Effects of Trimetazidine Treatment on the Lipoprotein-Associated Phospholipase A_2 Level and Exercise Parameters in Patients with Stable Angina Pectoris

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ABSTRACT

Introduction: We examined the clinical effectiveness of trimetazidine (TMZ), a metabolic anti-ischemic agent, on lipoprotein-associated phospholipase A_2 (Lp-PLA_2) levels, which is considered a risk factor for cardiovascular events, and on exercise parameters in patients with stable angina pectoris (SAP).

Patients and Methods: The study included 30 patients (mean age 62.1 ± 8.3 years; range 47 to 77 years) with SAP and a positive exercise test result. Serum Lp-PLA_2 levels were measured at baseline. Exercise testing and Lp-PLA_2 measurements were repeated after at least 12 weeks of TMZ treatment.

Results: After TMZ treatment, Lp-PLA_2 levels decreased significantly (p= 0.006), and workload increased significantly (p= 0.048).

Conclusion: Trimetazidine treatment reduces serum Lp-PLA_2 levels via shifting cardiac metabolism, resulting in decreased production of free oxygen radicals and inflammation. This finding, together with improvements in exercise test parameters, suggests that TMZ may have a beneficial effect on the prognosis of patients with SAP.

Key Words: Angina, stable; trimetazidine; lipoprotein-associated phospholipase A_2

Kararlı Anjina Pektorisli Hastalarda Trimetazidin Tedavisinin Lipoprotein İlişkili Fosfolipaz A_2 Düzeyi ve Egzersiz Parametreleri Üzerine Etkisi

ÖZET

Giriş: Kararlı anjina pektorisli hastalarda, metabolik bir anti-iskemik ilaç olan trimetazidin (TMZ) tedavisinin risk faktörü olarak kabul edilen lipoprotein ilişkili fosfolipaz A_2 (Lp-PLA_2) düzeyi ve egzersiz parametreleri üzerine etkisi araştırıldı.

Hastalar ve Yöntem: Egzersiz testi pozitif olan kararlı anjina pektorisli 30 hasta (ort. yaş 62.1 ± 8.3; dağılım 47-77) çalışmaya alındı. Trimetazidin tedavisi öncesinde Lp-PLA_2 düzeyleri ölçüldü; 12 haftalık TMZ tedavisi sonrasında egzersiz testi ve Lp-PLA_2 ölçümleri tekrarlandı.

Bulgular: Trimetazidin tedavisi sonrasında Lp-PLA_2 düzeyleri anlamlı düşüş (p= 0.006), egzersiz iş yükü anlamlı artış (p= 0.048) gösterdi.

Sonuç: Trimetazidin tedavisi kardiyak metabolizma değişikliği sonucu serbest oksijen radikal oluşumunu ve enflamasyonu azaltarak Lp-PLA_2 düzeyinde anlamlı düşüş sağlamaktadır. Bu bulgu, egzersiz parametrelerindeki iyileşmelerle birlikte, TMZ tedavisinin kararlı anjina pektorisli hastaların prognozunda olumlu katkı sağlayabileceğini göstermektedir.

Anahtar Kelimeler: Anjina, kararlı; trimetazidin; lipoprotein ilişkili fosfolipaz A_2

INTRODUCTION

Angina pectoris caused by coronary artery disease is a major cause of disability worldwide. Two general approaches to the treatment of angina have been proven effective in reducing symptoms and increasing exercise treadmill time: drugs and revascularization. Trimetazidine (TMZ) is a well-known metabolic anti-ischemic agent, used both alone and in combination with hemodynamic anti-angina drugs in the treatment of stable angina pectoris

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(SAP). Its cytoprotective effect is due to the direct inhibition of mitochondrial long-chain 3-ketoacyl coenzyme A thiolase[1]. Trimetazidine optimizes cardiac metabolism by switching energy substrate preference from fatty-acid oxidation to glucose oxidation. The preferential use of glucose, which requires less oxygen to produce the same amount of adenosine triphosphate, allows the production of the energy required by the heart in ischemic conditions. This specific mechanism of action protects the heart from the deleterious consequences of ischemia[1].

Lipoprotein-associated phospholipase A_2 (Lp-PLA_2) is an enzyme produced by inflammatory cells such as macrophages, foam cells, and mast cells, as well as T-lymphocytes in atherosclerotic plaques and by liver cells; 80% of Lp-PLA_2 circulates bound mainly to low-density lipoprotein (LDL) cholesterol[2]. Lp-PLA_2 is not only a risk factor markedly associated with a higher incidence of cardiovascular events, but also a potentially important pathogenic factor participating in the progression of atherosclerosis[3]. Lp-PLA_2 has been found in both stable and vulnerable atherosclerotic plaques[4].

The purpose of this study was to assess the clinical effectiveness of TMZ on exercise performance and on decreasing Lp-PLA_2, which is considered a risk factor for cardiovascular events in patients with SAP. We evaluated the effect of TMZ on various exercise testing parameters and serum Lp-PLA_2 levels.

PATIENTS and METHODS

We selected 30 patients who had SAP and a positive result on the exercise test, the majority of which were men (80%). Exclusion criteria included acute coronary syndrome, high-risk exercise testing, evidence of bundle branch block, ventricular hypertrophy, pre-excitation syndrome, intraventricular conduction delays, congenital heart disease, valvular heart disease, a history of recent myocardial infarction (< 3 months), inadequate exercise on stress test, and anemia. The study protocol was approved by the institutional ethics review committee, and written informed consent was obtained from all participating subjects. Drug therapy regimens were not changed in patients with existing drug treatment. Patients were treated with TMZ 20 mg, 3 times a day, for at last three months.

The patients underwent maximal exercise testing at baseline and after at least 12 weeks of TMZ treatment. The exercise testing was performed using a treadmill according to the Bruce protocol, with a 12-lead electrocardiogram (ECG) recorded on a thermo-sensitive paper. Criteria of termination of the exercise test included retrosternal chest pain, ST-segment depression by 0.2 mV, ST-segment elevation by 0.2 mV, significant ventricular arrhythmia (frequent ventricular ectopy, multifocal ectopy, ventricular salvoes, nonsustained ventricular tachycardia, sustained ventricular tachycardia, or R-on-T ventricular ectopic beats), the occurrence of atrial fibrillation and/or flutter, intraventricular or atrioventricular conduction abnormalities, blood pressure elevation above 220 mmHg systolic and/or 110 mmHg diastolic, no increase or decrease in heart rate during exercise, no increase or decrease in blood pressure during exercise, and the patient's request for termination. During the exercise test, the following parameters were evaluated: resting and maximal exercise-induced heart rate, resting and maximal exercise-induced systolic and diastolic blood pressure measured noninvasively, double product calculated as the maximal exercise-induced systolic blood pressure multiplied by the maximal exercise-induced heart rate, total duration of exercise, exercise duration to diagnostic ST-segment change and to chest pain, resting duration to correction of ST-segment changes and relief of pain, peak workload measured in metabolic equivalents (METs), the magnitude of ST-segment depression on 12-lead ECG and the Athens QRS score, which was calculated using the amplitude of the Q, R, and S waves in leads aVF and V5 measured manually at rest and peak exercise. The Athens QRS score was calculated as follows:

Athens QRS score (mm) = (R-Q-S) aVF + (R-Q-S) V5.

Blood samples for the measurement of Lp-PLA_2 and other biochemical parameters were drawn at admission. Lp-PLA_2 measurement was repeated before the second exercise testing. The Lp-PLA_2 concentration (mass) was measured by turbidimetric immunoassay for the quantitative determination of Lp-PLA_2 in serum on an automated clinical chemistry analyzer (Thermo Sci. Konelab™ PRIME 60 Clinical Chemistry Analyzer). The PLAC test is a turbidimetric immunoassay using two highly specific monoclonal antibodies (2C10 and 4B4) for the direct measurement of Lp-PLA_2 concentration in human serum. Lp-PLA2 binds to monoclonal antibodies in the patient's serum, and its turbidity is measured at 570 nm in an automated clinical chemistry analyzer (Thermo Sci. Konelab™ PRIME 60 Clinical Chemistry Analyzer, Vantaa, Finland). The reference range was 120 to 342 ng/mL for women and 131 to 376 ng/mL for men. Commercial kits were used for the other chemical parameters. All parameters were measured in serum on an automated clinical chemistry analyzer (Thermo Sci. Konelab).

Statistical Analysis

Data were expressed as mean ± standard error. Alterations in Lp-PLA_2 and treadmill test parameters were analyzed using the Wilcoxon matched-pairs signed rank test. Correlations of Lp-PLA_2 with other biomarkers were evaluated using the Spearman correlation. A P-value of less than 0.05 was considered statistically significant.

RESULTS

Table 1 summarizes the characteristics of the study subjects. Six women and 24 men aged between 47 and 77 years (mean age, 62.1 ± 8.3 years) were included in the study. Six of the patients had undergone cardiac interventions previously (4 coronary artery bypass grafting surgery, 2 stenting). Existing anti-ischemic medications included beta-blockers (n= 14), cholesterol-lowering drugs (n= 10), angiotensin-converting

Table 1. Baseline characteristics of the patients

	N	%
Mean age (years)	62.1 ± 8.3	
Gender (M/F)	24/6	80/20
History of		
Diabetes	7	23
Hypertension	14	47
COPD	1	3
CAD	6	20
Current smokers	3	10
Glucose (mg/dL)	101.7 ± 18.2	
Plasma cholesterol (mg/dL)	176.4 ± 45.3	
Plasma triglycerides (mg/dL)	136.1 ± 86.4	
LDL-cholesterol (mg/dL)	102.2 ± 40.4	
HDL-cholesterol (mg/dL)	48.3 ± 13.1	
Lp-PLA_2 (mg/dL)	287.4 ± 216.9	
Hematocrit (%)	40.6 ± 3.5	
Creatinine (mg/dL)	1.0 ± 0.2	

enzyme inhibitors or angiotensin II receptor blockers (n= 13), a calcium channel blocker (n= 1), and nitrate treatment (n= 4).

Our results regarding the effect of TMZ on exercise test parameters and Lp-PLA_2 levels are presented in Table 2. Twenty-two patients (73%) had a subsequent exercise test after TMZ treatment. Both the total duration of the exercise test and the duration of the exercise test to the occurrence of diagnostic ST-segment changes showed increases after 12 weeks of TMZ treatment, but these changes were not statistically significant. Double product, which reflects the adaptation of the cardiovascular system to exercise, decreased after TMZ treatment. The mean value of the double product decreased from 25.404.1 to 25.329.3, but this difference was not statistically significant (p= 0.787). Athens QRS scores both at rest and at peak and the duration of ST-segment recovery to baseline showed improvements, but these were not statistically significant. All subjects stopped exercise on exhaustion. Six patients (20%) had chest pain during exercise. There was no change in the duration from the onset to the relief of chest pain. Workload after TMZ treatment increased compared to baseline. The mean workload before TMZ treatment was 8.2 METs, compared to 9.6 METs after TMZ treatment. The difference of 1.4 METs was statistically significant (p< 0.05).

DISCUSSION

Stable angina is the main symptom of established CAD. In addition, atherosclerosis is the common pathological substrate of chronic stable angina and acute coronary syndromes. The aim of stable angina management is symptomatic relief and secondary prevention[5]. European guidelines on the management of stable CAD distinguish two basic medication types: survival-improving drugs (anti-platelet drugs, ACE-I, beta-blockers, and statins) and symptom-relieving agents preserving the quality of life (beta-blockers; nitrates; calcium channel blockers; sinus node inhibitors, such as ivabradine and molsidomine; and metabolic drugs such as TMZ)[6].

Exhibiting a metabolic mechanism of action, TMZ optimizes cardiac metabolism, leading to increased cellular tolerance to ischemia and a change in the oxygen supply-to-demand ratio. The anti-ischemic effect of TMZ is obtained at a cellular level by shifting the energy substrate preference from fatty-acid oxidation to glucose oxidation[1]. It may also contribute to the preservation of intracellular levels of phosphocreatine and ATP, the decrease in free radical-induced injury and the improvement in endothelial function[7-9].

Zhou et al. reported that TMZ protected against smoking-induced left ventricular remodeling via attenuating oxidative stress, apoptosis, and inflammation[10]. Kuralay et al. found that TMZ significantly reduced CRP and TNF-α levels after coronary angioplasty[11].

Lipoprotein-associated phospholipase A_2 is a novel and unique biomarker, highly specific for vascular inflammation and

Table 2. Comparison of the exercise parameters at baseline and after trimetazidine treatment

Test parameters	Baseline (n= 30)	12 weeks after TMZ treatment (n= 22)	p
Total exercise duration (s)	422.0 ± 143.5	440.0 ± 130.9	0.303
Duration of exercise to the occurrence of diagnostic ST-segment depression (s)	322.8 ± 121.5	325.7 ± 146.4	0.427
Duration of recovery to baseline (s)	257.0 ± 179.1	254.1 ± 215.4	0.474
Peak workload (METs)	8.2 ± 2.4	9.6 ± 2.2	0.048
Double product	25329.3 ± 4186.1	25404.1 ± 4786.1	0.787
Athens QRS score at rest	16.6 ± 14.3	12.2 ± 9.6	0.434
Athens QRS score at peak exercise	12.2 ± 9.6	10.7 ± 10.8	1.0
Lp-PLA_2 (mg/dL)	287.4 ± 216.9	176.3 ± 45.3	0.006

atherosclerosis, and a positive correlation with CV events has been sufficiently demonstrated by a large number of scientific and clinical studies[12-16]. Currently, Lp-PLA_2 is recommended as an adjunct to traditional risk factors in the process of CV risk assessment[17].

We think that TMZ reduced Lp-PLA_2 levels via shifting cardiac metabolism, resulting in decreased production of free oxygen radicals and inflammation.

The effectiveness of TMZ added to standard anti-ischemic treatment has been confirmed in many studies[18,19]. In our study, we evaluated the effectiveness of 12-week TMZ treatment on exercise test parameters. A comparison of the exercise test parameters before and after 12 weeks of TMZ treatment showed improvements in all parameters following TMZ treatment, including total exercise duration, peak workload, duration of the exercise to the occurrence of diagnostic ST-segment changes, severity of the ischemic changes (Athens score), and in parameters reflecting adaptation of the cardiovascular system to exercise (double product). Among them, the difference in the peak workload was statistically significant.

CONCLUSION

Growing evidence suggests that plasma Lp-PLA_2 activity plays both an independent and additive role among other common major cardiovascular risk factors, increasing coronary atherosclerotic burden. The present study provides novel evidence suggesting that 12-week treatment with TMZ reduces Lp-PLA_2 serum level and improves exercise test parameters. Further studies are required to determine whether these beneficial effects would actually improve morbidity and mortality in the long term.

CONFLICT of INTEREST

The authors reported no conflict of interest related to this article.

AUTHORSHIP CONTRIBUTIONS

Consept/Desing: CB, ZY
Analysis/Interpretation: OA, AK, CK
Data acquisition: ZY, EK, UC
Writing: CB
Critical revision: UC, AY, OA, ZY, EK, AK, CK
Final approval: All of authors

REFERENCES

1. Hu B, Li W, Xu T, Chen T, Guo J. Evaluation of trimetazidine in angina pectoris by echocardiography and radionuclide angiography: a meta-analysis of randomized, controlled trials. Clin Cardiol 2011;34:395-400.
2. Epps KC, Wilensky RL. Lp-PLA2-a novel risk factor for high-risk coronary and carotid artery disease. J Intern Med 2011;269:94-106.
3. Colley KJ, Wolfert RL, Cobble ME. Lipoprotein associated phospholipase A(2): role in atherosclerosis and utility as a biomarker for cardiovascular risk. EPMA J 2011;2:27-38.
4. Zalewski A, Macphee C. Role of lipoprotein-associated phospholipase A2 in atherosclerosis: biology, epidemiology, and possible therapeutic target. Arterioscler Thromb Vasc Biol 2005;25:923-31.
5. Siama K, Tousoulis D, Papageorgiou N, Siasos G, Tsiamis E, Bakogiannis C, et al. Stable angina pectoris: current medical treatment. Curr Pharm Des 2013;19:1569-80.
6. Fox K, Garcia MA, Ardissino D, Buszman P, Camici PG, Crea F, et al. Guidelines on the management of stable angina pectoris: executive summary: The Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology. Eur Heart J 2006;27:1341-81.
7. Bertomeu-Gonzalez V, Bouzas-Mosquera A, Kaski JC. Role of trimetazidine in management of ischemic cardiomyopathy. Am J Cardiol 2006;98(5A):19J-24J.
8. Maridonneau-Parini I, Harpey C. Effect of trimetazidine on membrane damage induced by oxygen free radicals in human red cells. Br J Clin Pharmacol 1985;20:148-51.
9. Park KH, Park WJ, Kim MK, Park DW, Park JH, Kim HS, et al. Effects of trimetazidine on endothelial dysfunction after sheath injury of radial artery. Am J Cardiol 2010;105:1723-7.
10. Zhou X, Li C, Xu W, Chen J. Trimetazidine protects against smoking-induced left ventricular remodeling via attenuating oxidative stress, apoptosis, and inflammation. PLoS One 2012;7:e40424.
11. Kuralay F, Altekin E, Yazlar AS, Onvural B, Goldeli O. Suppression of angioplasty-related inflammation by pre-procedural treatment with trimetazidine. Tohoku J Exp Med 2006;208:203-12.
12. Packard CJ, O'Reilly DS, Caslake MJ, McMahon AD, Ford I, Cooney J, et al. Lipoprotein-associated phospholipase A2 as an independent predictor of coronary heart disease. West of Scotland Coronary Prevention Study Group. N Engl J Med 2000;343:1148-55.
13. Corson MA, Jones PH, Davidson MH. Review of the evidence for the clinical utility of lipoprotein- associated phospholipase A2 as a cardiovascular risk marker. Am J Cardiol 2008;101:41F-50F.
14. Koenig W, Twardella D, Brenner H, Rothenbacher D. Lipoprotein-associated phospholipase A2 predicts future cardiovascular events in patients with coronary heart disease independently of traditional risk factors, markers of inflammation, renal function, and hemodynamic stress. Arterioscler Thromb Vasc Biol 2006;26:1586-93.
15. Gerber Y, McConnell JP, Jaffe AS, Weston SA, Killian JM, Roger VL. Lipoprotein-associated phospholipase A2 and prognosis after myocardial infarction in the community. Arterioscler Thromb Vasc Biol 2006;26:2517-22.
16. Sabatine MS, Morrow DA, O'Donoghue M, Jablonksi KA, Rice MM, Solomon S, et al. Prognostic utility of lipoprotein-associated phospholipase A2 for cardiovascular outcomes in patients with stable coronary artery disease. Arterioscler Thromb Vasc Biol 2007;27:2463-9.
17. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002;106:3143-421.
18. Güler N, Eryonucu B, Güneş A, Güntekin U, Tuncer M, Özbek H. Effects of trimetazidine on submaximal exercise test in patients with acute myocardial infarction. Cardiovasc Drugs Ther 2003;17:371-4.
19. Koylan N, Bilge AK, Adalet K, Mercanoğlu F, Büyüköztürk K, TTS Group. Comparison of the effects of trimetazidine and diltiazem on exercise performance in patients with coronary heart disease. The Turkish trimetazidine study (TTS). Acta Cardiol 2004;59:644-50.