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Original investigation

Differential effects of fenofibrate versus atorvastatin on the concentrations of E-selectin and vascular cellular adhesion molecule-1 in patients with type 2 diabetes mellitus and mixed hyperlipoproteinemia: a randomized cross-over trial

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Abstract

Background: Diabetic dyslipoproteinemia is characterized by hypertriglyceridemia, low HDL-cholesterol and often elevated LDL-cholesterol and is a strong risk factor for atherosclerosis. Adhesion molecule levels are elevated both in hyperlipoproteinemia and diabetes mellitus. It is unclear whether fibrate or statin therapy has more beneficial effects on adhesion molecule concentrations.

Methods: Atorvastatin (10 mg/d) was compared to fenofibrate (200 mg/d) each for 6 weeks separated by a 6 week washout period in 11 patients (6 male, 5 female; 61.8 ± 8.2 years; body mass index 29.8 ± 3.1 kg/m^2) with type 2 diabetes mellitus (HbA_{1c} 7.3 ± 1.1 %) and mixed hyperlipoproteinemia using a randomized, cross-over design. Fasting blood glucose, HbA_1c, lipid parameters, E-selectin, ICAM-1, VCAM-1, and fibrinogen concentrations were determined before and after each drug.

Results: Glucose and HbA_1c concentrations remained unchanged during the whole study period. LDL cholesterol was reduced during atorvastatin therapy, triglycerides were lowered more effectively with fenofibrate. Comparison of pre- and postreatment concentrations of E-selectin showed a reduction during atorvastatin (-7 %, $p = 0.11$) and fenofibrate (-10 %, $p < 0.05$) therapy. Atorvastatin treatment reduced VCAM-1 levels by 4% ($p < 0.05$), while VCAM-1 concentrations remained unchanged (+1%, ns) during fenofibate therapy. However, direct comparisons of post-treatment levels during both forms of therapy were not of statistical significance. ICAM-1 levels were not influenced by either form of therapy.

Conclusions: In addition to the different beneficial effects on lipid metabolism, both drugs appear to lower adhesion molecule plasma concentrations in a different manner in patients with type 2 diabetes and mixed hyperlipoproteinemia. Our observations should be confirmed in a larger cohort of such patients.

Background

Dyslipoproteinemia in patients with type 2 diabetes mellitus is characterized by elevated triglycerides, low HDL cholesterol and often elevated LDL cholesterol. HMGCoA reductase inhibitors have been shown to reduce atherosclerosis related morbidity and mortality in patients with diabetes mellitus [1,2]. On the other hand, fibrates are drugs that can decrease triglyceride concentrations and increase HDL cholesterol levels. In recent studies it was shown that they can reduce cardiovascular morbidity and mortality [3] and progression of coronary heart disease in patients with type 2 diabetes and hyperlipoproteinemia [4].

Elevated levels of adhesion molecules in plasma have been shown to be associated with diabetes mellitus [5] and dyslipoproteinemia [6-8]. There is strong evidence that the concentration of intercellular adhesion molecule-1 (ICAM-1) correlates positively with future cardiovascular risk in healthy men [9]. In type 2 diabetes, vascular cellular adhesion molecule-1 (VCAM-1) concentrations are positively correlated to future cardiovascular risk [10]. E-selectin is thought to indicate endothelial activation [11]. Several trials in patients with hypercholesterolemia revealed inconsistent results: In one study, HMGCoA reductase inhibitors lowered E-selectin levels in patients with hypercholesterolemia [7], another study observed an ICAM-1 reduction [12]. However, more recent publications did not confirm these findings and did not show an influence of statin therapy on adhesion molecule concentrations in patients with hyperlipoproteinemia [13,14].

There are few intervention trials which focus on the relationship between adhesion molecule levels and dyslipidemia in patients with diabetes mellitus. In type 2 diabetic patients with poor metabolic control intensive insulin treatment normalized initially elevated levels of the adhesion molecules E-selectin and VCAM-1 [5]. Atorvastatin therapy for 12 months lowered E-selectin and VCAM-1 levels in patients with diabetes mellitus and hypercholesterolemia [15]. The effect of fibrate therapy on adhesion molecule levels has not been studied yet in diabetic dyslipoproteinemia.

It is currently unclear from which form of lipid lowering therapy patients with diabetic dyslipoproteinemia benefit most. However, we have recently shown that atorvastatin lowers LDL cholesterol and fenofibrate lowers triglycerides in patients with type 2 diabetes and mixed hyperlipoproteinemia. Both drugs reduced total cholesterol and increased HDL cholesterol [16]. In addition, fenofibrate induced a beneficial shift in LDL subtype distribution. We now report the effects of atorvastatin and fenofibrate administration for 6 weeks on the plasma concentrations of the adhesion molecules E-selectin, VCAM-1, and ICAM-1 in these patients with type 2 diabetes mellitus and mixed hyperlipoproteinemia.

Subjects and Methods

We performed an analysis on the plasma samples of 11 patients of a previously published trial [16]. Unfortunately, one plasma sample was lost for the post hoc analysis. Therefore, another patient with type 2 diabetic and mixed hyperlipoproteinemia was recruited.

In brief, 11 non-smoking patients (6 males, 5 females; age 61.8 ± 8.2 years; body mass index 29.8 ± 3.1 kg/m2) with type 2 diabetes mellitus (duration 12 ± 7 years; hemoglobin A1c 7.3 ± 1.1 %) and mixed hyperlipoproteinemia (LDL cholesterol > 130 mg/dL; triglycerides > 200 mg/dL) without evidence of coronary heart, cerebrovascular, peripheral arterial disease or either microvascular complications (i.e. diabetic retinopathy, nephropathy or polyneuropathy) were included in the study after giving written informed consent. The study was approved by the ethics committee of the Ludwig-Maximilians-University Munich.

The study was designed and performed as a prospective, randomized, open labeled, cross-over trial. Following a 6-week wash-out period with no lipid-lowering drug therapy, patients were randomized to receive either 10 mg atorvastatin or 200 mg fenofibrate daily for 6 weeks. Following another wash-out period of 6 weeks patients were then crossed to the other arm and received fenofibrate or atorvastatin, respectively. The effects on lipid concentrations, which have been published previously for all except one patient are shown in table 1.

Before and after each treatment venous blood was drawn for laboratory analysis after an overnight fast. Plasma had been separated within 30 min and was stored at -80°C until analysis. E-selectin, VCAM-1 and ICAM-1 concentrations were determined from deep-frozen plasma following the instructions of a commercially available ELISA kit (R&D Systems, Wiesbaden, Germany). Absorbance was measured at 450 nm (Sunrise, TECAN, Crailsheim, Germany). All measurements were done at least twice and in one assay. The intra-assay coefficient of variability was < 3 % for E-selectin and < 2 % for both VCAM-1 and ICAM-1.

The results are reported as the mean ± standard deviation. All statistical analyses were performed with SPSS 10.0 (SPSS Software, Munich, Germany). Baseline and post-treatment concentrations of lipids, fibrinogen, and adhesion molecules as well as their absolute and relative changes during therapy, respectively, were analyzed for correlation using the Spearman test. Potential differences between baseline values before treatment periods (with either fenofibrate or atorvastatin, respectively) were

Table 1: Lipoprotein and fibrinogen concentrations during atorvastatin and fenofibrate therapy (n = 11).

	atorvastatin			fenofibrate		
	before (mg/dL)	during (mg/dL)	change (%)	before (mg/dL)	during (mg/dL)	change (%)
Total cholesterol	260 ± 46	193 ± 45	-25***	270 ± 48	219 ± 26	-17***
Total triglycerides	313 ± 198	210 ± 63	-11	320 ± 190	162 ± 48	-42***
LDL-cholesterol	150 ± 39	108 ± 39	-28**	161 ± 48	142 ± 23	-7
large, buoyant	15.2 ± 7.1	10.8 ± 5.4	-27**	17.8 ± 9.4	14.2 ± 3.6	-10
intermediate dense	57.8 ± 25.2	42.8 ± 19.4	-22*	61.8 ± 29.0	75.9 ± 20.2	+31
small, dense	85.9 ± 13.4	57.8 ± 17.5	-23*	91.8 ± 17.8	61.9 ± 19.2	-32*
HDL-cholesterol	46.8 ± 9.4	51.1 ± 10.4	+15*	50.6 ± 12.6	55.1 ± 11.6	+14*
Fibrinogen	406 ± 41	400 ± 41	-1	411 ± 57	329 ± 32	-19**

a: *p < 0.05; **p < 0.01; ***p < 0.005. b: LDL subtypes refer to following density intervals: large buoyant LDL 1.020 – 1.029 g/mL, intermediate dense LDL 1.030 – 1.034 g/mL, small dense LDL 1.041–1.066 g/mL. c: The data from 10 out of 11 patients were published previously [16].

evaluated using co-variance analysis (ANCOVA) [17]. Differences between treatments were analyzed using the Wilcoxon matched-pairs signed-rank test.

Results

The effect of both medications on lipoprotein and fibrinogen concentrations has been described in detail earlier [16]. In summary (table 1), there were significant reductions of total cholesterol by 25 % (atorvastatin) and 17 % (fenofibrate), of LDL cholesterol by 28 % (atorvastatin), and of triglycerides by 42 % (fenofibrate). While the concentration of all LDL subtypes decreased during atorvastatin therapy, small, dense LDL decreased and intermediate dense LDL increased during fenofibrate therapy. HDL cholesterol levels increased significantly with both drugs (+ 15 % and + 14 %). Fibrinogen concentrations were reduced during fenofibrate treatment only (-19 %). Antidiabetic treatment and control of hyperglycemia remained unchanged during the whole study period as reflected by similar fasting blood glucose and HBA_1c levels.

There was no difference of adhesion molecule concentrations after the washout periods, respectively. The levels of the intercellular adhesion molecule-1 (ICAM-1) were not changed by either drug (table 2). E-selectin was lowered with borderline significance during atorvastatin treatment (-7%, p = 0.11), E-selectin reduction during fenofibrate therapy was statistically significant (-10%, p < 0.05). In contrast, VCAM-1 levels remained unchanged during fenofibrate therapy, but were reduced by 4 % during atorvastatin treatment (p < 0.05). Direct comparison of post-treatment values confirmed greater reductions of E-selectin concentrations during fenofibrate therapy and VCAM-1 levels during atorvastatin therapy. However, these findings were not of statistical significance (p = 0.13 and p = 0.32, respectively).

While the relative reduction in LDL cholesterol during atorvastatin therapy correlated with the relative reduction in VCAM-1 (p < 0.05, r = 0.64), we did not observe any other correlation between either baseline or therapy induced changes in lipid concentrations with either baseline or therapy induced changes in adhesion molecule concentrations. Particularly, there was no correlation of triglyceride levels and LDL subtype distribution with adhesion molecule concentrations or their reductions during both forms of therapy, respectively.

Discussion

The greatest limitation of this study is probably the low number of participants. However, recruitment of study patients was very difficult, because patients with macro- or microvascular complications had to be excluded from this study for ethical reasons. Unfortunately, medications were not administered in a placebo-controlled way. This fact contributes to the weaknesses of this study. Another limitation of this study consists of the relative shortness of treatment periods compared to life-long therapy in clinical practice. However, treatment periods had to be relatively short for ethical reasons, because International Guidelines propagate target values for LDL cholesterol < 100 mg/dl in patients with diabetes mellitus type 2 and dyslipoproteinemia. This target values were reached only by a minority of patients during each treatment period.

In addition to the expected changes in lipid concentrations atorvastatin and fenofibrate therapy resulted in differential effects on several adhesion molecule plasma concentrations in diabetic dyslipoproteinemia. The concentrations of E-selectin were lowered during atorvastatin (-7%, ns) and fenofibrate (-10%, p < 0.05) therapy. Atorvastatin treatment reduced VCAM-1 levels by 4% (p < 0.05), while VCAM-1 concentrations remained unchanged (+1%, ns) during fenofibate therapy. ICAM-1

Table 2: Adhesion molecule concentrations during atorvastatin and fenofibrate therapy (n = 11).

	atorvastatin			fenofibrate		
	before (ng/mL)	during (ng/mL)	change (%)	before (ng/mL)	during (ng/mL)	change (%)
E-Selectin	70.3 ± 37.3	67.5 ± 40.1	-7	71.9 ± 42.5	62.8 ± 33.2	-10*
VCAM-1	779 ± 177	745 ± 166	-4*	752 ± 176	757 ± 161	+1
ICAM-1	285 ± 70	286 ± 69	+1	310 ± 65	296 ± 67	-4

*$p < 0.05$

levels were not influenced by either form of therapy. However, these reductions were found to be statistically significant when pre- and post-treatment concentrations of adhesion molecules were compared. Direct comparison of post-treatment values for each drug showed a trend for greater reductions of E-selectin levels during fenofibrate therapy, and VCAM-1 during atorvastatin therapy, but these reductions were not of statistical significance.

Two studies evaluating larger cohorts of hypertriglyceridemic patients with low HDL cholesterol levels revealed negative correlations between HDL cholesterol and adhesion molecule levels. However, their findings were not very conclusive. One study [18] observed decreasing HDL cholesterol levels were associated with increasing levels of VCAM-1 and ICAM-1, but not associated with E-selectin levels. On the other hand, another study [8] did not observe an association of VCAM-1 levels in patients groups with high, intermediate, or low HDL cholesterol. In individuals with HDL cholesterol levels (below the 10^{th} percentile), this study found an correlation of HDL cholesterol concentrations with ICAM-1 and E-selectin, but not with VCAM-1. The results of the intervention part of the last-mentioned study was partly in concordance with our findings. In a group of 20 non-diabetic patients with similar lipid profile (i.e. similar triglyceride, LDL and HDL cholesterol concentrations) fenofibrate therapy led to a decrease of E-selectin levels [8]. This decrease of E-selectin was weakly associated with the observed and well-known increase of HDL cholesterol during fibrate therapy. Possibly, our study group consisted of too few patients to confirm this weak association. However, other, lipid-independent mechanisms of fibrate action seem also plausible: Fibrates like thiazolidinediones (insulin sensitizer) activate the peroxisome proliferator-acitaved receptor (PPAR) system. Treatment of type 2 diabetes mellitus with troglitazone led to a reduction of E-selectin levels by 23 % [19]. Thus, common activation of the PPAR system during both fibrate and glitazone therapy could explain similar effects on E-selectin levels. Therefore, E-selectin reduction during fibrate therapy could be a lipoprotein-independent, i.e. pleiotropic effect of fibrate therapy. However, during troglitazone treatment the lower E-selectin levels were associated with a lower oxidative susceptibility of LDL cholesterol [19]. Since fenofibrate induces a shift in LDL subtype distribution from small, dense LDL to intermediate dense LDL [16], which are less susceptible to oxidation [20], fenofibrate may also have induced E-selectin reduction via a beneficial shift in LDL subtype distribution.

Although E-selectin level reduction during atorvastatin treatment was not significant in our study, treatment with HMGCoA reductase inhibitors have reduced E-selectin levels effectively in hypercholesterolemic patients [7] and in patients with diabetic dyslipoproteinemia [15]. The more profound effect on E-selectin concentrations in these studies might have been mediated by the more profound reduction of LDL cholesterol [7] and the longer period of treatment [15], respectively. Again, it is also possible that E-selectin reduction during HMGCoA inhibitor therapy is mediated by the reduction of small, dense LDL, because the absolute reductions of small, dense LDL cholesterol were similar during therapies with atorvastatin or fenofibrate [16]. However, mediation of E-selectin levels by small, dense LDL appears unlikely because there was no correlation between baseline levels or relative reductions of LDL cholesterol and E-selectin levels, respectively. Moreover, others studies did not demonstrate an influence of statin therapy on E-selectin concentrations in non-diabetic patients with hyperlipoproteinemia [12,13].

While ICAM-1 concentrations were not influenced by either form of lipid lowering therapy in this study, VCAM-1 concentrations were reduced by atorvastatin only. This reduction was correlated with LDL cholesterol reduction ($p < 0.05$). This finding is consistent with in-vitro studies which revealed an enhanced VCAM-1 gene expression during exposure of LDL to endothelial cell culture [21]. The VCAM-1 reduction during atorvastatin therapy confirms the findings of Dalla Nora et al. [15], who found an even more pronounced reduction of VCAM-1 levels after 12 months of treatment.

Thus, the observed changes in adhesion molecule concentrations may relate either to changes in lipids, pleiotropic

effects of lipid lowering medications or simply reflect the fact that there is less active atherosclerosis during lipid lowering treatment. Changes in lipids may play an important role, because we and others [7] observed that some but not all of the changes in adhesion molecule concentrations correlate with the changes in the concentration and/or lipid composition. Pleiotropic effects of statins, which have been described in detail elsewhere [22,23] account for the lipid-independent effects of these drugs and refer to changes in thrombogenicity, inflammation as well as arterial myocyte proliferation and migration [23], and endothelial function [24]. In contrast to the often-discussed pleiotropic effects of HMGCoA reductase inhibitors, less is known about pleiotropic effects of fibrates. However, it has been recently shown that fenofibrate lowers E-selectin and ICAM-1 concentrations [8] and improves vascular function in patients with hypertriglyceridemia [25]. It is quite likely that an improvement in endothelial function will also result in changes in adhesion molecule concentration. Finally, changes in adhesion molecule concentration may represent less active atherosclerosis. This is supported by studies which indicate that other approaches (i.e. ACE inhibitor therapy) also decrease adhesion molecule concentrations [26,27]. Our study was not designed to elucidate the mechanisms linking lipid lowering therapy to changes in adhesion molecule concentration, but it is possible that all of the above mentioned mechanisms contribute to the observed changes of plasma levels of E-selectin and VCAM-1.

Although the exact mechanisms remain unclear, there is no doubt that adhesion molecules are clinically important in atherosclerosis. E-selectin concentrations indicate endothelial activation [11] and are higher in diabetics compared to controls [5,17]. Cardiovascular morbidity and mortality in type 2 diabetic patients with hyperlipoproteinemia can be reduced by lipid lowering therapy with statins [1,2] or fibrates [3]. It is possible that the reduction of atherosclerosis in clinical trials is at least partly due to the reduction of E-selectin levels. VCAM-1 was shown to be associated with cardiovascular mortality in type 2 diabetics in a recent study [10]. The reduction of cardiovascular risk during therapy with HMGCoA reductase inhibitors might be partly represented by VCAM-1 reduction.

Conclusions

The optimal lipid lowering therapy of patients with type 2 diabetes and mixed hyperlipoproteinemia remains an unsolved problem. The improvements of lipoprotein concentrations during either HMGCoA reductase inhibitor (i.e. mainly LDL cholesterol reduction) or fibrate (triglyceride reduction plus a beneficial shift from small, dense LDL to intermediate LDL) therapy have been described elsewhere [16]. Irrespective of the limitations of this study, our results indicate that in addition to the differential effects on lipoprotein metabolism, both drugs may lower adhesion molecule levels in type 2 diabetics with mixed hyperlipoproteinemia in a different manner, i.e. in our patients fenofibrate lowered the concentration of E-selectin, and atorvastatin reduced VCAM-1 levels and showed a trend to lower E-selectin levels. It would be useful to prove these effects of lipid-lowering therapy on adhesion molecule concentrations in a larger group of patients with diabetes mellitus type 2 and mixed hyperlipoproteinemia, because these effects may contribute to the beneficial effects of atorvastatin and fenofibrate therapy.

List of abbreviations

ACE - angiotensin converting enzyme

HbA_1c - hemoglobin A_1c

HDL - high density lipoprotein

HMGCoA - hydroxy-methyl-glutaryl-coenzyme

ICAM-1 - intercellular adhesion molecule-1

LDL - low density lipoprotein

PPAR - peroxisome proliferator-acitaved receptor

VCAM-1 - vascular adhesion molecule-1

Authors' contributions

KE carried out the measurements of adhesion molecule concentrations, contributed to the statistical analysis and drafted the manuscript. RJAF was responsible for patient recruitment and performed the measurements of lipid concentrations. HCG and CO participated in the design of the study and contributed to the statistical analysis and interpretation of the data. KGP conceived of the study and participated in its design and coordination as well as the analysis and interpretation of the data. All authors have read and approved the final manuscript.

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