Evaluation of Pleiotropic Effects of Statins in Chronic Renal Failure Patients

Kronik Böbrek Yetmezlikli Hastalarda Statinlerin Pleiotropik Etkilerinin Değerlendirilmesi

ABSTRACT

OBJECTIVES: Atherosclerosis is seen more frequently in patients with chronic renal failure (CRF) due to the oxidative stress, chronic inflammation and endothelial dysfunction. Besides lowering total and low density lipoprotein (LDL) cholesterol levels, statins also lower the frequency of cardiovascular incidents in patients with chronic renal failure by their pleiotropic effects. We aimed to investigate whether atorvastatin had pleiotropic effects in dialysis patients.

MATERIAL and METHODS: 21 hyperlipidemic dialysis patients (12 on hemodialysis and 9 peritoneal dialysis) with LDL cholesterol levels over 130 mg/dl were included in this study. Atorvastatin was titrated and given to patients for 6 months. After LDL cholesterol level were reduced to under 100mg/day, we evaluated oxidized LDL, malondialdehyde (MDA), interleukin-6 (IL-6), high sensitive C reactive protein (hsCRP), fibrinogen, platelet count, sedimentation rate, nitric oxide (NO), Von Willebrand factor antigen (vWF ag), factor VIII (FVIII) and homocysteine.

RESULTS: Significant reductions were obtained in total cholesterol, LDL-cholesterol (p<0.001), triglyceride (p<0.05), oxidized LDL (p<0.001), sedimentation value (p<0.01) and platelet count (p<0.05) with atorvastatin treatment. No differences were seen in the other parameters.

CONCLUSION: Atorvastatin is associated with significant improvement of lipid profile and reduction of ox-LDL, platelet count, and sedimentation in dialysis patients.

KEY WORDS: Statins, Chronic kidney failure, Oxidative stress, Endothelium

ÖZ

AMAÇ: Kronik böbrek yetmezlikli hastalarda oksidatif stres, kronik inflamasyon ve endotel işlev bozukluğudan dolayı ateroskleroz daha sık görülür. Kronik böbrek yetmezlikli hastalarda statinler, toplam ve düşük dansiteli lipoprotein (LDL) kolesterolü düşürücü etkilerinin yanında pleiotropik etkileri ile kardiyovasküler olay sıklığını azaltırlar. Biz diyaliz hastalarında statinlerin pleiotropik etkilerinin olup olmadığını araştırmayı amaçladık.

GEREÇ ve YÖNTEMLER: Çalışmaya LDL kolesterol düzeyi 130 mg/dl'den yüksek olan 21 diyaliz hastası (12 hemodiyaliz, 9 periton diyalizi) alındı. Atorvastatin titre edilerek 6 ay süreyle verildi. LDL kolesterol düzeyi 100 mg/dl altına indikten sonra oksidize LDL, malondialdehid (MDA), interleukin 6 (IL-6), yüksek duyarlıklı C reaktif protein (ydCRP), fibrinojen, platelet sayısı, sedimentasyon hızı, nitrik oksid (NO), Von Willebrand faktör antijeni (vWF ag), faktör VIII (FVIII) ve homosistein düzeylerini değerlendirdik.

BULGULAR: Atorvastatin tedavisi ile total kolesterol, LDL kolesterol (p<0,001), trigliserid (p<0,05), oksidize LDL (p<0,001), sedimentasyon hızı (p<0,01) ve trombosit sayısında (p<0,05) anlamlı düşme gözlendi. Diğer göstergelerde anlamlı farklılık yoktu.

SONUÇ: Atorvastatin diyaliz hastalarında lipid profilinde önemli iyileşme ile oksidize LDL, trombosit sayısı ve sedimentasyon hızında azalma sağlamaktadır.

ANAHTAR SÖZCÜKLER: Statinler, Kronik böbrek yetmezliği, Oksidatif stres, Endotel

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INTRODUCTION

Despite the developments in renal replacement treatments, mortality rates due to cardiovascular diseases in chronic dialysis patients are higher than in the normal population (1-4). Cardiovascular conditions are the most common causes of mortality and morbidity in dialysis patients with end-stage renal disease. The mortality rates in these cases can be up to 40-50% (5). It is not possible to explain the increase in cardiovascular mortality in dialysis patients with the conventional risk factors and potential risk factors due to uremia are therefore studied. The rapid progression of atherosclerosis in uremia is explained by the effect of mechanisms such as increased oxidative stress, endothelial dysfunction, malnutrition, inflammation, hyperhomocysteinemia, dyslipidemia, hemodynamic overcharge, anemia, and hypercalcemia (3, 6).

It is accepted that oxidative stress contributes to both atherosclerosis and kidney injury. Antioxidant mechanisms are inefficient in chronically hemodialyzed patients, which results in increased formation of reactive oxygen species and other free radicals and consequently in oxidative stress. This is related to numerous factors, including a considerable concentration of uremic toxins and the influence of the hemodialysis procedure itself (activation of inflammatory mediators, elimination of low-molecular antioxidants by hemodialysis). In such patients, a rapid progression of atherosclerosis also is observed, which may be linked among other factors to abnormal lipid metabolism (7).

Malnutrition and inflammation are associated with end-stage renal disease. Inflammation leads to reduced synthesis of albumin, transferrin and other negative acute-phase proteins and increases their catabolic rates. The causes of inflammation are multi-factorial, including oxidative modification of plasma proteins, interaction of blood with non-biocompatible membranes and other infectious processes. Inflammation parameters powerfully predict death from cardiovascular disease in dialysis patients as well as progression of vascular injury (8).

End-Stage Renal Failure (ESRF) is seen with disturbed endothelial dysfunction. Also, the progression of atherosclerosis is related to endothelial cell dysfunction. von Willebrand Factor (vWF), a procoagulant glycoprotein that is released from endothelial cells, is a transporter of factor VIII besides helping adhesion and aggregation of thrombocytes at the region where vascular damage occurs. Increased levels of plasma soluble vWF antigens and factor VIII indicate endothelial cell activation or dysfunction in patients with atherosclerotic heart disease (9-12).

Dyslipidemia is seen frequently in hemodialysis patients. Statins reduce the cardiovascular event rate by decreasing atherogenic dyslipidemia. According to two recent studies, statins have more beneficial effects in peritoneal dialysis patients than hemodialysis patients as the first group has a much larger quantity of atherogenic particles but it has also been stated that statins have some cardiovascular beneficial effects in hemodialysis patients(13,14).

Considering the fact that most patients with chronic renal failure have lipid disorders, the use of statins (HMG-CoA reductase inhibitors) has become common in recent years. Many confirm that statins are safe and effective drugs in hemodialyzed patients. The use of statins in patients with chronic renal failure, and especially in hemodialyzed patients, seems advantageous in view of the known high frequency of oxidative and inflammatory states linked to enhanced risk of atherosclerosis in these patients (7). Statins may protect the vasculature via a pleiotropic effect not directly related to lipid lowering. These include adjustments in cell-signaling pathways that play a role in atherogenesis and affect the expression on inflammatory elements, curtail oxidative stress, and enhance endothelial function (15).

There is evidence in the literature that statins have anti-oxidant and anti-inflammatory effects and may have an important role in cardiovascular protection by reducing nontraditional cardiovascular risk factors, known as the pleiotropic effect (7,16). We aimed to evaluate the pleiotropic effects of atorvastatine in dialysis patients.

MATERIAL and METHODS

This study includes 21 patients (12 men and 9 women) consisting of 12 hemodialysis (HD) and 9 peritoneal dialysis (PD) patients between the ages 20-60 (mean 54.66±12,27). Patients who had been on dialysis for at least a year and had a LDL cholesterol level over ≥130 mg/dl were included in this study. Atorvastatin was titrated (10-40 mg/day) and given to patients for 6 months. Hemodialysis with bicarbonate was applied to the patients three days a week and for a total of 12 hours. Polysulfone dialyzer was used for HD and all PD patients were on continuous ambulatory peritoneal dialysis (CAPD). The etiological reasons of end-stage renal disease in 11 patients were hypertension, diabetes mellitus in 1 patient, glomerulonephritis in 1 patient, polycystic renal disease in 1 patient, renal lithiasis in 1 patients and unknown in 6 patients. Patients with cardiovascular disease, alcohol use, sepsis, chronic inflammatory disease, neoplasm, collagen tissue disease, hepatic failure or a medication history that could affect the acute phase response were excluded. Patient information and approval forms are completed before the study and the study was approved by the ethical committee of Eskisehir Osmangazi University.

Blood samples were obtained from the patients at the beginning of the study and from patients whose LDL cholesterol levels had decreased beyond 100 mg/dl after 6 months of therapy. Fasting blood samples were collected early in morning before dialysis and markers of serum lipid levels, oxidative stress and inflammation and endothelial dysfunction were studied in venous blood.

Samples for blood counts were drawn into Beckton Dickinson (BD) anticoagulated tubes and complete counts were performed

with the Beckmann Coulter Gen-S SM, USA, automated blood counting device. Erythrocyte sedimentation rate was measured using the automated Sed Rate screener device (Grainer-Bio-One Germany).Total cholesterol, LDL cholesterol, and triglyseride were measured using an enzymatic colorimetric assay and lipoprotein (a) and hsCRP levels were determined using an ımmunoturbidimetric assay by Modular Systems (Roche Diagnostics, Switzerland). Fibrinogen levels for each sample were measured by STA compact using the Diagnostica Stago kit. Factor VIII activity were determined with the automated coagulometer STA Compact using the deficient VIII kit of Stago (Diagnostica Stago). The immunoturbidimetric method was used for the quantitative measurement of von Willebrand factor (vWF) antigen (STA-Liatest vWF, Diagnostiga Stago). Serum oxidized LDL levels were measured by using a Mercodia oxidized LDL ELISA kit. Homocysteine levels were determined using theAxis Homocysteine EIA kit (Axis-shield, UK). IL-6 concentrations in serum samples were measured by using an ELISA kit (Biosource International). The RD Systems NO kit was used for determination of nitric oxide levels in serum samples. MDA levels were assayed by the measurement of absorbance at 532 nm on the basis of MDA reacting with thiobarbituric acid, according to the method of Ohkawa et al.

Statistical Analyses

We analysed data with SPSS (version 15.0 for Windows, SPSS, Inc., Chicago, IL, USA) and expressed data as mean ± standard deviation. The distribution of variables was checked initially by the Shapiro Wilk's Test. The independent samples t test and paired samples t test were applied to data with normal distribution, whereas the Mann Whitney U and Wilcoxon tests were applied to data with non-normal distribution. We considered a p value < 0.05 as statistically significant.

RESULTS

Clinical characteristics of the patients are shown in Table I. Before treatment, the LDL value of the patients was 131 mg/dl to 255 mg/dl. After treatment these values were 46 mg/dl and 117 mg/dl respectively.

After the treatment with atorvastatin titration (10-40 mg/day), a significant decrease in total cholesterol (255.42±33.39 mg/dl vs. 163.04±18.97 mg/dl, p<0.001), LDL cholesterol (160.40±29.14 mg/dl vs. 78.36±16.82 mg/dl, p<0.001), oxidized LDL (90.23±21.63 U/L vs. 60.00±13.50 U/L, p<0.001), triglyceride (215.80±75.88 mg/dl vs. 179.80±53.95 mg/dl, p<0.05), platelet count (269.90±73.24 x10³/mm³ vs. 249.14±58.27 x10³/mm³, p<0.05) and sedimentation rate (73.90±29.11 mm/h vs. 54.33±34.70 mm/h, p<0.01) were observed in the 21 dialysis patient that had an LDL cholesterol level over 130 mg/dl, (Table II). A statistically non-significant decrease was observed in fibrinogens, MDA, lipoprotein (a), FVIII, homocysteine and hsCRP values (Table II). The vWF ag, IL-6 and NO value did not change significantly after the treatment (p>0.05) (Table II).

Table I: Clinical characteristics of patients.

Characteristics(N=21)	
Age(y)	54.66±12.27
Gender(M/F)	12/9
Dialysis(HD/PD)	12/9
Nephropathies	
Hypertension	11
Diabetes mellitus	1
Glomerular	1
Polycystic kidney	1
Renal lithiasis	1
Unknown	6
Kt/V HD	1.28±0.19
PD	2.59±1.17
nPCR(g/kg/day)	1.32±0.69

nPCR; the normalized protein catabolic rate.

The creatine kinase (CK) level was not affected by atorvastatin treatment (77.85±56.05 U/L vs. 96.80±71.41 U/L, p>0.05).

DISCUSSION

Oxidative stress, inflammation and endothelial dysfunction markers were studied after 6 months of atorvastatin treatment in patients whose LDL cholesterol levels decreased beyond 100 mg/dl. A statistically significant decrease in total cholesterol, TG and LDL cholesterol levels was found after treatment, in accordance with the literature, whereas a non-significant decrease in lipoprotein (a) levels were observed. There are many studies on Lp(a) in the literature with various results (16,17). Statins influence oxidation by decreasing the atherogenic duration. Besides their direct antioxidant effects, they lower the oxidized LDL levels and inhibits the uptake by macrophages (18). Van den Akker et al. have shown that atorvastatin and simvastatin reduced oxidized LDL levels in hemodialysis patients (19). The oxidized LDL levels in our study were found to be reduced in accordance with the literature and this reduction was found to be statistically significant. There are very few studies that indicate that atorvastatin reduces oxidative stress in dialysis patients. According to our study atorvastatin may exhibit additional inhibitory effects on atherogenesis, such as modulation of the immune system as triggered by oxidatively modified LDL.

Malondialdehyde (MDA) is an important indicator of lipid peroxidation (20). In our study, we detected a non-significant decrease in malondialdehyde levels. Castro et al. investigated the pleiotropic effects of atorvastatin in patients with heart failure and MDA levels were found to be decreased (21). However, in another study, Chang et al., reported that there was no difference in MDA levels after the treatment with simvastatin (22).

Table II: Oxidative stress, inflammation and endothelial dysfunction parameters in patients.

Parameters		Before Treatment	After Treatment	P
Hemoglobin(g/dl)	(11.7-15.7)	10.87 ± 1.45	10.62 ± 1.68	>0.05
Plt number (x10³/mm³)	(150-440)	269.90 ± 73.24	249.14 ± 58.27	<0.05
Fibrinogen (sec)	(200-400)	546.52 ± 171.03	514.95 ± 106.37	>0.05
Sedimentation(mm/h)	(0-20)	73.90 ± 29.11	54.33 ± 34.70	<0.01
T chol (mg/dl)	(112-200)	255.42 ± 33.39	163.04 ± 18.97	<0.001
TG (mg/dl)	(25-170)	215.80 ± 75.88	179.80 ± 53.95	<0.05
LDL-chol (mg/dl)	(0-100)	160.40 ± 29.14	78.36 ± 16.82	<0.001
Ox LDL (U/L)	(26-117)	90.23 ± 21.63	60.00 ± 13.50	<0.001
Lp(a) (mg/dl)	(0-30)	51.11 ± 37.24	50.58 ± 34.68	>0.05
MDA (mmol/L)		2.97 ± 0.67	2.62 ± 0.63	>0.05
IL-6 (pg/ml)	(0-56)	10.09 ± 11.28	19.78 ± 33.30	>0.05
HsCRP (mg/L)	(0.1-3)	16.77 ± 23.91	13.98 ± 21.99	>0.05
NO (μmol/L)	(13-97)	75.80 ± 24.78	73.97 ± 14.02	>0.05
vWF ag (%)	(50-160)	207.95 ± 67.74	237.61 ± 95.05	>0.05
FVIII (%)	(50-150)	192.73 ± 20.49	185.54 ± 29.43	>0.05
Homocysteine (μmol/L)	(5-12)	11.96 ± 9.11	11.55 ± 6.57	>0.05

Plt; platelet, **T chol;** serum total cholesterol, **TG;** triglyceride, **LDL chol;** low density lipoprotein cholesterol, **Ox LDL;** oxidized low density lipoprotein cholesterol, **Lp(a);** lipoprotein (a), **MDA;** malondialdehyde, **IL-6;** interleukin-6, **HsCRP;** high sensivity C reactive protein, **NO;** nitric oxide, **vWF ag;** Von Willebrand factor antigen, **FVIII;** Factor VIII

The reported pleiotropic effects of HMG CoA reductase inhibitors are related to a reduction in cellular cholesterol biosynthesis and isoprenoid levels. It has been demonstrated that statins regulate nitric oxide production by different mechanisms. These include, increasing levels of endothelial nitric oxide and preventing formation of reactive oxygen species (23). On the contrary, we did not find the increase in NO levels after the atorvastatin treatment was observed that had been expected from the literature information. There have been studies that report statins are not effective on the homocysteine levels that can cause endothelial dysfunction and increased thrombosis (1, 24). In our study, we observed a statistically non-significant decrease in homocysteine levels after treatment.

There is a relationship between cardiovascular diseases, atherosclerosis progression and vascular endothelial cell dysfunction. vWF, a procoagulant glycoprotein that is secreted from endothelial cell and trombocyte, is a transporter for FVIII besides providing trombocyte adhesion and aggression to the location that vascular damage occurs. Increased levels of plasma soluble vWF antigens are an index for designation of endothelial cell activation and/or dysfunction in patients with atherosclerotic heart disease (11). In a study on 805 patients (having DM,

ESRF, ischemic heart disease and venous thrombosis), the antigen levels of vWF were found to be high, and an increase in hemodialysis membrane bio-inconsistency and vWF antigens that are endothelial dysfunction markers used as indicators of arterio-venous fistula thrombosis were observed in patients with ESRF (25). In our study, vWF antigen levels were found to be higher than the normal levels but the vWFag level was not affected by atorvastatin treatment. FVIII levels were higher than normal in the beginning of the study but a statically non-significant decrease was observed after the treatment. To the best of our knowledge there is no study on the effects of statins on vWF antigens and FVIII levels in dialysis patients. However, a remarkable decrease in vWF antigen levels were detected in hyperlipidemic coronary heart disease patients in a study (26). However, plasma vWF levels were found to be unaffected with 10 mg atorvastatin treatment in renal transplant receivers in another article (27).

Increases in CRP, fibrinogen and HsCRP levels are found in 30-50 % of the patients on hemodialysis and peritoneal dialysis as indicators of active inflammation, The most commonly used one in clinic is the high sensitive CRP named as HsCRP. Recently, the levels of IL-6, another inflammation indicator, has been used

for risk determination. The plasma fibrinogen level is used as an indicator as it shows both the inflammatory response and thrombotic tendency. Studies indicate that fibrinogens increase coronary risks significantly (28). In two different studies, 10 mg atorvastatin caused a significant decrease in HsCRP levels (1, 29). However, in another study, treatment with atorvastatin and simvastatin did not cause any meaningful decrease in HsCRP (19). Our IL-6 levels did not change significantly after the treatment. Earlier, Goicoechea et al. showed that atorvastatin did not cause a statistical decrease in IL-6 levels in chronic renal failure patients (30), on the other hand, Li and coworkers showed that simvastatin inhibits the release of IL-6 in human monocyte cultures (31). In our findings, fibrinogen, shown to cause an increase in the coronary risk, decreased a non-significantly. A statistically significant decrease was observed in sedimentation and platelet levels, known to be acute phase reactants. In the literature, there are no studies on the effects of atorvastatin on fibrinogen, sedimentation and platelet numbers but studies in hyperlipidemic patients have shown that treatment with atorvastatin significantly decreases fibrinogen levels (27). On the other hand fluvastatin did not affect the fibrinogen levels in renal transplant patients (24). Kadıkoylu and coworkers conducted a study on primer hypercholesterolemia patients that compares the effect of atorvastatin and simvastatin on hemostatic profiles and showed that both drugs resulted in a non-significant decrease in platelet count. It was also observed that atorvastatin provided a non-significant reduction whereas simvastatin caused a significant reduction in fibrinogen levels (32). Sedimentation rate did not completely become normal but it was quite decreased. Platelet count was also decreased although within normal limits. Decline in the values of these parameters, known as acute phase reactants, may be interpreted as an anti inflammatory response. The variable effects of statins on lipid levels and coagulation parameters requires attention because of the tendency of dialysis patients for coagulation due to hypercholesterolemia and uremia. Large scale trials are needed to verify this observation.

In conclusion, statins may contribute to cardiovascular protection by partially improving oxidative stress and inflammatory conditions in dialysis patients besides their lipid lowering effects. Large clinical trials are needed to demonstrate their pleiotropic effects more clearly. Atorvastatin treatment did not affect the creatinine kinase level, and no classical adverse effects were observed during the study. These results suggest that atorvastatin is safe in hemodialysis patients.

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