Effects of Fenofibrate Treatment on Aortic Stiffness in Patients with Pure Hypertriglyceridemia

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ABSTRACT

Introduction: Hypertriglyceridemia is known as an independent risk factor for coronary artery disease (CAD). Fenofibrate that is used for the treatment of hypertriglyceridemia can prevent cardiovascular events in patients with CAD. However, there is little information regarding the vascular effects of fenofibrate on arterial wall stiffness in patients with hypertriglyceridemia and without CAD, diabetes mellitus (DT), and hypertension (HT). The objective of this study is to evaluate the effects of fenofibrate treatment on the arterial stiffness in the patients with pure hypertriglyceridemia.

Patients and Methods: We included 37 patients with hypertriglyceridemia without CAD, HT, and DT in this study. We performed pre- and post-treament physical examination of the patients and took their blood samples. Patients were allocated fenofibrate for a duration of 168 ± 14 days for its administration. We assessed arterial stiffness by aortic pulse wave velocity (PWV) using a SphygmoCor device. Importantly, we estimated central arterial pressure waveform parameters by radial artery applanation tonometry and used augmentation index (AIx) as a measure of wave reflections.

Results: Fenofibrate treatment resulted in significantly greater reductions in total cholesterol (201.3 ± 61.0 mg/dL vs. 270.0 ± 93.4 mg/dL), triglycerides (261.3 ± 234.3 mg/dL vs. 704.7 ± 338.7 mg/dL), and the C/H levels (5.3 ± 2.6 vs. 7.2 ± 1.9, respectively) as compared with the pretreatment levels ($p< 0.001$). There was a tendency of high-sensitivity C-reactive protein (hs-CRP) to decline after fenofibrate treatment as change in hs-CRP was significant (0.47 ± 0.41 mg/dL vs. 0.32 ± 0.31 mg/dL respectively, $p< 0.01$). AIx remained unchanged from the pretreatment levels (24.2% ± 12.4% vs. 22.0% ± 11.4%, respectively, $p> 0.05$). There was a significant reduction in PWV after fenofibrate treatment (11.3 ± 2.9 m/s vs. 9.2 ± 2.2 m/s, $p= 0.001$).

Conclusion: Fenofibrate treatment appears to effectively improve the arterial wall stiffness in the patients with pure hypertriglyceridemia.

Key Words: Hypertriglyceridemia; aortic stiffness; pulse wave velocity; fenofibrate; augmentation index

İzole Hipertrigliseridemi Hastalarında Fenofibrat Tedavisinin Aortik Sertlik Üzerine Etkisi

ÖZET

Giriş: Hipertrigliseridemi, koroner arter hastalığı (KAH) için bağımsız bir risk faktörü olarak bilinir. Hipertrigliseridemi tedavisinde kullanılan fenofibratın KAH hastalarında kardiyovasküler olayları önleyebildiği bilinmektedir. Bununla birlikte, fenofibratın KAH'ı, diabetes mellitusu ve hipertansiyonu olmayan saf hipertrigliseridemi hastalarında arter duvar sertliği üzerindeki vasküler etkileri hakkında çok az bilgi vardır. Bu çalışmada saf hipertrigliseridemi hastalarında fenofibrat tedavisinin arteryel duvar sertliğe olan etkisini değerlendirmek amaçlanmıştır.

Hastalar ve Yöntem: Çalışmaya KAH'ı, hipertansiyonu ve diabetes mellitusu olmayan 37 saf hipertrigliseridemi hastası dahil edildi. Tedavi öncesi ve sonrasında hastaların fizik muayeneleri yapıldı ve kan örnekleri alındı. Hastalara 168 ± 14 gün boyunca fenofibrat tedavisi verildi. Arteryel duvar sertliği, bir SphygmoCor cihazı kullanılarak aort nabız dalgası hızı (PWV) ile değerlendirildi. Santral arteryel basınç dalga formu parametreleri radyal arter aplikasyon tonometrisi ile hesaplandı ve dalga yansımasının ölçüsü olarak augmentasyon indeksi (AIx) kullanıldı.

Bulgular: Fenofibrat tedavisi, tedavi öncesi ile karşılaştırıldığında toplam kolesterol, trigliserit ve C/H düzeylerinde belirgin şekilde anlamlı düşüşler sağlamıştır (201.3 ± 61.0 mg/dL, 270.0 ± 93.4 mg/dL ve 261.3 ± 234.3 mg/dL, 704.7 ± 338.7 mg/dL ve 5.3 ± 2.6 ve 7.2 ± 1.9, sırasıyla, $p< 0.001$). Hs-CRP'de fenofibrat tedavisinden sonra anlamlı düşme eğilimi tespit edilmiştir (sırasıyla 0.47 ± 0.41 mg/dL ve 0.32 ± 0.31 mg/dL, sırasıyla, $p< 0.01$). AIx'de anlamlı değişim izlenmemiştir (sırasıyla %24.2 ± 12.4 ve %22.0 ± 11.4, $p> 0.05$). Fenofibrat tedavisinden sonra PWV'de anlamlı bir azalma izlenmiştir (11.3 ± 2.9 m/s ve 9.2 ± 2.2 m/s, $p= 0.001$).

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Sonuç: Fenofibrat tedavisinin, saf hipertrigliseridemi hastalarında arteryel duvar sertliğini olumlu şekilde etkilediği gösterilmiştir.

Anahtar Kelimeler: Hipertrigliseridemi; aort sertliği; nabız dalga hızı; fenofibrat; augmentasyon indeksi

INTRODUCTION

Atherosclerosis is an inflammatory process that develops because of hyperlipidemia and lipid oxidation in the vascular intima layer[1]. Several clinical studies have been conducted to date with the aim to reduce cardiovascular mortality and the lower-density lipid (LDL) cholesterol in the foreground. Investigation of cardiovascular effects of isolated triglyceride (TG) elevation is difficult because there are many comorbidities associated with this group of patients. A study found that TG elevation was an independent predictor of cardiovascular risk after major meta-analyses and studies[2]. These data have encouraged clinicians to treat the TG levels in patients with optimal LDL cholesterol levels. Fenofibrates are fibric acid derivatives that are administered orally and used conventionally for the treatment of hypertriglyceridemia[3]. Fibrates can decrease TG concentrations and elevate the high-density lipid (HDL) cholesterol[4,5]. In patients with significant hypertriglyceridemia, some trials have evaluated the benefits of a TG-lowering therapy on cardiovascular morbidity and mortality[6,7].

A large number of non-invasive methods have been developed to evaluate the abnormalities of the arterial walls for defining the atherosclerotic process. Pulse wave velocity (PWV) and augmentation index (AIx) are some non-invasive methods that are used to show aortic stiffness. Aortic stiffness can predict cardiovascular mortality in the patients with end-stage renal disease, hypertension (HT), and diabetes mellitus (DM)[8-10]. AIx can predict all the causes and cardiovascular mortality in patients with end-stage renal failure[11]. In Framingham cohort, arterial stiffness (assessed by PWV) was associated with an increased risk for developing a first cardiovascular event[12,13].

The purpose of this study is to determine the effects of fenofibrate medication on PWV, AIx, and inflammatory markers in patients with isolated hypertriglyceridemia and without CAD, HT, and DM.

PATIENTS and METHODS

Subjects

This study included 37 patients (32 males and 5 females) with pure hypertriglyceridemia that cannot be controlled by lifestyle changes and who were eligible for fulfilling the following lipid criteria: > 500 mg/dL of serum TGs, < 250 mg/dL of serum cholesterol, and < 130 mg/dL of serum LDL levels. Fenofibrate was administered at a dose of 267 mg/day for about 168 ± 14 days to lower the TG levels without the use of any other lipid-lowering drugs. We included the control group to show the high PWV values in the patient group before the treatment. In total, 28 (19 males and 9 females) age- and gender-matched healthy control group subjects were included in this study.

We excluded the patients with the following diseases or problems from the study: CAD, stable angina pectoris, unstable angina pectoris, acute coronary syndromes, DT, HT, chronic liver or kidney diseases (serum creatinine level of > 1.5 mg/dL or elevation of the alanine transaminase levels more than threefold the upper limit of normal), anemia, endocrine or neurological diseases, malignancy, taking lipid-lowering medications, immunosuppression treatments, steroids, and alcohol overuse. An informed consent letter was obtained from all the patients with the confirmation of local ethic committee approval no. 2014.3/25.

Laboratory Analyses

Before and after fenofibrate treatment with 12-hour fasting period, the blood samples were collected in the citrate-treated tubes for measuring the lipids, plasma glucose, renal and kidney function tests for all the patients. Immunoturbidimetric assay modular system random access analyzer (Dade Behring, Deerfield, IL, USA) was used for measuring the concentrations of hs-CRP. After 12 hours of fasting, the patients removed heavy outer clothing, shoes, and any heavy accessories. Then, digital weight and height measurement was performed. Body mass index (BMI) was calculated by the formula of weight (in kilograms) over height squared (in meters). LDL cholesterol levels were determined by using the Friedewald formula in the laboratory because of the lack of specific kit for LDL measurement.

Measurement of PWV and AIx

Measurements were taken under standardized conditions and according to the guidelines on PWV analysis[14]. A single investigator used the applanation tonometry (SPC-301, Millar Instruments, Houston, Texas) to measure the pressure waves from the femoral, carotid, and radial arteries. Data were analyzed with the SphygmoCor Blood Pressure Analysis System (BPAS-1, AtCor Medical, Sydney, Australia). Measurements were applied from the carotid to femoral artery for PWV that was referenced to a contemporaneously recorded electrocardiogram. The time difference between the measurement time of carotid and femoral waveforms was defined as the transit time. The distance between the surface markings of the sternal notch and the femoral artery was used to estimate the difference in path length, and then PWV adjusted for mean blood pressure was calculated.

The radial pulse of non-dominant arms was used for measuring the aortic AIx. The systolic part of the central arterial waveform is characterized by two pressure peaks: the first peak is caused by left ventricular ejection and the second peak is the result of pulse wave reflection. The degree of difference between both the pressure peaks reflects the central arterial pressure that is augmented by wave reflection. AIx is a measurement of the difference between the second and first systolic peaks defined as a percentage of the pulse pressure (pp). Three readings were taken for each patient, and the average of these readings was used for the analysis. Heart rate (HR) and pp were calculated automatically by SphygmoCor Blood Pressure Analysis System. Pressure waveforms were recorded from the radial arteries for corresponding central aortic pressure measurement[15].

Statistical Analysis

Statistical analyses were performed using SPSS 17.0 (Chicago). The Kolmogorov–Smirnov test was used to analyze the normality of the data. Continuous data were expressed as mean ± standard deviation, and categorical data were expressed as percentages. Chi-square test was used to assess the differences in categorical variables between the groups. The relationships among the parameters were assessed by using Pearson's or Spearman's correlation analysis according to the normality of the data. The differences between the patient subgroups were tested using Mann-Whitney U test or Student's t-test wherever deemed appropriate. Pre- and post-treatment data were analyzed using paired t-test. p value < 0.05 was considered statistically significant for this study. By using the G power software, the alpha level of 0.05 and the power value (1-beta) of 0.80 was obtained. The calculated effect size was 0.35, and the actual power was 0.80. The number of total subjects to be included in the study was predicted to be 70.

RESULTS

This study included patient and healthy control groups for the comparison of pretreatment arterial stiffness. Age, BMI, sex distribution, and smoking status did not differ between the groups at baseline evaluation.

The pretreatment lipid profile parameters of the patient and control groups were all significantly different except HDL levels (42.6 ± 6.8 mg/dL vs. 38.2 ± 10.7 mg/dL), TG (224.2 ± 42.4 mg/dL vs. 704.7 ± 338.7 mg/dL), total cholesterol (168.0 ± 36.8 mg/dL vs. 270.0 ± 93.4 mg/dL), LDL (96.3 ± 27.4 mg/dL vs. 114 ± 14.9 mg/dL), and C/H measurements (3.9 ± 1.4 vs. 7.2 ± 1.9) were significantly different between the control group and patients (p< 0.05). However, HDL levels were not significantly different (42.6 ± 6.8 mg/dL vs. 38.2 ± 10.7 mg/dL, respectively, p> 0.05). Pretreatment mean PWV values of patient and control groups were statistically significant (11.3 ± 2.9 m/s vs. 10.2 ± 2.7 m/s respectively, p= 0.04). Additionally, the mean central systolic blood pressure between the patient and control groups was statistically significant (125.2 ± 19.1 mmHg vs. 112.0 ± 15.6 mmHg, respectively, p= 0.007) within the normal values of arterial tension measurements. The pp (44.4 ± 15.0 mmHg vs. 41.4 ± 12.3 mmHg respectively, p> 0.05), HR (74.6 ± 10.0 bpm vs. 74.8 ± 12.2 bpm respectively, p> 0.05), and AIx measurements (24.2 ± 12.4% vs. 22.6% ± 12.6%, respectively, p> 0.05) in the patient and control groups were not significantly different (Table 1).

As expected, fenofibrate treatment resulted in significantly greater reductions in total cholesterol (201.3 ± 61.0 mg/dL vs. 270.0 ± 93.4 mg/dL), TGs (261.3 ± 234.3 mg/dL vs. 704.7 ± 338.7 mg/dL), and the C/H levels (5.3 ± 2.6 vs. 7.2 ± 1.9, respectively) as compared with the pretreatment values (p< 0.001). LDL (109.3 ± 24.7 mg/dL vs. 114 ± 14.9 mg/dL) and HDL (40.8 ± 11.6 mg/dL vs. 38.2 ± 10.7 mg/dL) remained statistically unchanged (p> 0.05). There was a tendency for hs-CRP to decline after fenofibrate treatment, and change in hs-CRP was noticed to be significant (0.47 ± 0.41 mg/dL vs. 0.32 ± 0.31 mg/dL, respectively, p< 0.01). Uric acid levels were significantly reduced (6.0 ± 1.3 mg/dL vs. 4.4 ± 0.9 mg/dL, p< 0.001) after fenofibrate treatment. There is a tendency for aspartate transaminase to increase after fenofibrate treatment, but the magnitude of change in the values was insignificant (24.7 ± 12.3 IU/L vs. 26.4 ± 9.3 uı, p> 0.05).

Systolic blood pressure and HR decreased similarly over time (138.4 ± 17.4 mmHg vs. 127.2 ± 12.3 mmHg and 74.6 ± 10.0 bpm vs. 69.4 ± 8.7 bpm, respectively, p< 0.001). Decrease in diastolic blood pressure (81.4 ± 14.1 mmHg vs. 79.3 ± 11.2 mmHg, respectively) and mean arterial pressure (101.4 ± 14.7 mmHg vs. 96.8 ± 10.8 mmHg, respectively) was not significant (p> 0.05). Additionally, central systolic pressure (125.2 ± 19.1 mmHg vs. 118.1 ± 17.6 mmHg, respectively), central pulse pressure (44.4 ± 15.0 mmHg vs. 43.4 ± 12.3 mmHg), and AIx (24.2% ± 12.4% vs. 22.0% ± 11.4%, respectively) remained unchanged (p> 0.05). Table 2 shows the subject characteristics at baseline and after treatment.

There was a significant reduction in PWV after fenofibrate treatment (11.3 ± 2.9 m/s vs. 9.2 ± 2.2 m/s, p= 0.001) (Figure 1).

DISCUSSION

Our short-time study showed that fenofibrate treatment had reduced PWV in the patients with pure hypertriglyceridemia and without DT, HT, and CAD, whereas Alx remained unchanged.

Epidemiologic and clinical studies have shown that PWV is measured through the gold standard method for the non-

Table 1. Baseline characteristics of patients and individuals in control group

	Control group (n= 28)	Patient group (n= 37)	p
Age (years)	51.2 ± 13.2	46.8 ± 9.4	0.09
Gender			
Male (n, %)	19 (67.9)	32 (86.5)	0.07
Female (n, %)	9 (32.1)	5 (13.5)	
Smoker	4	6	0.09
Height (cm)	169.1 ± 6.1	172.4 ± 8.4	0.04
Weight (kg)	80.4 ± 16.4	87.0 ± 12.2	0.01
BMI (kg/m^2)	28.0 ± 5.0	29.2 ± 3.2	0.13
Pulse wave parameters			
PWV (m/s)	10.2 ± 2.7	11.3 ± 2.9	0.04
cSP (mmHg)	112.0 ± 15.6	125.2 ± 19.1	0.007
cPP (mmHg)	41.4 ± 12.3	44.4 ± 15.0	0.54
HR (bpm)	74.8 ± 12.2	74.6 ± 10.0	0.86
Alx (%)	22.6 ± 12.6	24.2 ± 12.4	0.49
Lipid parameters			
TG (mg/dL)	224.2 ± 42.4	704.7 ± 338.7	< 0.001
TC (mg/dL)	168.0 ± 36.8	270.0 ± 93.4	< 0.001
LDL (mg/dL)	96.3 ± 27.4	114 ± 14.9	< 0.05
HDL (mg/dL)	42.6 ± 6.8	38.2 ± 10.7	0.089
C/H	3.9 ± 1.4	7.2 ± 1.9	< 0.05

BMI: Body mass index, PWV: Pulse wave velocity, cSP: Central systolic pressure, cPP: Central pulse pressure, HR: Heart rate, AIx: Augmentation index, TG: Triglyceride, TC: Total cholesterol, LDL: Low density lipoprotein, HDL: High-density lipoprotein.

invasive assessment of aortic stiffness[16]. Recent studies have demonstrated that PWV reflects the central elastic arteries rather than peripheral vascular arterial stiffness[17,18]. Increased arterial stiffness causes abnormal coronary blood flow, micro-vascular damage, atherogenic environment, and increased cardiac afterload, which are the risk factors for cardiovascular events[19,20]. Higher PWV values were associated with increased mortality and morbidity in patients with CAD[21]. In patients with hypercholesterolemia, the usage of long-term statin treatment has shown improvement in arterial stiffness. Nevertheless, the beneficial outcomes of the usage of short-term statins on the improvement of arterial stiffness are still conflicting[22,23].

Fenofibrate is commonly referred as peroxisome proliferator–activated receptor-α agonists. Fenofibrate has anti-inflammatory and endothelium-protecting effects. Fibrates increase HDL levels and decrease the plasma levels of TG. Fibrates inhibits the leukocyte migration into the intima by decreasing the secretion of monocyte chemoattractant protein 1 in the endothelial cells[24]. Numerous experimental and clinical studies suggest that fibrate therapy improves endothelial function by reducing the oxidative stress and antiangiogenic effects[25]. Improvement in the endothelial function and a reduction in arterial stiffness were observed in glucose-tolerant men with obesity after treatment with fenofibrate and pioglitazone[26]. In subjects with type II DT, fenofibrate treatment for a long time was not associated with beneficial changes on the carotid intima media thickness and AIx[27]. The diabetes atherosclerosis intervention study demonstrated a significant reduction in the burden of focal angiographic coronary artery lesions after three years of fenofibrate treatment in 418 men with type II diabetes[7,13]. In a Japanese study of 594 patients with HT and without diabetes, fenofibrate did not change the mean intima media thickness (IMT), but slowed the progression of IMT/arterial diameter ratio[28].

Just like previous studies, significant changes were observed in the hs-CRP levels in our study. In some other studies, fenofibrate treatment was reported to reduce the plasma CRP levels[29]. No significant changes were observed in Alx in our study. On the contrary, the study of 16 men with obesity and

Table 2. Pretreatment and post-treatment measurements of the patients

	Pretreatment (n= 37)	Post-treatment (n= 37)	p
TG (mg/dL)	704.7 ± 338.7	261.3 ± 234.3	< 0.001
TC (mg/dL)	270.0 ± 93.4	201.3 ± 61.0	< 0.001
LDL (mg/dL)	114 ± 14.9	109.3 ± 24.7	0.46
HDL (mg/dL)	38.2 ± 10.7	40.8 ± 11.6	0.17
C/H	7.2 ± 1.9	5.3 ± 2.6	< 0.001
SBP (mmHg)	138.4 ± 17.4	127.2 ± 12.3	< 0.001
DBP (mmHg)	81.4 ± 14.1	79.3 ± 11.2	< 0.001
MAP (mmHg)	101.4 ± 14.7	96.8 ± 10.8	< 0.001
UA (mg/dL)	6.0 ± 1.3	4.4 ± 0.9	< 0.001
AST (IU/L)	24.7 ± 12.3	26.4 ± 9.3	0.48
hs-CRP (mg/dL)	0.47 ± 0.41	0.32 ± 0.31	0.01
Pulse wave parameters			
PWV (m/s)	11.3 ± 2.9	9.2 ± 2.2	< 0.001
cSP (mmHg)	125.2 ± 19.1	118.1 ± 17.6	0.01
cPP (mmHg)	44.4 ± 15.0	43.4 ± 12.3	0.42
HR (bpm)	74.6 ± 10.0	69.4 ± 8.7	0.009
AIx (%)	24.2 ± 12.4	22.0 ± 11.4	0.22

TG: Triglyceride, TC: Total cholesterol, LDL: Low density lipoprotein, HDL: High-density lipoprotein, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure, UA: Uric acid, AST: Aspartate transaminase, hs-CRP: High-sensitivity C-reactive protein, PWV: Pulse wave velocity, cSP: Central systolic pressure, cPP: Central pulse pressure, HR: Heart rate, AIx: Augmentation index.

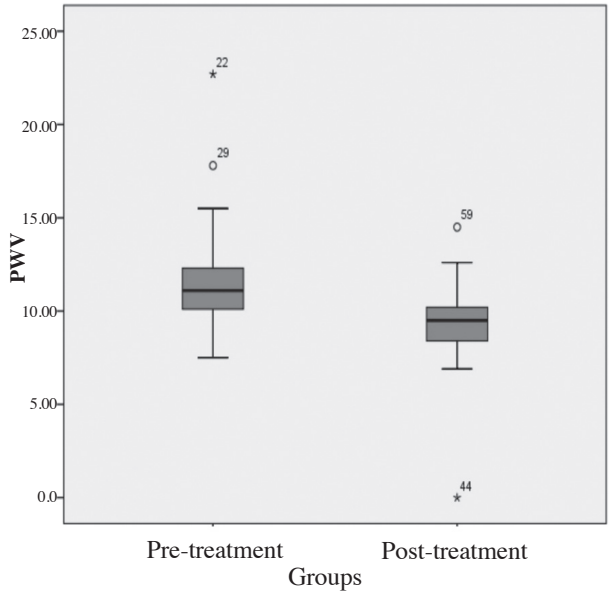

Figure 1. Pretreatment and post-treatment measurements of PWV.

without diabetes, three-month treatment with fenofibrate significantly reduced AIx, whereas in long-term fibrate treatment in patients with type II DT, no effect on AIx was observed[26,27]. These opposing results may be related to the number or demographic characteristics of the patients included in the study.

In the existing literature, there are studies of subjects with CAD, DT, and HT. Yu et al. showed that fibrates reduce arterial stiffness in the patients with CAD[30]. Wang et al. demonstrated decline in PWV values after fibrate treatment in the patient group with CAD, HT, and diabetes[31].

The effect of fenofibrate treatment on arterial stiffness cannot be clearly determined because of conflicting results in the literature. The involvement of patient groups with comorbid diseases in previous studies may explain different outcomes. Our study was different from the other studies as it observed the effect of fenofibrate therapy in a homogeneous patient population as closely as possible without any comorbid diseases. In our short-term study, the impact of age-dependent changes can also be overlooked. In the same population, after about 168 ± 14 days of treatment, there was significant changes in the PWV values of patients without CAD, DT, and HT after fenofibrate treatment.

In our study, the reduction in PWV values could be explained by the fenofibrate effect on improving the endothelial function

while reducing the oxidative stress; however, the mechanisms of fenofibrate treatment still remain unclear. In our daily practice, the lowering of LDL cholesterol values is prioritized. In our study, TG treatment was shown to be crucial in preventing the cardiovascular diseases.

CONCLUSION

This study shows that fenofibrate treatment for about six month reduces aortic stiffness (PWV) in patients with pure hypertriglyceridemia and without CAD, HT, and DT. These positive effects of fenofibrate on arterial stiffness can reduce the cardiovascular risk in patients with pure hypertriglyceridemia.

LIMITATIONS

This study was a single center study with a small number of patients. Non-HDL cholesterol could not be used because it was not included in the lipid panel results in our laboratory. We could not use the specific LDL kit due to high cost. This study should be performed in larger patient groups and similar results should be renewed.

Ethics Committee Approval: Ethics committee approval was received for this study from the Kartal Koşuyolu High Speciality Training and Research Hospital local ethic committee (Number: 2014.3/25).

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept/Design - SE, İİ ,CK; Analysis/Interpretation - SE, AG, SO; Data Collection - SE, EA, MY, SK; Writing - SE, SO; Critical Revision - İİ, CK; Final Approval - All of authors; Statistical Analysis - SE, SO; Overall Responsibility – All of authors.

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REFERENCES

1. Hennekens CH, Gaziano JM . Antioxidants and heart disease: epidemiology and clinical evidence. Clin Cardiol 1993;16:10-3.
2. Sarwar N, Danesh J, Eiriksdottir G, Sigurdsson G, Wareham N, Bingham S, et al. Triglycerides and the risk of coronary heart disease: 10 158 incident cases among 262 525 participants in 29 Western prospective studies. Circulation 2007;115:450-8.
3. Balfour JA, McTavish D, Heel RC. Fenofibrate. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic use in dyslipidaemia. Drugs 1990;40:260-90.
4. Robins SJ, Collins D, Wittes JT, Papademetriou V, Deedwania PC, Schaefer EJ, et al. Relation of gemfibrozil treatment and lipid levels with major coronary events: VA-HIT: A randomized controlled trial. JAMA 2001;285:1585-91.
5. Frost RJ, Otto C, Geiss HC, Schwandt P, Parhofer KG. Effects of atorvastatin versus fenofibrate on lipoprotein profiles, low-density lipoprotein subfraction distribution, and hemorheologic parameters in type 2 diabetes mellitus with mixed hyperlipoproteinemia. Am J Cardiol 2001;87:44-8.
6. Reiner Z. Are elevated serum triglycerides really a risk factor for coronary artery disease? Cardiology 2015;131:225-7.
7. Acartürk E, Dörtlemez H. Efficacy and safety of fenofibrate in primary hyperlipidemic subjects. Turk Kardiyol Dern Ars 2000;28:121-5.
8. Boutouyrie P, Isabelle A, Asmar R, Gatier I, Benetos A, Lacolley P, et al. Aortic stiffness is an independent predictor of primary coronary events in hypertensive patients: A longitudinal study. Hypertension 2002;39:10-5.
9. Pannier B, Guerin AP, Marchais SJ, Safar ME, London GM. Stiffness of capacitative and conduit arteries: Prognostic significance for endstage renal disease patients. Hypertension 2005;45:592-6.
10. Cruickshank K, Riste L, Anderson SG, Wright JS, Dunn G, Gosling RG. Aortic pulse-wave velocity and its relationship to mortality in diabetes and glucose intolerance: an integrated index of vascular function? Circulation 2002;106:2085-90.
11. Blacher J, Guerin AP, Pannier B, Marchais SJ, Safar ME, London GM. Impact of aortic stiffness on survival in end-stage renal disease. Circulation 1999;99:2434-9.
12. Mitchell GF, Wang N, Palmisano JN, Larson MG, Hamburg NM, Vita JA, et al. Hemodynamic correlates of blood pressure across the adult age spectrum: noninvasive evaluation in the Framingham Heart Study. Circulation 2010;122:1379-86.
13. Boutouyrie P, Bruno RM. The clinical significance and application of vascular stiffness measurements. Am J Hypertens 2018;32:4-11.
14. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, et al. European network for non-invasive investigation of large arteries. Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J 2006;27:2588.
15. O'Rourke MF, Gallagher DE. Pulse wave analysis. J Hypertens Suppl 1996;14:147-57.
16. Fortier C, Agharazii M. Arterial stiffness gradient. Pulse (Basel) 2016;3:159-66.
17. Tanaka H, Munakata M, Kawano Y, Ohishi M, Shoji T, Sugawara J, et al. Comparison between carotid-femoral and brachial-ankle pulse wave velocity as measures of arterial stiffness. J Hypertens 2009;27:2022-7.
18. Tsuchikura S, Shoji T, Kimoto E, Shinihara K, Hatsuda S, Koyama H, et al. Brachial-ankle pulse wave velocity as an index of central arterial stiffness. J Atheroscler Thromb 2010;17:658-65.
19. McEniery C, Cockcroft J. Does arterial stiffness predict atherosclerotic coronary events? Adv Cardiol 2007;44:160-72.
20. O'Rourke MF, Hashimoto J. Mechanical factors in arterial aging: a clinical perspective. J Am Coll Cardiol 2007;50:1-13.
21. Ikdahl E, Rollefstad S, Hisdal J, Olsen I, Pedersen T, Kvien T, et al. Sustained improvement of arterial stiffness and blood pressure after longterm rosuvastatin treatment in patients with inflammatory joint diseases: results from the RORA-AS study. PLoS One 2016;11:e0153440.
22. Kanaki AI, Sarafidis PA, Georgianos PI, Kanovas K, Tziolas I, Zebekakis P, et al. Effects of low-dose atorvastatin on arterial stiffness and central aortic pressure augmentation in patients with hypertension and hypercholesterolemia. Am J Hypertens 2013;26:608-16.
23. Rosenson RS. Statins in atherosclerosis: lipid-lowering agents with antioxidant capabilities. Atherosclerosis 2014;173(1):1-12.
24. Pasceri V, Cheng JS, Willerson JT, Yeh ET, Chang J. Modulation of C-reactive protein-mediated monocyte chemoattractant protein-1 induction in human endothelial cells by anti-atherosclerosis drugs. Circulation 2001;103:2531-4.
25. Noonan JE, Jenkins AJ, Ma JX, Keech AC, Wang JJ, Lamoureux EL. An update on the molecular actions of fenofibrate andits clinical effects on diabetic retinopathy and other microvascular endpoints in patients with diabetes. Diabetes 2013;62:3968-75.
26. Ryan KE, McCance DR, Powell L, McMahon R, Trimble ER. Fenofibrate and pioglitazone improve endothelial function and reduce arterial stiffness in obese glucose tolerant men. Atherosclerosis 2007;194:123-30.

27. Hiukka A, Westerbacka J, Leinonen ES, Watanabe H, Wiklund O, Hulten LM, et al. Long-term effects of fenofibrate on carotid intima-media thickness and augmentation index in subjects with type 2 diabetes mellitus. J Am Coll Cardiol 2008;52:2190-7.

28. Zhu S, Su G, Meng QH. Inhibitory effects of micronized fenofibrate on carotid atherosclerosis in patients with essential hypertension. Clin Chem 2006;52:2036-42.

29. Wang TD, Chen WJ, Lin JW, Cheng CC, Chen MF, Lee YT. Efficacy of fenofibrate and simvastatin on endothelial function and inflammatory markers in patients with combined hyperlipidemia: relations with baseline lipid profiles. Atherosclerosis 2003;170:315-23.

30. Yu J, Jin N, Wang G, Zhang F, Mao J, Wang X. PPAR-γ agonist improved arterial stiffness in type 2 diabetes patients with coronary artery disease. Metabolism 2007;56:1396.

31. Wang G, He L, Liu J, Yu J, Feng X, Li F, et al. Coronary flow velocity reserve is improved by PPAR-α agonist fenofibrate in patients with hypertriglyceridemia. Cardiovasc Ther 2013;31:161-7.