# The Effect of Ezetimibe on Plasma Viscosity, Fibrinogen and Lipid Profile

Nurver Turfaner Sipahioglu[1], Denizhan Karis[2], Hafize Uzun[3], Fikret Sipahioglu[1], Selcuk Ercan[4], Alev Meltem Ercan[2]*

## Abstract

**Objective:** The aim of this study is to reveal the effect of ezetimibe monotherapy on plasma viscosity and fibrinogen levels in hyperlipidemia.

**Material and Methods:** A study group of 31 hyperlipidemic patients was treated for twelve weeks with a monotherapy of ezetimibe 10 mg/day. A healthy control group of 31 individuals with normal plasma lipid profile was also admitted to the study. PV, fibrinogen and fasting lipid parameters were evaluated. PV was measured by Harkness Capillary Viscometer.

**Results:** PV and fibrinogen levels decreased significantly with ezetimibe monotherapy (p<0.01). Total cholesterol and low density lipoprotein (LDL) levels were statistically significantly lower than ezetimibe monotherapy group (p<0.001), whereas high density lipoprotein (HDL) level was significantly higher than ezetimibe monotherapy group (p<0.01). HDL level increased significantly in ezetimibe monotherapy group (p<0.01). PV and fibrinogen levels of the control group were lower than ezetimibe monotherapy group before treatment (p<0.01 and p<0.001; respectively). Besides, fibrinogen level of control group was significantly lower than ezetimibe monotherapy group after treatment (p<0.01). Total cholesterol and LDL levels of control group were lower than ezetimibe monotherapy group before and after treatment (p<0.001 and p<0.01; p<0.001, respectively). HDL level of control group was significantly higher than ezetimibe monotherapy group before treatment (p<0.01).

**Conclusions:** Ezetimibe monotherapy ameliorates lipid profile and PV parameters in hyperlipidemic individuals. Increased PV and deteriorations in lipid profile may induce endothelial damage in cardiovascular diseases. Being a biophysical mechanical marker, PV may be useful for diagnosis, treatment and follow-up of hyperlipidemic patients treated with ezetimibe monotherapy.

**Key words:** Ezetimibe; viscosity; fibrinogen; hyperlipidemia

## Introduction

Cardiovascular diseases related with atherosclerosis are the leading causes of worldwide mortality [1]. Prolonged dyslipidemia ends up with the initiation of atherosclerosis [2]. Hemorheological factors, such as viscosity, are significant in determining blood flow characteristics and play an important role in the pathogenesis of thrombotic events and, therefore, cardio- and cerebro-vascular diseases.

The source of cholesterol that affects lipid profile depends majorly on intestinal absorption of dietary and biliary cholesterol [3]. Ezetimibe, which is the first member of a new class of selective cholesterol absorption inhibitors and is found to inhibit acylcoenzyme A, has positive effects both on lipid profile and cardiovascular events [4,5].

Moreover, ezetimibe monotherapy may be a favourable option acting as a non-synthetic agent having few side-effects. Ezetimibe diminishes cholesterol absorption by 40% to 50% [6], and reduces low density lipoprotein (LDL) levels by approximately 18 % [7,8]. Despite the fact that cholesterol has deteriorating effects over blood flow [9], the impacts of ezetimibe monotherapy on plasma viscosity (PV) have not been fully elucidated in the literature.

Recently, studies concerning blood flow in atherosclerosis reveal that atherogenesis is further accelerated by impaired blood flow. PV plays an important part in the formation and progression of atherosclerotic lesions [10]. PV is a major determinant of capillary blood flow through the microcirculation - an increase in blood viscosity (BV) reduces blood

flow in the circulation. Elevated PV may contribute to tissue damage by impairing microcirculatory flow due to shear stress damage at the blood-endothelial interface [10-14].

Either PV and/or fibrinogen have been defined as atherogenic risk factors for cardiovascular diseases. Fibrinogen is generally accepted as a factor that has the greatest effect on PV [10]. Fibrinogen, which is one of the plasma proteins, has a pronounced impact on PV despite its lower concentration than albumin and globulin. The reason why fibrinogen is responsible of 22% for the PV can be elucidated by its asymmetry and big molecular structure. As being an acute phase reactant, high fibrinogen levels might result from underlying pathologies including endothelial dysfunction and inflammation and may consequently increase PV [15]. Hypercoagulability and decreased fibrinolysis are often encountered in the clinical field related with cardiovascular diseases [16,17].

The aim of our study is to reveal the effect of ezetimibe monotherapy on plasma viscosity and fibrinogen levels which were analyzed in hyperlipidemic patients and compared with the control group. Thus, variations in plasma viscosity and fibrinogen were analyzed in the ezetimibe monotherapy applied hyperlipidemic group and compared with the control group.

## Materials and Methods

This study was performed with 31 hyperlipidemic patients [male (M) / female (F): 17/14; mean age: $47 \pm 8$ years; body mass index (BMI): $25.8 \pm 3.1$ kg/m$^2$] admitted to the Outpatient Clinic of Family Medicine at Istanbul University, Cerrahpasa Medical Faculty between September 2007 and September 2008. Asymptomatic patients with LDL cholesterol levels that needed to be treated according to the Adult Treatment Panel III (ATP III) guidelines were enrolled in the study. A group of healthy controls with normal total and LDL cholesterol levels and matched for body weight (BMI: $26.4 \pm 4.6$ kg/m$^2$), age (mean: $44 \pm 9$ years), and sex (M/F: 14/16) was included. Routine biochemical parameters were measured both in ezetimibe monotherapy and control groups. Patients in the ezetimibe monotherapy group were treated with ezetimibe 10 mg/day for twelve weeks, while no intervention was given to the control group. A full medical history was obtained from each individual. Physical examination, 12-lead electrocardiogram and echocardiography were performed. Patients were excluded from the study if they had alcohol abuse or smoked heavily (>10 cigarettes/day), if they were pregnant or if they had diabetes mellitus, liver insufficiency, serious renal disorders (serum creatinine >1.6 mg/dL), myocardial infarction, unstable angina, coronary revascularization, a clinical history of cardiovascular disease, peripheral vascular surgery, a percutaneous interventional procedure, acute cerebrovascular disease, or deep venous thrombosis. They were also excluded if they were treated with statins, antioxidant vitamins, or other herbal drugs. The protocol for sample collection was approved by Istanbul University, Cerrahpasa Medical Faculty, Ethical Commitee. The study was performed in accordance with the Helsinki Declaration, and informed consent was obtained from all patients and controls prior to their inclusion in the study.

After 12 hours of overnight fasting, venous blood samples were drawn into chilled dry polypropylene tubes containing one-tenth volume of 0.1 M sodium citrate without venous stasis. After immediate centrifugation (3000 g) for 10 min at 4°C, plasma was stored at -70°C until assayed for determination of the parameters. Serum was used directly for measurements of routine biochemical parameters and lipid profile. Total cholesterol, high density lipoprotein (HDL), LDL, very low density lipoprotein (VLDL) and triglyceride levels were analyzed within lipid profile. All reagents were analytical grade and purchased from Sigma (St. Louis, MO, USA) and Merck (Darmstadt, Germany). All parameters were analyzed in all samples together in a single batch, after the protocol was finished (control and patient samples were analyzed in the same batch).

Fibrinogen was assessed using Clauss method with MDA180 device (Trinity Biotech Company) and expressed as mg/dL.

Blood samples for PV measurements were drawn into vacutainers with potassium EDTA as anticoagulant and were processed in two hours following collection in accordance with the committee of hemorheology standardization [18]. PV was measured by Harkness capillary viscometer (Coulter Electronics LTD Serial Number 6083, England) at 37°C, which allows measurement of sizes as low as 0.5 ml within 1 min. The flow rate, measured in seconds (s), of each plasma sample (Tp) was compared with that of distilled water (Tw) to obtain the relative plasma viscosity (coefficient of variation, 1,00%). For quality control, measurements were compared with tap water. PV measurements were carried out in triplicate. The PV was expressed as in milliPascal × seconds (mPa.s; 1 mPa.s = 1 centipoise).

$$P_v = \eta_w \frac{T_P(s)}{T_w(s)} \qquad \eta w = 0.693 \text{ mPa.s}$$

## Statistical analysis

For each variable, values were expressed as mean ± standard error of the mean. Statistical calculations were performed with the NCSS 2007 program. Besides standard descriptive statistical calculations (mean and standard deviation), paired t-test was used in the assessment of pretreatment and

post-treatment values, and the Chi square test was performed during the evaluation of qualitative data. The Pearson correlation test was used for determination of correlation between biochemical parameters and other variables.

## Results

The demographic characteristics of the patients and controls were expressed as means ± SEM in the methods section. There were no significant differences in demographic data (gender, age, BMI, systolic and diastolic blood pressure) and biochemical parameters (hemoglobin, hematocrit, C-reactive protein (CRP), fasting blood glucose, hemoblobin A1c (HbA1c), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and creatinine) between the two groups (Table 1). Twelve weeks of monotherapy with ezetimibe caused an improvement in the lipid profile, in accordance with the literature.

The value of PV decreased significantly from 1.31 ± 0.17 mPa.s to 1.26 ± 0.13 mPa.s in the ezetimibe monotherapy group after the treatment period (p<0.01). The value of PV in the control group was measured as 1.24 ± 0.10 mPa.s with a significant value compared with ezetimibe monotherapy group before treatment (p<0.01).

Ezetimibe monotherapy significantly reduced fibrinogen level by 11% after 90 days of treatment. Fibrinogen level of the ezetimibe monotherapy group decreased from 352.3 ± 36.2 mg/dL to 310.7 ± 37.1 mg/dL after ezetimibe monotherapy (p<0.01). Fibrinogen level of the control group was measured as 268.52 ± 47.4 mg/dL, compared statistically significantly with ezetimibe monotherapy group before treatment (p<0.001). Fibrinogen level of the control group was measured significantly lower than the ezetimibe monotherapy group after treatment (p<0.01).

Total cholesterol level and and LDL level of the ezetimibe monotherapy group both decreased statistically significantly from 280.75 ± 27.98 mg/dL to 241.77 ± 31.07 mg/dL and from 180.36 ± 26.30 mg/dL to 142.48 ± 25.93 mg/dL, respectively (p<0.001). Total cholesterol level of the control group (192.06 ± 12.54 mg/dL) was measured statistically significantly lower than the ezetimibe monotherapy group before treatment and significantly lower than the ezetimibe monotherapy after treatment (p<0.001 and p<0.01, respectively). LDL level of the control group (110.46 ± 22.10 mg/dL) was measured statistically significantly lower than the ezetimibe monotherapy group both before and after therapy (p<0.001). HDL level increased significantly from 43.83 ± 10.58 mg/dL to 46.27 ± 11.02 mg/dL in the ezetimibe monotherapy group (p<0.01). HDL level of the control group revealed significantly lower results than the ezetimibe monotherapy group before treatment (p<0.01). VLDL level in the ezetimibe monotherapy was measured as 28.51 ± 10.85 mg/dL and 26.46 ± 13.82 mg/dL before and after treatment with no statistical significance, respectively. VLDL level in the control group was measured as 25.42 ± 11.15 mg/dL. Trigyceride levels in both ezetimibe monotherapy and control group did not show any statistical significance with levels of 140.25 ± 61.54 mg/dL, 132.82 ± 72.34 mg/dL and 113.28 ± 52.67 mg/dL with no significance, respectively. The effects of ezetimibe monotherapy on PV, fibrinogen and lipid profiles are summarized in Table 2.

**Table 1.** Demographic data and biochemical parameters of ezetimibe monotherapy and control groups.

| | Ezetimibe Monotherapy Group (n: 31) | | Control Group (n:30) | p |
|---|---|---|---|---|
| **Gender (Male / Female)** | 17 / 14 | | 14 / 16 | |
| **Age (years)** | 47 ± 8 | | 44 ± 9 | |
| | **Before Therapy** | **After Therapy** | | |
| **BMI (kg/m$^2$)** | 25.8 ± 3.1 | | 26.4 ± 4.6 | NS |
| **SBP (mmHg)** | 129 ± 9 | | 127 ± 6 | NS |
| **DBP (mmHg)** | 82 ± 6 | | 72 ± 4 | NS |
| **Hemoglobin (mg/dL)** | 14.02 ± 2.5 | 14.35 ± 1.52 | 13.72 ± 1.24 | NS |
| **Hematocrit (%)** | 40.75 ± 4.92 | 41.48 ± 4.68 | 43.5 ± 4.21 | NS |
| **CRP (mg/L)** | 3.1 ± 0.9 | 2.8 ± 0.7 | 3.3 ± 0.6 | NS |
| **Fasting blood glucose (mg/dL)** | 89 ± 8 | 85 ± 6 | 87 ± 9 | NS |
| **HbA1c (%)** | 5.9 ± 0.5 | 5.7 ± 0.3 | 5.6 ± 0.4 | NS |
| **ALT (U/L)** | 23.1 ± 5.8 | 22.7 ± 4.3 | 20.4 ± 7.2 | NS |
| **AST (U/L)** | 20.2 ± 3.7 | 19.6 ± 3.4 | 21.5 ± 6.8 | NS |
| **Creatinin (mg/dL)** | 0.91 ± 0.12 | 0.86 ± 0.28 | 0.81 ± 0.21 | NS |

Values are represented as (mean ± SEM). BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; CRP: C-reactive protein; HbA1c: hemoglobin A1c; ALT: alanine aminotransferase; AST: aspartate aminotransferase; NS: non-significant.

The Pearson correlation test was used for determination of correlation between parameters and variables. A statistical positive correlation was found between PV and fibrinogen in the study group before treatment with ezetimibe monotherapy (r = + 0.429; p = 0.026). There was no correlation between PV and lipid profile in the ezetimibe monotherapy group before treatment. Despite the fact that there was statistically reduction in PV, fibrinogen, total cholesterol and LDL levels in the ezetimibe monotherapy group after treatment, no correlation was found between these variables. A statistical positive correlation was found between PV and fibrinogen in the control group (r = + 0.299; p = 0.078).

## Discussion

In our study, we observed that with three months of ezetimibe monotherapy; PV, fibrinogen, total cholesterol and LDL levels decreased significantly. Ezetimibe monotherapy resulted in a decrease in PV levels by 3.8%. Ezetimibe monotherapy significantly reduced fibrinogen levels by 12% at the end of the treatment period. There was also a reduction in total cholesterol by 14.2% and in LDL by 21.3%. The assessment of blood sample of the control group was not repeated after 12 weeks, since no intervention was given to the control group.

As we could reach the literature, we didn't encounter the studies related with the effects of ezetimibe monotherapy on PV. In our study, we focused on the investigation of the effects of ezetimibe monotherapy on PV and fibrinogen.

Ezetimibe is known as the first member of a new class of selective cholesterol absorption inhibitors. Several studies revealed that ezetimibe monotherapy combined with statins and other anti-hyperlipidemic agents have a positive influence in lipid-lowering [4,5,19]. It is well known that prolonged hyperlipidemia, increased PV and fibrinogen levels could be affected in the pathologic process in cardiovascular diseases [9,14,20].

The fact that blood flowing has more important roles in subsequent cardiovascular events is a widely accepted data in the literature [21]. Similarly with the literature, we found out that PV was higher in ezetimibe monotherapy group before treatment than control group. PV decreased to values almost reaching control group after treatment with ezetimibe monotherapy. Plasma is a cell-free or cell-depleted marginal layer adjacent to the endothelium of the vessel wall. Thus, PV points out the qualitative and quantitative assessment of the endothelium layer [22]. In their study on 27 patients with cerebrovascular diseases Laszlo et al. [23] found out that in chronic cerebrovascular patients with hyperlipidemia who were treated with atorvastatine 10 mg daily for 3 months, plasma total cholesterol level was reduced by 28%, LDL cholesterol level was decreased by 40% and BV was improved (p<0.05). They concluded that besides lipid lowering, atorvastatin may improve hemorheological parameters, platelet aggregation and endothelial dysfunction after short-term and long-term therapy. Van der Loo et al. [20] reported that atorvastatin 80 mg/daily for 6 months was not more effective in decreasing major hemorheologic parameters like PV, red cell aggregation and BV in comparison with lower doses of statin usage in peripheric arterial disease patients.

Atherosclerosis consists of early and late phases within a process of coagulation and fibrinolysis pathologies and complications [5]. Only a few studies have been reported on the effect of ezetimibe monotherapy on PV, fibrinogen and fibrinolytic activity. In our study, fibrinogen decreased significantly in ezetimibe monotherapy group after treatment. Fibrinogen level in control group was statistically significantly lower than ezetimibe monotherapy group before treatment. Being one of the plasma proteins, fibrinogen has a pronounced effect on PV. The increase in fibrinogen levels might result from underlying pathologies including endothelial dysfunction and inflammation [15]. Yano et al. [24] concluded that patients with high fibrinogen could encounter with an increase in cardiovascular

**Table 2.** The effect of ezetimibe monotherapy on plasma viscosity, fibrinogen and lipid profile.

| | Ezetimibe Monotherapy Group (n: 31) | | Control Group (n:30) |
|---|---|---|---|
| | **Before Therapy** | **After Therapy** | |
| **Plasma viscosity (m.Pa.s)** | $1.31 \pm 0.17$ | $1.26 \pm 0.13$ [†][**] | $1.24 \pm 0.10$ [†][**] |
| **Fibrinogen (mg/dL)** | $352.3 \pm 36.2$ | $310.7 \pm 37.1$ [†][**] | $268.52 \pm 47.4$ [†][***],[‡][**] |
| **Total Cholesterol (mg/dL)** | $280.75 \pm 27.98$ | $241.77 \pm 31.07$ [†][***] | $192.06 \pm 12.54$ [†][***],[‡][**] |
| **HDL (mg/dL)** | $43.83 \pm 10.58$ | $46.27 \pm 11.02$ [†][**] | $50.17 \pm 15.41$ [†][**] |
| **LDL (mg/dL)** | $180.36 \pm 26.30$ | $142.48 \pm 25.93$ [†][***] | $110.46 \pm 22.10$ [†][***],[‡][***] |
| **VLDL (mg/dL)** | $28.51 \pm 10.85$ | $26.46 \pm 13.82$ | $25.42 \pm 11.15$ |
| **Triglyceride (mg/dL)** | $140.25 \pm 61.54$ | $132.82 \pm 72.34$ | $113.28 \pm 52.67$ |

Values are represented as (mean ± SEM). HDL: high density lipoprotein; LDL: low density lipoprotein; VLDL: very low density lipoprotein, †: Statistical comparison before treatment; ‡: Statistical comparison after treatment; * p < 0.05; **p < 0.01; ***p < 0.001.

morbidity and mortality. PV and fibrinogen level build up the vital functions of the vessel wall and their increase has been shown to be responsible for starting endothelial damage. The ability of ezetimibe to decrease fibrinogen level has been pointed out by Krysiak et al. [5]; and supports its role in hemorheologic mechanisms. Turfaner et al. [25] found out that the balance between fibrinolytic markers was maintained and fibrinolysis was prevented by ezetimibe monotherapy. Thus, the decrease in fibrinogen might be due to the improvement of profibrinolytic activity. In their study of the effect of ezetimibe and simvastatin on hemostasis, Krysiak et al. [5] stated that ezetimibe monotherapy reduced fibrinogen levels by 18.9% after 90 days of treatment. Because, even it has small differences, in the plasma levels of fibrinogen was associated with the effect of ezetimibe on clinical manifestation.

Studies have shown that there is a correlation between PV and cholesterol levels of the individuals. PV correlates strongly with cholesterol status of the individuals [10]. In a study held by Ercan et al. [26] hypercholesterolemic patients were declared to have significantly higher PV, LDL and triglyceride levels compared with normocholesterolemic patients; and HDL was significanly lower in hypercholesterolemic patients than in normocholesterolemic patients . Kikuchi et al. [4] pointed in their study of postprandial hyperlipidemia and hyperglycemia that the reductions in LDL with ezetimibe monotherapy was thought to have resulted from the inhibition of cholesterol absorption. Besides, Miyashita et al. [19] reported that ezetimibe monot herapy significantly decreased LDL levels by 23%. Similarly with the literature, our study revealed that ezetimibe monotherapy reduced fibrinogen, total cholesterol and LDL and increased HDL in hyperlipidemic patients. There was statistical decrease in levels of PV together with fibrinogen and improvement in lipid profile in ezetimibe monotherapy group after treatment; however no correlation was analyzed with PV between these parameters. Thus, this fact might be evaluable in considering the PV as an independent variable.

## Conclusion

Ezetimibe monotherapy may be a favourable option for the treatment of the patients with hyperlipidemia via its effects over PV and fibrinogen. Depending on the fact that  PV is a marker of the hemorheologic and fibrinolytic features of both the endothelium and blood, the amelioration of PV in individuals treated with ezetimibe is a promising result. It should be taken into account that it may not be as effective as statin monotherapy on some parameters like LDL cholesterol and fibrinogen levels [4, 19, 27]. Ezetimibe monotherapy administration may be considered in order to decrease atherogenic events encountered in cardiovascular diseases with its

improving effects on PV. Since effects of statin monotherapy and statin-ezetimibe combination therapy on plasma viscosity have been evaluated in several other concomitant studies, we only compared the plasma viscosity values before and after ezetimibe monotherapy in the ezetimibe monotherapy group which has been rarely done in the literature and we did not include another statin therapy group.

As a result, being a non-invasive, repeatable and economic parameter plasma viscosity might be evaluated as one of cardiovascular risk factors and be assessed as a biomechanical / biophysical marker in the efficiency of the diagnosis, treatment and follow-up of hyperlipidemia.

**Limitations:** The limitation of our study is the absence of flow mediated dilatation assessment of our study and control group. Another limitation is that the rheologic and lipid parameters of the control group were only assesed once. It could have been measured at the end of the study to detect the changes that result from the life-style, although they were on a stable diet. We evaluated plasma viscosity, lipid status and fibrinogen in hyperlipidemic patients with ezetimibe monotherapy. The positive effects of ezetimibe monotherapy on human health have not been elucidated thoroughly. The pleiotropic benefits of ezetimibe should be assessed in detail with large-scale studies.

**Conflict of Interest:** The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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