.00)	4.5 (3.00–30.00)	0.036

FMD: flow-mediated dilatation; HDL: high density lipoprotein; LDL: low-density lipoprotein; TG: triglyceride; TC: total cholesterol; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; WBC: white blood cell

Table 3. Comparison of demographic and clinical characteristics between patients with microalbuminuria and patients without microalbuminuria

	Patients with microalbuminuria (n=11)	Patients without microalbuminuria (n=43)	p
FMD	12.3±1.0	14.2±2.2	0.001
Sex (Female/Male) (n,%)	32 (74.4)/11 (25.6)	6 (54.5)/5 (45.5)	0.202
Age (years)	25.80±8.61	22.27±5.00	0.092
Duration of disease (years)	5.86±8.34	2.83±1.60	0.053
Dose of colchicine (mg/day)	1.29±0.46	1.25±0.27	0.766

FMD: flow-mediated dilatation

Discussion

Endothelial dysfunction is associated with atherosclerosis and the development of glomerulosclerosis. However, few data exist on the role of endothelial dysfunction in renal involvement in FMF. Because we haven't got patient's renal biopsy data. The primary mechanism is known to be due to amyloidosis. FMD may play a role in predicting amyloidosis-associated early renal injury. We found that FMD percentages were significantly lower in patients with FMF than in the control group. Elevated inflammatory response is observed in patients with FMF. Serum levels of some proinflammatory cytokines are always elevated in patients with FMF. Subclinical inflammation causes endothelial dysfunction. The endothelium has an important role in the vessel and renal function. Several vessels respond to shear stress with dilatation. It is known that FMF is mediated by NO (12). The shear stress causes excessive calcium influx into the cell, which triggers the synthesis of endothelial nitric oxide synthase (10, 13-14). Endothelial damage or use of nitric oxide synthase inhibitors are associated with impaired FMD. Imbalances in vasoconstriction, vasodilatation, smooth muscle cell proliferation, thrombogenesis, and fibrinolysis result in endothelial dysfunction (15). FMD measurement is a non-invasive method for assessing endothelial function.

Kiss et al. (16) showed that FMD percentages were significantly lower in patients with systemic lupus erythematosus than in the control group. Low percentage of FMD was also found in patients with rheumatoid arthritis because

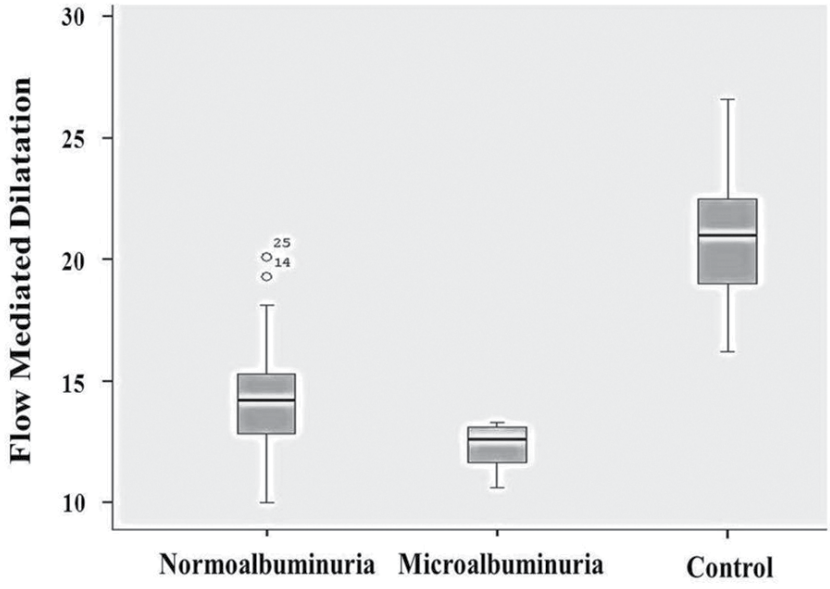

Figure 1. Comparison of flow-mediated dilatation (FMD) percentages in trial patients group

Table 4. Correlation analysis between FMD percentage in patients with FMF and other parameters

	Age	Age at diagnosis	TG	LDL	HDL	Microalbuminuria
FMD	r= - 0.088 p=0.534	r= - 0.027 p=0.863	r= - 0.199 p=0.212	r= - 0.224 p=0.130	r=0.318 p=0.213	r= - 0.290 p=0.041

FMD: flow-mediated dilatation; FMF: familial Mediterranean fever; HDL: high-density lipoprotein; LDL: low-density lipoprotein; TG: triglyceride

of chronic inflammation (17-18). Jin et al. (19) found that FMD percentages were lower in patients with diabetes mellitus (DM) than in the control group.

We found that FMD percentages were significantly lower in FMF patients with microalbuminuria than in FMF patients without microalbuminuria, which is similar to the current knowledge on endothelial dysfunction. Microalbuminuria is defined as the excretion of albumin ranging from 30 to 300 mg in a 24-h urine collection, and it is also used for the early detection of renal dysfunction (20) . The endothelial dysfunction has an important role in the development of atherosclerosis and glomerulosclerosis in patients without DM (21-22). Increased vascular permeability and NO synthesis due to proinflammatory cytokines may result in albuminuria (23). Endothelial dysfunction results in increased intracapillary glomerular pressure and also causes mesangial cell proliferation. Therefore, microalbuminuria can be observed in the setting of endothelial dysfunction (24). Endothelial dysfunction can explain the relationship between the extrarenal complication and microalbuminuria (25-26).

In conclusion, we found the relationship between microalbuminuria in FMF and endothelial dysfunction because of the subclinical inflammation. Another study has found a similar relation (27). We also observed negative correlation between FMD and microalbuminuria. This result showed that endothelial dysfunction in brachial artery may indirectly reflect endothelial dysfunction in renal artery. In lights of these results, microalbuminuria and FMD can be used for the early detection of renal dysfunction.

This study had some limitations. Our study had a relatively small sample size; furthermore, causes of microalbuminuria were not verified with histopathological examination. Another limitation to the study was the exclusion of patients with amyloidosis; therefore, the results should not be generalized to all patients with FMF. Further larger-scale and multi-center studies are needed to confirm these findings.

Ethics Committee Approval: Ethics Committee approval was received for this study from Cumhuriyet University.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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References

1. Lidar M, Livneh A. Familial Mediterranean fever: clinical, molecular and management advancements. Neth J Med 2007; 65: 318-24.
2. Bhat A, Naguwa SM, Gershwin ME. Genetics and New Treatment Modalities for Familial Mediterranean Fever. Ann N Y Acad Sci 2007; 1110: 201-8. [CrossRef]
3. Orbach H, Chetrit E. Familial mediterranean fever- a review and update. Minerva Med 2001; 92: 421-30.
4. Sarı İ, Birlik M, Kaşifoğlu T. Familial Mediterranean fever: An updated review. Eur J Rheumatol 2014; 1: 89-91. [CrossRef]
5. Obici L, Merlini G. Amyloidosis in autoinflammatory syndromes. Autoimmun Rev 2012; 12: 14-7. [CrossRef]
6. Van der Hilst JC, Simon A, Drenth JP. Hereditary periodic fever and reactive amyloidosis. Clin Exp Med 2005; 5: 87-98. [CrossRef]
7. Sohar E, Gafni J, Pras M, Heller H. Familial Mediterranean fever. A survey of 470 cases and review of the literatüre. Am J Med 1967; 43: 227-53. [CrossRef]
8. Laurent S, Lacolley P, Brunel P, Laloux B, Pannier B, Safar M. Flow-dependent vasodilation of brachial artery in essential hypertension. Am J Physiol 1990; 258: H1004-11.
9. Anderson EA, Mark AL. Flow-mediated and reflex changes in large peripheral artery tone in humans. Circulation 1989; 79: 93-100. [CrossRef]
10. Celermajer DS, Sorensen KE, Gooch VM. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. Lancet 1992; 340: 1111-5. [CrossRef]
11. Sorensen KE, Celermajer DS, Spiegelhalter DJ. Non-invasive measurement of human endothelium dependent arterial responses. accuracy and reproducibility. Br Heart J 1995; 74: 247-53. [CrossRef]
12. Coretti MC, Anderson TJ, Benjamin EJ, Celermajer D, Charbonneau F, Creager MA, et al. Guidelines for the ultrasound assessment of endothelial-dependent flow mediated vasodilation of the brachial artery: a report of the international brachial artery reactivity task force. J Am Coll Cardiol 2002; 39: 257-65. [CrossRef]
13. Joannides R, Haefeli WE, Linder L, Richard V, Bakkali EH, Thuillez C, et al. Nitric oxide is responsibl for flow-dependent dilation of human peripheral conduit arteries in vivo. Circulation 1995; 91: 1314-9. [CrossRef]
14. Sun D, Huang A, Smith CJ, Stackpole CJ, Conetta JA, Shesely EG, et al. Enhanced release of prostaglandins contributes to flow-induced arteriolar dilatation in eNOS knock out mice. Circ Res 1999; 79: 984-91.

15. Quyyumi A. Endothelial function in health and disease: New insights into the genesis of cardiovascular disease. Am J Med; 1998: 105: 32-9. [CrossRef]
16. Kiss E, Soltesz P, Der H, Kocsis Z, Tarr T, Bhattoa H, et al. Reduced flow-mediated vasodilation as a marker for cardiovascular complications in lupus patients. J Autoimmun 2006; 27: 211-7. [CrossRef]
17. Murdaca G, Colombo BM, Cagnati P, Gulli R, Spanò F, Puppo F. Endothelial dysfunction in rheumatic autoimmune diseases. Atherosclerosis 2012; 224: 309-17. [CrossRef]
18. Veselinovic MV, Zivkovic VI, Toncev S, Tasic N, Bogdanovic V, Djuric DM, et al. Carotid artery intima-media thickness and brachial artery flow-mediated vasodilatation in patients with rheumatoid arthritis. Vasa 2012; 41: 343-51. [CrossRef]
19. Jin SM, Noh C, Yang SW, Bae EJ, Shin CH, Chung HR, et al. Endothelial Dysfunction and Microvascular Complications in Type 1 Diabetes Mellitus. J Korean Med Sci 2008; 23: 77-82. [CrossRef]
20. Deveci K, Gokakın AK, Senel H, Deveci H, Uslu AU, Sancakdar E. Cystatin C in serum as an early marker of renal involvement in Familial Mediterranean Fever patients. European Review for Medical and Pharmacological Sciences 2013; 17: 253-60.
21. Ross R. The pathogenesis of atherosclerosis: A perspective for the 1990s. Nature 1993; 362: 801-9. [CrossRef]
22. Diamond JR, Karnovsky MJ. Focal and segmental glomerulosclerosis: analogies to atherosclerosis. Kidney Int 1998; 33: 917-24. [CrossRef]
23. Pruijma M, Ponte B, Vollenweider P, Moose V, Paccaud F, Waeber G, et al. Not All Inflammatory Markers Are Linked to Kidney Function: Results from a Population-Based Study. Am J Nephrol 2012; 35: 288-94. [CrossRef]
24. Stehouwer CDA, Henry RMA, Dekker JM, Nıjpels G, Heine RJ, Bouter LM. Microalbuminuria is associated with impaired brachial artery,flow-mediated vasodilation in elderly individual without and diabetes: Further evidence for a link between microalbuminuria and endothelial dysfunction-The Hoorn Study. Kidney Int Suppl 2004; 92: S42-4. [CrossRef]
25. Stehouwer CDA, Schaper NC. The pathogenesis of vascular complications of diabetes mellitus: one voice or many? Eur J Clin Invest 1996; 26: 535-43. [CrossRef]
26. Stehouwer CDA. Von Willebrand factor, dysfunction of the vascular endothelium, and the development of renal and vascular complications in diabetes. In: Mogensen CE, ed. The Kidney and Hypertension in Diabetes Mellitus. 3rd ed. Boston: Kluwer; 1997. p. 155-63.
27. Özer S, Yılmaz R, Sönmezgöz E, Karaaslan E, Taşkın S, Bütün İ, et al. Simple Markers for Subclinical Inflammation in Patients with Familial Mediterranean Fever. Med Sci Monit 2015; 21: 298-303. [CrossRef]