Pleiotropic Effects of Atorvastatin and Fenofibrate in Metabolic Syndrome and Different Types of Pre-Diabetes

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OBJECTIVE — To compare extra-lipid effects of statins and fibrates in relation to the baseline metabolic status of patients.

RESEARCH DESIGN AND METHODS — The study involved a group of 242 metabolic syndrome patients with or without pre-diabetes and randomized to atorvastatin, fenofibrate, or placebo.

RESULTS — Compared with matched healthy subjects, metabolic syndrome patients exhibited higher plasma levels/activities of high-sensitivity C-reactive protein (hs-CRP), fibrinogen, factor VII, plasminogen activator inhibitor 1, and enhanced monocyte cytokine release. These abnormalities were alleviated by both atorvastatin and fenofibrate treatment. CRP-lowering and monocyte-suppressing actions were more pronounced for atorvastatin in subjects with impaired fasting glucose and for fenofibrate in patients with impaired glucose tolerance.

CONCLUSIONS — The presence of pre-diabetes potentiates metabolic syndrome–induced abnormalities in plasma markers of inflammation and hemostasis and in monocyte secretory function. Both atorvastatin and fenofibrate exhibit multidirectional pleiotropic effects in subjects with metabolic syndrome, the strength of which seem to be partially determined by the type of pre-diabetes.

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The anti-inflammatory, endothelial-protective, antioxidant, and antithrombotic actions of statins and fibrates are observed not only in patients with dyslipidemia (1–5) but also in subjects with early and late glucose metabolism abnormalities (6–8). This suggests that metabolic syndrome (MS) patients may receive more benefits from statin or fibrate treatment than individuals suffering from isolated lipid or glucose metabolism disturbances. No previous study has examined whether the presence and type of pre-diabetes determines cardiovascular risk factor concentrations and the extra-lipid effects of lipid-lowering agents in MS patients.

RESEARCH DESIGN AND METHODS

— The study included 242 patients with recently diagnosed and previously untreated MS. MS was diagnosed using National Cholesterol Education Program Adult Treatment Panel III criteria. The exclusion criteria and power calculations are described in the online appendix (available at http://care.diabetesjournals.org/cgi/content/full/dc10-0272/DC1). The study protocol was approved by the local ethics committee. All enrolled MS patients were given detailed advice on how to achieve the goals of lifestyle modification: a reduction in weight of 7% or more if necessary; total fat intake less than 30% of total energy intake; saturated fat intake less than 7% of energy consumed; cholesterol intake less than 200-mg per day; an increase in fiber intake to 15-g per 1,000 kcal; and moderate-to-vigorous exercise for at least 30 min per day. On the basis of fasting plasma glucose, MS patients were allocated into one of the two groups: patients with pre-diabetes (n = 183) and patients with normal glucose tolerance (NGT) (n = 59) (online appendix). The former group was additionally divided into three subgroups: patients with isolated fasting glucose (IFG) (n = 61), patients with isolated impaired glucose tolerance (IGT) (n = 62), and patients with concomitant IFG and IGT (IFG + IGT) (n = 60). The patients in each group were randomized in a double-blind fashion to micronized fenofibrate (200 mg), atorvastatin (40 mg), or placebo, which were administered once daily for 90 days. MS patients were compared with age- and sex-matched healthy subjects without lipid and glucose metabolism abnormalities (n = 48). Plasma lipid/lipoprotein profile, total free fatty acids, fasting and 2-h postchallenge glucose levels, A1C, homeostasis model assessment (HOMA) index, high-sensitivity C-reactive protein (hs-CRP), fibrinogen, factor VII, plasminogen activator inhibitor 1 (PAI-1), and monocyte production of tumor necrosis factor-α, interleukin (IL)-1β, IL-6, and monocyte chemoattractant protein-1 were determined before and after 30 and 90 days of therapy (4,6,9). Statistical analysis was performed as previously described (4,6).

RESULTS

— Apart from disturbances in lipid profile and glucose metabolism markers, the presence of MS was associated with higher plasma levels/activity of hs-CRP, fibrinogen, factor VII, and PAI-1, and increased monocyte release of tumor necrosis factor-α, IL-1β, IL-6, and monocyte chemoattractant protein-1 (online appendix Table 1). No serious adverse effects were observed throughout the study, and 234 patients completed the study (online appendix).

In pre-diabetic patients, only feno-

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Table 1—*Atorvastatin and fenofibrate effects on lipid/lipoprotein profile, glucose metabolism, low-grade inflammation, hemostasis, and cytokine secretion by stimulated monocytes in MS patients coexisting with pre-diabetes or NGT*

	Control subjects	MS without pre-diabetes			MS with pre-diabetes		
		Placebo	Atorvastatin	Fenofibrate	Placebo	Atorvastatin	Fenofibrate
n	48	18	19	19	56	61	61
Total cholesterol (mg/dl)							
Baseline	159.0 ± 4.3	240.0 ± 5.5*	234.5 ± 5.0*	231.2 ± 5.8*	234.4 ± 3.8*	229.1 ± 5.1*	233.5 ± 6.0*
After 30 days	156.2 ± 4.5	235.1 ± 4.5*	145.1 ± 4.3†	200.3 ± 4.9†*	235.8 ± 4.1*	149.2 ± 4.6†	207.2 ± 5.2†*
After 90 days	155.1 ± 3.9	238.2 ± 4.2*	141.1 ± 4.0†‖	195.2 ± 6.2†*	230.1 ± 4.4*	143.3 ± 4.2†‖	199.7 ± 7.0†*
LDL cholesterol (mg/dl)							
Baseline	104.8 ± 3.0	146.2 ± 3.4*	145.0 ± 3.1*	142.5 ± 5.6*	138.4 ± 3.6*	142.1 ± 2.9*	137.9 ± 4.5
After 30 days	103.9 ± 3.2	144.1 ± 4.5*	104.2 ± 3.4†	123.1 ± 4.2†*	142.1 ± 4.0*	107.7 ± 4.1†	121.2 ± 4.1†*
After 90 days	103.1 ± 2.9	145.6 ± 2.2*	101.1 ± 3.2†‖	119.1 ± 4.1†*	140.4 ± 3.8*	103.2 ± 3.6†‖	116.2 ± 3.9†*
HDL cholesterol (mg/dl)							
Baseline	53.0 ± 0.8	34.1 ± 0.7*	34.4 ± 0.9*	33.0 ± 1.4*	33.2 ± 0.9*	34.7 ± 0.6*	33.4 ± 1.1*
After 30 days	53.4 ± 0.9	35.2 ± 0.8*	37.2 ± 0.9*	37.5 ± 1.3*	33.1 ± 0.8*	38.8 ± 1.0†*	37.9 ± 1.2†*
After 90 days	53.9 ± 1.2	34.6 ± 1.1*	38.5 ± 0.5†*	39.0 ± 1.1†*	34.4 ± 0.8*	39.7 ± 0.6†*	39.2 ± 1.0†*
Triglycerides (mg/dl)							
Baseline	112.7 ± 3.5	264.2 ± 8.0*	256.9 ± 11.1*	265.4 ± 9.8*	249.2 ± 9.8*	253.9 ± 7.5*	260.3 ± 11.2*
After 30 days	108.4 ± 3.2	267.1 ± 7.3*	225.1 ± 8.9†*	180.5 ± 10.1†*	242.2 ± 7.5*	220.5 ± 8.6†*	191.0 ± 10.4†*
After 90 days	106.0 ± 4.2	270.9 ± 7.4*	220.2 ± 6.4†*	175.7 ± 8.6†*‖	245.1 ± 7.0*	221.7 ± 8.2†*	177.3 ± 9.9†*‖
Free fatty acids (μmol/l)							
Baseline	223.2 ± 11.5	410.3 ± 34.1*	398.3 ± 35.2*	396.5 ± 32.2*	454.1 ± 39.1*	466.9 ± 39.2*	452.1 ± 34.2*
After 30 days	216.4 ± 12.3	425.2 ± 30.2*	336.8 ± 30.4†*	335.2 ± 26.5†*	452.3 ± 30.5*	410.2 ± 31.1†*	379.3 ± 46.5†*
After 90 days	218.4 ± 14.2	431.1 ± 34.0*	334.2 ± 32.1†*	325.1 ± 29.0†*	445.4 ± 40.0*	384.4 ± 22.6†*	354.4 ± 43.5†*
Oxidized LDLs (U/l)							
Baseline	31.3 ± 3.2	70.2 ± 8.1*	67.9 ± 6.2*	65.2 ± 7.9*	73.2 ± 5.5*	76.9 ± 7.4*	78.2 ± 7.5*
After 30 days	30.2 ± 3.1	72.3 ± 6.9*	36.2 ± 5.0†	55.2 ± 6.4*	77.8 ± 6.2*	30.4 ± 5.3†	56.3 ± 6.9*†
After 90 days	32.0 ± 3.7	74.0 ± 6.8*	32.2 ± 7.8†‖	47.2 ± 5.2†*	71.1 ± 6.1*	33.1 ± 6.0†‖	49.2 ± 5.4†*
Apoprotein A-I (mg/dl)							
Baseline	178.5 ± 14.6	128.3 ± 11.9*	129.1 ± 9.2*	132.5 ± 10.3*	131.1 ± 12.0*	128.0 ± 10.1*	128.6 ± 10.5*
After 30 days	176.1 ± 13.6	130.1 ± 10.9*	132.2 ± 10.2*	145.5 ± 9.5*	134.4 ± 11.2*	129.1 ± 11.3*	146.3 ± 10.1*
After 90 days	175.0 ± 14.0	126.7 ± 10.6*	140.2 ± 9.8*	152.1 ± 8.6†*‖	131.5 ± 13.6*	138.1 ± 12.4*	155.2 ± 9.5†*‖
Apoprotein B (mg/dl)							
Baseline	101.5 ± 9.6	153.2 ± 14.1*	156.4 ± 11.0*	152.2 ± 12.2*	148.4 ± 13.5*	151.9 ± 10.7*	155.9 ± 12.9*
After 30 days	103.5 ± 10.0	155.4 ± 12.1*	114.1 ± 9.8†*	129.0 ± 10.6*	144.7 ± 12.7*	115.3 ± 8.8†*	133.0 ± 14.5†*
After 90 days	105.0 ± 12.1	156.4 ± 13.2*	108.3 ± 9.2†‖	122.5 ± 6.2†*	143.2 ± 11.0*	101.1 ± 8.6†‖	124.2 ± 8.3†*
Fasting plasma glucose (mg/dl)							
Baseline	86.1 ± 2.3	91.3 ± 2.4	89.9 ± 1.8	89.2 ± 2.2	104.3 ± 3.8*§	108.1 ± 2.0*§	109.2 ± 1.9*§
After 30 days	87.2 ± 2.1	89.4 ± 2.5	86.5 ± 2.8	87.2 ± 2.1	100.1 ± 4.4*	106.2 ± 2.1*	104.1 ± 2.2†*
After 90 days	85.2 ± 1.8	89.0 ± 2.9	88.7 ± 2.2	87.0 ± 2.0	102.3 ± 4.2*	107.7 ± 2.2*	103.1 ± 1.8†*‖
2-h postglucose load plasma glucose levels (mg/dl)							
Baseline	118.2 ± 3.6	123.1 ± 3.8	119.3 ± 4.1	125.4 ± 5.2	149.9 ± 4.2*§	152.8 ± 5.5*§	156.1 ± 6.4*§
After 30 days	116.1 ± 3.2	119.2 ± 2.9	120.3 ± 2.4	121.1 ± 6.5	146.2 ± 4.1*	149.4 ± 4.4*	144.2 ± 4.2†*
After 90 days	115.8 ± 3.0	117.0 ± 3.5	122.3 ± 2.5	118.2 ± 6.0	144.1 ± 3.6*	153.0 ± 4.1*	143.8 ± 3.9†*‖

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Table 1—*Continued*

	Control subjects	MS without pre-diabetes			MS with pre-diabetes		
		Placebo	Atorvastatin	Fenofibrate	Placebo	Atorvastatin	Fenofibrate
HOMA							
Baseline	1.3 ± 0.1	3.4 ± 0.3*	3.5 ± 0.2*	3.7 ± 0.2*	4.7 ± 0.3*§	4.9 ± 0.2*§	4.9 ± 0.3*§
After 30 days	1.2 ± 0.1	3.5 ± 0.2*	3.4 ± 0.3*	2.5 ± 0.2†*	4.5 ± 0.3*	5.1 ± 0.3*	3.8 ± 0.3†*
After 90 days	1.3 ± 0.1	3.6 ± 0.3*	3.8 ± 0.2*	2.2 ± 0.2†*‖	4.5 ± 0.2*	5.0 ± 0.3*	2.9 ± 0.2†*‖
A1C (%)							
Baseline	4.8 ± 0.2	4.9 ± 0.1	4.9 ± 0.2	5.0 ± 0.1	5.2 ± 0.3	5.4 ± 0.2	5.3 ± 0.3
After 30 days	4.9 ± 0.2	5.0 ± 0.1	4.9 ± 0.2	4.9 ± 0.3	5.0 ± 0.2	5.4 ± 0.2	5.0 ± 0.2
After 90 days	4.7 ± 0.1	4.8 ± 0.2	5.0 ± 0.1	4.7 ± 0.2	5.0 ± 0.2	5.3 ± 0.1	4.6 ± 0.2†‖
hs-CRP (mg/l)							
Baseline	0.9 ± 0.1	1.7 ± 0.3*	1.5 ± 0.1*	1.7 ± 0.2*	2.7 ± 0.4*§	2.5 ± 0.3*§	2.4 ± 0.2*§
After 30 days	0.8 ± 0.2	1.4 ± 0.2*	1.1 ± 0.1†*	1.2 ± 0.2†*	2.7 ± 0.3*	1.8 ± 0.3†*	1.7 ± 0.2†*
After 90 days	1.0 ± 0.3	1.5 ± 0.1*	0.8 ± 0.2†	0.9 ± 0.1†	2.4 ± 0.4*	1.4 ± 0.3†	1.2 ± 0.1†‡
Fibrinogen (mg/dl)							
Baseline	3.0 ± 0.1	4.2 ± 0.2*	4.0 ± 0.2*	4.2 ± 0.1*	4.4 ± 0.2*	4.5 ± 0.3*	4.6 ± 0.3
After 30 days	2.9 ± 0.1	4.1 ± 0.2*	4.2 ± 0.3*	3.5 ± 0.2†*	4.4 ± 0.1*	4.4 ± 0.2*	3.6 ± 0.2†*
After 90 days	3.1 ± 0.2	4.0 ± 0.2*	3.9 ± 0.2*	3.2 ± 0.2†‖	4.2 ± 0.2*	4.4 ± 0.3*	3.4 ± 0.2†‖
Factor VII activity (%)							
Baseline	98.2 ± 3.2	126.0 ± 4.4*	124.8 ± 4.6*	123.2 ± 5.0*	155.1 ± 4.5*§	155.3 ± 3.9*§	153.1 ± 4.9§
After 30 days	96.5 ± 4.1	123.8 ± 5.0*	100.2 ± 5.2†	101.1 ± 6.2†	154.1 ± 5.1*	115.6 ± 4.2†	112.9 ± 5.2†*
After 90 days	95.8 ± 4.2	125.0 ± 5.1*	96.2 ± 4.9†	98.2 ± 6.1†	157.4 ± 4.8*	93.3 ± 5.0†‡	99.9 ± 4.8†‡
PAI-1 (ng/ml)							
Baseline	42.2 ± 4.1	89.2 ± 3.5*	92.1 ± 4.0*	83.8 ± 5.1*	118.4 ± 7.9*§	120.1 ± 6.0*§	118.6 ± 5.5*§
After 30 days	43.4 ± 3.6	86.4 ± 3.1*	67.4 ± 4.4†*	62.2 ± 6.4†*	116.5 ± 7.2*	75.2 ± 4.8†*	86.4 ± 6.0†*
After 90 days	44.5 ± 4.0	85.0 ± 3.7*	40.3 ± 3.5†‡‖	57.8 ± 4.3†*	121.1 ± 3.2*	52.1 ± 3.4†‡‖	69.6 ± 5.9†*
TNF-α release (pg/ml)							
Baseline	852.3 ± 102.3	1,395.2 ± 164.2*	1,520.8 ± 153.3*	1,470.2 ± 109.3*	2,280.1 ± 156.7*§	2,362.9 ± 172.3*§	2,345.7 ± 164.1*§
After 30 days	830.1 ± 78.5	1,370.1 ± 132.9*	1,112.1 ± 135.0†*	1,098.3 ± 115.2†*	2,210.5 ± 149.2*	1,521.1 ± 134.0†*	1,798.3 ± 115.2†*
After 90 days	804.0 ± 81.3	1,298.8 ± 111.2*	798.2 ± 122.2†‡	781.1 ± 99.1†‡	2,142.4 ± 160.1*	1,155.1 ± 133.5†‡*	1,168.8 ± 87.8†‡*
IL-1β release (pg/ml)							
Baseline	71.4 ± 9.0	123.1 ± 10.9*	118.9 ± 7.5*	119.8 ± 12.5*	198.3 ± 14.3*§	201.0 ± 11.2*§	208.2 ± 14.1*§
After 30 days	69.0 ± 8.3	120.1 ± 9.8*	88.2 ± 7.1†*	89.1 ± 10.1†*	193.1 ± 12.9*	154.2 ± 8.7†*	154.7 ± 12.2†*
After 90 days	70.8 ± 7.5	119.6 ± 8.5*	62.9 ± 6.4†‡	64.2 ± 11.1†‡	199.1 ± 13.8*	106.1 ± 9.1†‡*	112.2 ± 10.5†‡*
IL-6 release (ng/ml)							
Baseline	5.9 ± 0.4	8.2 ± 0.9*	8.2 ± 0.8*	8.0 ± 0.7*	12.4 ± 0.3*§	13.1 ± 0.9*§	12.9 ± 0.5*§
After 30 days	6.2 ± 0.5	8.1 ± 0.7*	6.2 ± 0.8†	6.4 ± 0.5†	12.5 ± 0.5*	9.6 ± 0.9†*	8.9 ± 0.4†*
After 90 days	6.0 ± 0.4	8.1 ± 0.5*	5.7 ± 0.6†	5.8 ± 0.2†	12.8 ± 0.3*	7.7 ± 0.7†‡*	7.5 ± 0.6†‡*
MCP-1 release (ng/ml)							
Baseline	10.4 ± 0.8	16.2 ± 2.0*	16.4 ± 1.4*	16.6 ± 1.6*	20.9 ± 1.4*	21.2 ± 1.2*§	20.7 ± 1.1*§
After 30 days	10.9 ± 0.7	16.5 ± 2.2*	13.1 ± 1.6†*	13.3 ± 1.4†*	19.3 ± 2.0*	16.2 ± 1.3†*	15.5 ± 1.2†*
After 90 days	11.1 ± 0.6	16.0 ± 1.9*	10.1 ± 1.5†	10.2 ± 1.5†	20.4 ± 1.5*	12.2 ± 1.1†‡	12.4 ± 1.4†‡

Data are means ± SEM. *P* values less than 0.05 were considered statistically significant. *Statistically significant vs. control subjects. †Statistically significant vs. baseline values. ‡Statistically significant vs. values after 30 days of treatment. §Statistically significant vs. the same treatment group in patients without pre-diabetes in baseline conditions. ‖Treatment-induced changes at the end of the treatment stronger than for the other drug in the same group of patients.

fibrate decreased fasting and postchallenge plasma glucose, HOMA index, and A1C (Table 1). In MS patients with NGT or pre-diabetes, atorvastatin and fenofibrate improved lipid/lipoprotein profile, reduced monocyte cytokine release, and decreased plasma levels/activity of hs-CRP, factor VII, and PAI-1. Fenofibrate also decreased plasma fibrinogen. In MS patients with either pre-diabetes or NGT, atorvastatin stronger than fenofibrate reduced plasma levels of total and LDL cholesterol, apoprotein B, oxidized LDLs, and PAI-1, while fenofibrate to a greater extent than atorvastatin affected triglycerides, apoprotein A-I, and fibrinogen. In MS patients with NGT and, when analyzed together, also in MS patients with pre-diabetes, both drugs were equipotent in their effect on plasma hs-CRP and monocyte cytokine release.

Fenofibrate was superior to atorvastatin in reducing fasting and postglucose load plasma glucose in IGT and IFG + IGT patients, as well as in reducing HOMA index and A1C in all subgroups of pre-diabetic patients (online appendix Table 2). Fenofibrate more markedly decreased fasting plasma glucose in IFG + IGT patients than in the remaining groups of pre-diabetic subjects. Atorvastatin action on hs-CRP and monocyte cytokine release was stronger in IFG and IFG+ IGT patients than in IGT patients. In turn, fenofibrate action on these markers was more pronounced in IGT and IFG + IGT patients than in IFG patients. In IFG subjects, atorvastatin stronger than fenofibrate reduced plasma hs-CRP and monocyte cytokine release, whereas the opposite relationship was found in IGT patients. In IFG + IGT subjects, the effect of both drugs on hs-CRP and cytokine release was similar to each other, and their post-treatment values remained higher than in control subjects. The atorvastatin- or fenofibrate-induced reduction in IL-1β release reached the highest degree in patients with concomitant IFG and IGT. Correlations are presented in the online appendix Supplemental Results.

CONCLUSIONS — This prospective, randomized, placebo-controlled study has shown that cytokine release, low-grade inflammation, coagulation, and fibrinolysis were more profoundly disturbed in pre-diabetic patients, particularly in those with concomitant presence of IFG and IGT than in MS subjects with NGT. Considering that the assessed variables are proven vascular risk factors (2,10–12), the obtained results suggest the earlier development and faster progression of cardiovascular and cerebrovascular disorders if MS is accompanied by pre-diabetes and partially explain the differences in the clinical course between IFG and IGT (13–15). Coexistence of both pre-diabetic conditions seems to be associated with a greater cardiovascular and cerebrovascular risk than the presence of only one of them.

The study has documented the superiority of the fibrate over the statin treatment in influencing glucose homeostasis and has revealed that fenofibrate action on glycemic control was pre-diabetes–type dependent. This indicates that only fibrates may delay the development of diabetes in MS patients, particularly in individuals with either isolated IGT or with coexisting IFG and IGT.

The magnitude of the reduction in monocyte cytokine release and plasma levels/activities of factor VII and hs-CRP was similar for both agents. Although fenofibrate was superior to atorvastatin in reducing fibrinogen, the latter drug more markedly decreased PAI-1. These results indicate that both fibrates and statins effectively reduce vascular risk in MS patients. Although the global anti-inflammatory and monocyte-suppressing effect was similar in magnitude for atorvastatin and fenofibrate in the entire population of pre-diabetic patients, the strength of this action depended on the patients' metabolic profiles. This finding suggests that IGT patients may benefit more from fibrate treatment, whereas IFG subjects may be better candidates for statin therapy.

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R.K. researched the data and wrote the manuscript. A.G.-D. researched the data and contributed to the discussion. R.B. researched the data and contributed to the discussion. B.O. researched the data and reviewed and edited the manuscript.

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