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Original Investigation

Evaluation of arterial stiffness with plasma GGT levels and pulse wave velocity measurement in patients with FMF

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Abstract

Objective: Pulse wave velocity (PWV) is a non-invasive technique used to evaluate the arterial elasticity, which is an early indicator of atherosclerosis. Lately, gamma glutamyl transferase (GGT) is considered a determiner of arterial stiffness (AS). In this study, we aimed to evaluate the relationship between GGT levels and AS with PWV in patients with Familial Mediterranean fever (FMF).

Material and Methods: The study was conducted with 60 patients with FMF and 40 controls. Genetic analysis of the patients were performed. AS was assessed by PWV and, after the measurement of PWV, the presence of AS was determined.

Results: Mean PWV values and AS frequency were significantly higher in patients with FMF compared with the control group ($p<0.001$ and $p=0.004$, respectively). Mean GGT levels of FMF patients were higher than in the control group but the difference was not statistically different. In the correlation analysis, PWV and AS were positively correlated with FMF ($r=0349$, $p<0.001$; $r=0.435$, $p<0.001$, respectively). FMF duration and FMF were associated with GGT ($r=0.300$, $p=0.02$; $r=0199$, $p=0.047$, respectively).

Conclusion: Increased PWV values in FMF patients may indicate arterial stiffness. These patients may be followed closely with PWV as an early indicator of atherosclerosis. Therefore, the cardiovascular risk can be determined in the early stages of disease and it may be possible to take necessary precautions.

Key words: Familial Mediterranean fever, arterial stiffness, pulse wave velocity measurement, gamma glutamyl transferase

Introduction

Familial Mediterranean fever (FMF; recurrent polyserositis, periodic disease) is a hereditary disease characterised by recurrent attacks of fever and peritonitis, pleuritis, arthritis, or erysipelas-like skin disease. Recent studies have shown that subclinical inflammation may continue in some FMF cases, even in the symptom-free periods (1, 2). Inflammation is an important cause of the development and progression of atherosclerosis (3). Chronic inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematosus and scleroderma can cause cardiac involvement in various ways (4, 5). Arterial vessel wall injury, due to inflammation, reduces arterial compliance and elasticity causing endothelial dysfunction (6).

Pulse wave velocity (PWV) is an indicator of arterial elasticity. PWV is inversely related to arterial distensibility and compliance. PWV measurements are thought to be used in determining cardiovascular risk in clinical situations such as diabetes mellitus, hypertension, and chronic renal failure (7-9). Arterial inflammation increases PWV by disrupting vascular function. PWV measurements may be used to determine the arterial stiffness in Rheumatoid arthritis, collagen, connective tissue diseases, and inflammatory diseases such as vasculitis (10).

Gamma glutamyl transferase (GGT) is a diagnostic test for hepatobiliary disease and alcoholic liver disease. However, recently it has been thought to be associated with cardiovascular mortality, morbidity, and atherosclerosis. GGT activity was determined in the atherosclerotic plaques of carotid artery and coronary arteries (11, 12).

There are a limited number of studies with different results evaluating the relationship between PWV in patients with FMF (13). However, there has not been any study evaluating PWV as well as GGT levels. In this study, we aimed to investigate PWV measurements and serum GGT levels for arterial stiffness in patients with FMF and healthy controls.

Material and Methods

The present study was performed between June 2011 and December 2011 in Internal Medicine and Cardiology clinics. Sixty patients diagnosed with FMF and 40 age and sex-matched controls were included

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in the study. The study protocol was approved by the local ethics committee and written informed consent was obtained from all study participants.

All patients and the control group were included in a detailed medical history and physical examination. Patients were diagnosed according to the Tell Hashomer criteria for the diagnosis of FMF (14). Patients with coronary artery disease, peripheral artery disease, hypertension, hyperlipidaemia, diabetes mellitus, chronic renal failure, and those using drugs affecting arterial stiffness (e.g. anti-hypertensive, anti-diabetic and anti-lipidaemic drugs) were excluded from the study.

To evaluate the arterial stiffness, Pulse wave velocity was measured automatically by 6000 Pulse trace module device (Micromedical, Rochester, United Kingdom).

Continuous Wave Doppler (CWD) were recorded from the patients lying in a quiet environment with 4 mHz probe placed on the carotid and femoral arteries, accompanied by an electrocardiogram (Nihon-Kohden Cardiofax EC-G1350K, Tokyo, Japan). PWV was automatically calculated by the device. To obtain the PWV value, the ratio of the distance between the recorded two points and the transition time of the pulse wave between two points was calculated. PWV values were recorded in m/sn. (PWV = the distance between the carotid artery and the femoral artery/the pulse wave reach time from the carotid artery to the femoral artery: m/s). After calculating the PWV of the patients and the control group, the presence of AS was determined according to the age of the participants in accordance with the recommendations of "The Reference Values for Arterial Stiffness' Collaboration" (15).

Statistical Analysis

Continuous variables were presented as mean±SD and categorical variables were expressed as percentages. The Kolmogorov-Smirnov test was used to evaluate the distribution of variables. Student's t-test was used for continuous variables in cases with normal distribution and the Mann-Whitney U test was used for continuous variables without normal distribution. Chi-square test was used for categorical variables. Spearman correlation analysis was performed for the correlations. For statistical calculations, SPSS statistical software (SPSS for Windows, version 15.0. Inc. Chicago, IL, USA) was used.

Results

The mean age of patients included in the study was 29.8±9.3 (17-55), and that of the control group was 31.8±9.2 (17.0-55.0). General characteristics were similar in patients with FMF and controls. Demographic characteristics of the patients and the control group were shown in Table 1.

Table 1. Demographic characteristics of patients with FMF and control group

Variables		FMF (n=60)	Control (n=40)	p
Age (year)		29.8±9.3	31.8±9.2	0.286
Sex†	Male	28.0 (46.7)	15.0 (37.5)	0.364
	Female	32.0 (53.3)	25.0 (62.5)	
BMI (kg/m²)		24.4±4.7	24.1±3.4	0.816

All parameters were expressed as mean±S.D and compared by Student t test, unless otherwise stated.
†Expressed as number (per cent) and comparison by Chi square test.

None of the patients had proteinuria. All patients were treated with colchicine at a dose of 1-2 mg/day. The characteristics of FMF patients are shown in Table 2.

Table 2. Disease characteristics of FMF patients

Family history	
None	23 (38.3%)
1st graduate relative	37 (61.7%)
Disease duration†	63.08±73.99 (1-276)
Colchicine dose	
0.5 mg	3 (5%)
1 mg	35 (58.3%)
1.5 mg	22 (36.7%)
Type of attacks	
Abd. pain	6 (10%)
Arthralgia	1 (1.7%)
Abd. pain + fever	21 (35.0%)
Fever + arthralgia	8 (13.3%)
Fever + arthralgia + Abd. pain	24 (40%)

FMF: familial Mediterranean fever; Abd. pain: abdominal pain
All parameters were expressed as number (per cent)
†Expressed as mean±S.D (min-max), (month)

Mean PWV values (7.3±1.1; 6.4±1.13 respectively) and AS frequency of the FMF group (78.3% and 35%, respectively) were significantly higher than those in the control group (p<0.001 and p<0.001, respectively). Mean GGT levels were 19.0±14.8 and 14.0±6.9, respectively, in FMF patients and the control group. Mean GGT levels of FMF patients were higher than the control group, but it was not statistically different.

Familial Mediterranean fever duration and GGT levels were significantly associated (r=0.300, p=0.02). Laboratory findings of the groups were shown in Table 3.

Discussion

There have been many studies evaluating AS in patients with FMF. However, our study is the first to evaluate GGT levels with PWV measurements in patients with FMF.

Pulse wave velocity, which is an early sign of atherosclerosis, is affected in chronic inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematosus, and systemic sclerosis (16-18). FMF is a disease in which subclinical inflammation can be seen, except during attack times (1, 2, 19). In our study, we found higher PWV values and frequency of AS in patients with FMF. In parallel with our findings, Yıldız et al. (13) found high PWV levels in patients with FMF. According to these results, it can be said that PWV, which is an indicator of arterial stiffness, may influence FMF and PWV measurements can be used as a precursor.

Akdoğan et al. (20) have identified that endothelium-dependent vasodilatation is impaired in FMF, except for during attack times; this was assessed by using brachial artery flow-mediated dilation. Also, increased carotid artery intima-media thickness was observed. Eventually, they reported an impaired endothelial function and an increased risk of atherosclerosis in FMF patients. In another study with FMF patients, carotid artery intima-media thickness and brachial artery flow-mediated dilation values were found to be similar to those in the control group. However, this result was tied to using regular colchicine by all patients participating in the study (21). In our study, all patients had been treated with Colchicine, but, despite this, PWV values and the AS frequency of patients were significantly higher than in the control group.

Gamma glutamyl transferase levels, which are cheap, easy and widely used, can be considered a marker for the development of atherosclerosis (22). In our study, GGT levels were higher in FMF patients but did not reach a statistically significant level. Despite this, GGT levels were correlated with the duration of FMF. This result may have occurred due to the small number of patients. We believe that studies with wider participation will be helpful.

As a result of the existence of subclinical inflammation in FMF patients outside the attacks, they carry risk for cardiovascular diseases.

Table 3. Laboratory findings of the patient and the control group

Variables	FMF (n=60)	Control (n=40)	p
WBC (µL)	7485.8±2055.2	7065.0±1519.7	0.271
Haemoglobin (g/dL)	13.8±2.0	14.2±1.4	0.322
PLT (µL)	261500.0±77723.6	249125.0±41326.8	0.540
ESR (mm/sn)	15.3±16.6	5.6±3.7	0.001
CRP (mg/L)	2.8±6.0	0.2±0.2	0.001
Fibrinogen	400.2±161.2	282.0±113.0	<0.001
GGT (mg/dL)	19.0±14.8	14.0±6.9	0.118
LDL (mg/dL)	91.9±23.8	101.6±20.6	0.021
HDL (mg/dL)	43.9±15.4	52.7±14.1	0.001
T. cholesterol (mg/dL)	154.3±29.6	171.1±25.0	0.004
Triglycerides (mg/dL)	106.9±54.5	81.6±30.6	0.036
PWV	7.3±1.1	6.4±1.13	<0.001
AS†	47 (%78.3)	14 (%35)	<0.001

All parameters were expressed as mean±S.D and compared by Student t test, unless otherwise stated.
†Expressed as number (per cent) and comparison by Chi square test.
AS: arterial stiffness; GGT: gamma glutamyl transferase; PWV: pulse wave velocity; WBC: white blood cell; PLT: platelets, ESR: sedimentation; CRP: C-reactive protein; LDL: low-density lipoprotein cholesterol; HDL: high-density lipoprotein cholesterol

These patients should be followed more closely. Measurements of PWV and serum GGT levels may be helpful to detect arterial stiffness in FMF patients. Therefore, cardiovascular risk can be predicted early in the disease, and required measures can be taken.

Ethics Committee Approval: Ethics committee approval was received for this study from the Afyonkarahisar Clinical Studies Ethics Committee.

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

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References

1. Duzova A, Bakkaloglu A, Besbas N, Topaloglu R, Ozen S, Ozaltin F, et al. Role of A-SAA in monitoring subclinical inflammation and in colchicine dosage in familial Mediterranean fever. Clin Exp Rheumatol 2003; 21: 509-14.
2. Lachmann HJ, Sengül B, Yavuzşen TU, Booth DR, Booth SE, Bybee A, et al. Clinical and subclinical inflammation in patients with familial Mediterranean fever and in heterozygous carriers of MEFV mutations. Rheumatology (Oxford) 2006; 5: 746-50. [CrossRef]
3. Langevitz P, Livneh A, Neumann L, Buskila D, Shemer J, Amolsky D, et al. Prevalence of ischemic heart disease in patients with familial Mediterranean fever. Isr Med Assoc J 2001; 3: 9-12.
4. Onat A, Direskeneli H. Excess cardiovascular risk in inflammatory rheumatic diseases: pathophysiology and targeted therapy. Curr Pharm Des 2012; 18: 1465-77. [CrossRef]
5. Ngian GS, Sahhar J, Wicks IP, Van Doornum S. Cardiovascular disease in systemic sclerosis--an emerging association? Arthritis Res Ther 2011; 13: 237. [CrossRef]
6. Aksu K, Donmez A, Keser G. Inflammation-induced thrombosis: mechanisms, disease associations and management. Curr Pharm Des 2012; 18: 1478-93. [CrossRef]
7. Tomochika Y, Okuda F, Tanaka N, Wasaki Y, Tokisawa I, Aoyagi S, et al. Improvement of atherosclerosis and stiffness of the thoracic descending aorta with cholesterol-lowering therapies in familial hypercholesterolemia. Arterioscler Thromb Vasc Biol 1996; 16: 955-62. [CrossRef]
8. Neutel JM, Smith DH, Graettinger WF, Weber MA. Dependence of arterial compliance on circulationg neuroendocrine and metabolic factors in normal subjects. Am J Cardiol 1992; 69: 1340-4. [CrossRef]
9. Stancanelli B, Malatino LS, Malaponte G, Noto P, Giuffrè E, Caruso A, et al. Pulse pressure is an independent predictor of aortic stiffness in patients with mild to moderate chronic kidney disease. Kidney Blood Pres Res 2007; 30: 283-8. [CrossRef]
10. Kerekes G, Soltész P, Nurmohamed MT, Gonzalez-Gay MA, Turiel M, Végh E, et al. Validated methods for assessment of subclinical atherosclerosis in rheumatology. Nat Rev Rheumatol 2012; 8: 224-34. [CrossRef]
11. Dogan A, Icli A, Aksoy F, Varol E, Erdogan D, Ozaydin M, et al. Gamma-glutamyltransferase in acute coronary syndrome patients without ST elevation and its association with stenotic lesion and cardiac events. Coron Artery Dis 2012; 23: 39-44. [CrossRef]
12. Pompella A, Emdin M, Passino C, Paolicchi A. The significance of serum gamma-glutamyltransferase in cardiovascular diseases. Clin Chem Lab Med 2004; 42: 1085-91. [CrossRef]
13. Yildiz M, Masatlioglu S, Seymen P, Aytac E, Sahin B, Seymen HO. The carotid-femoral (aortic) pulse wave velocity as a marker of arterial stiffness in familial Mediterranean fever. Can J Cardiol 2006; 22: 1127-31. [CrossRef]
14. Livneh A, Langevitz P, Zemer D, Zaks N, Kees S, Lidar T, et al. Criteria for the diagnosis of familial mediterranean fever. Arthritis Rheum 1997; 40: 1879-85. [CrossRef]
15. Reference values for arterial stiffness' collaboration. Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: 'establishing normal and reference values. Eur Heart J 2010; 31: 2338-50. [CrossRef]
16. Yildiz M, Soy M, Kurum T, Ozbay G. Increased pulse wave velocity and shortened pulse wave propagation time in young patients with rheumatoid arthritis. Can J Cardiol 2004; 20: 1097-100.
17. Yildiz M, Yildiz BS, Soy M, Tutkan H. Impairment of arterial distensibility in premenopausal women with systemic lupus erythematosus. Kardiol Pol 2008; 66: 1194-9.
18. Cypiene A, Laucevicius A, Venalis A, Dadoniene J, Ryliskyte L, Petrulioniene Z, et al. The impact of systemic sclerosis on arterial wall stiffness parameters and endothelial function. Clin Rheumatol 2008; 27: 1517-22. [CrossRef]
19. Tunca M, Kirkali G, Soytürk M, Akar S, Pepys MB, Hawkins PN. Acute phase response and evolution of familial Mediterranean fever. Lancet 1999; 353: 1415. [CrossRef]
20. Akdogan A, Calguneri M, Yavuz B, Arslan EB, Kalyoncu U, Sahiner L, et al. Are familial Mediterranean fever (FMF) patients at increased risk for atherosclerosis? Impaired endothelial function and increased intima media thickness are found in FMF. J Am Coll Cardiol 2006; 48: 2351-3. [CrossRef]
21. Sari I, Karaoglu O, Can G, Akar S, Gulcu A, Birlik M, et al. Early ultrasonographic markers of atherosclerosis in patients with familial Mediterranean fever. Clin Rheumatol 2007; 26: 1467-73. [CrossRef]
22. Turgut O, Yilmaz A, Yalta K, Karadas F, Birhan Yilmaz M. Gammaglutamyltransferase is a promising biomarker for cardiovascular risk. Med Hypotheses 2006; 67: 1060-4. [CrossRef]