

Pleiotropic Action of Short-Term Metformin and Fenofibrate Treatment, Combined With Lifestyle Intervention, in Type 2 Diabetic Patients With Mixed Dyslipidemia

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OBJECTIVE — To compare the effect of short-term metformin and fenofibrate treatment, administered alone or in sequence, on glucose and lipid metabolism, cardiovascular risk factors, and monocyte cytokine release in type 2 diabetic patients with mixed dyslipidemia.

RESEARCH DESIGN AND METHODS — We studied 128 type 2 diabetic patients with mixed dyslipidemia complying throughout the study with lifestyle intervention who were randomized twice, initially to either metformin or placebo, and then to micronized fenofibrate or placebo.

RESULTS — Fenofibrate alleviated diabetic dyslipidemia–induced changes in plasma high-sensitivity C-reactive protein, fibrinogen, and plasminogen activator inhibitor (PAI)-1 and in monocyte cytokine release, whereas metformin or lifestyle intervention improved mainly glucose and lipid metabolism. The strongest pleiotropic effect was observed when fenofibrate was added to metformin.

CONCLUSIONS — Fenofibrate, particularly administered together with metformin, is superior to metformin and lifestyle intervention in exhibiting beneficial effects on systemic inflammation, hemostasis, and monocyte secretory function in type 2 diabetic patients with mixed dyslipidemia.

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Peroxisome proliferator–activated receptor (PPAR)- α activators (fibrates) administered to patients with dyslipidemia (1–4) or early glucose metabolism abnormalities (5) produce many non-lipid-related effects, including anti-inflammatory, antioxidant, and antithrombotic actions and improvement in endothelial function. Apart from normalizing glucose metabolism, metformin, the only oral antidiabetic medication shown to decrease cardiovascular events independent of glycemic control (6), improved dyslipidemia, hemostasis, and systemic inflammation (7). To the best of our knowledge, no previous clinical study has ever compared clinical benefits of

metformin and fibrates when it comes to their pleiotropic effects and assessed whether metformin–fibrate combination is superior to treatment with only one of these drugs.

RESEARCH DESIGN AND METHODS — The patients included in the study met the following criteria: 1) recently diagnosed and previously untreated type 2 diabetes (fasting plasma glucose at least 126 mg/dl or plasma glucose concentration 2 h after a glucose load at least 200 mg/dl) and 2) mixed dyslipidemia (plasma total cholesterol >200 mg/dl, LDL cholesterol >130 mg/dl, triglycerides >150 mg/dl). The exclusion

criteria are presented in the supplemental data, available in an online appendix at <http://care.diabetesjournals.org/cgi/content/full/dc08-2335/DC1>. The study protocol was approved by the local ethics committee. All included patients ($n = 128$) were given detailed advice about how to achieve the goals of lifestyle modification, which were a reduction in weight of 7% or more if necessary, total fat intake <30% of total energy intake, saturated fat intake <7% of energy consumed, cholesterol intake <200 mg/day, an increase in fiber intake to 15 g per 1,000 kcal, and moderate to vigorous exercise for at least 30 min/day. The patients were randomized in a double-blind fashion to metformin (850 mg; $n = 66$) or placebo ($n = 62$), which were administered twice daily for 60 days. After 30 days of treatment, patients of each group were again randomized to receive once daily at bedtime either micronized fenofibrate (267 mg daily) or placebo, and the treatment with metformin + fenofibrate ($n = 33$), metformin + placebo ($n = 33$), placebo + fenofibrate ($n = 31$), or placebo + placebo ($n = 31$) together with lifestyle intervention were continued for the following 30 days. All treatment groups were compared with two age-, sex-, and weight-matched groups of patients: type 2 diabetic subjects with mixed dyslipidemia ($n = 32$) and control normoglycemic and normolipidemic subjects ($n = 32$). Patients belonging to both of these groups were briefly informed about the benefits of a healthy diet but were not prescribed any special dietary and exercise recommendations. Lipid profile, plasma glucose, insulin, high-sensitivity C-reactive protein (hsCRP), fibrinogen, plasminogen activator inhibitor (PAI)-1, homeostasis assessment (HOMA) index, A1C, and monocyte release of tumor necrosis factor (TNF)- α and interleukin-1 β were determined before and after 30 and 60 days of therapy (3,5). Statistical analysis was performed as previously described (3,5).

RESULTS — At baseline, there was no difference between the groups in terms of sex, weight, age, medical background, and clinical characteristics. Apart from

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Pleiotropic action of metformin and fenofibrate treatment

Table 1—Effect of metformin and fenofibrate, administered alone or in sequence, together with lifestyle intervention on lipid profile, glucose metabolism, low-grade inflammation, hemostasis, and cytokine secretion by stimulated monocytes in type 2 diabetic patients with mixed dyslipidemia

	Type 2 diabetic patients with mixed dyslipidemia complying with lifestyle intervention				Patients not complying with lifestyle intervention	
	Placebo + placebo	Metformin + placebo	Placebo + fenofibrate	Metformin + fenofibrate	Diabetic dyslipidemia	Control subjects [¶]
Number of patients	30	31	30	33	32	32
Fasting glucose (mg/dl)						
Baseline	169.1 ± 4.4***	168.8 ± 4.1***	164.5 ± 3.1***	165.9 ± 3.2***	165.8 ± 4.6***	90.1 ± 2.2
After 30 days	141.0 ± 5.6***††	121.8 ± 4.9***†††	139.4 ± 3.6***†	120.5 ± 3.1***†††	162.2 ± 4.0***	90.5 ± 2.0
After 60 days	147.5 ± 3.9***†	109.6 ± 4.3***††††	142.1 ± 3.2***†	106.1 ± 3.7***††††	167.2 ± 3.8***	88.2 ± 1.9
HOMA						
Baseline	11.5 ± 0.7***	11.7 ± 0.6***	11.3 ± 0.8***	11.9 ± 0.7***	11.4 ± 0.8***	2.1 ± 0.2
After 30 days	11.1 ± 0.6***	8.0 ± 0.6***†	10.9 ± 0.5***	8.9 ± 0.8***†	11.6 ± 0.6***	2.0 ± 0.1
After 60 days	10.3 ± 0.5***†	6.8 ± 0.4***†††	8.7 ± 0.6***†††	5.0 ± 0.4***†††††	11.3 ± 0.9***	2.2 ± 0.2
A1C (%)						
Baseline	7.5 ± 0.2***	7.4 ± 0.2***	7.5 ± 0.2***	7.4 ± 0.1***	7.4 ± 0.3***	5.1 ± 0.2
After 30 days	7.0 ± 0.2***†	6.5 ± 0.2***††	7.0 ± 0.2***†	6.5 ± 0.2***††	7.4 ± 0.2***	5.0 ± 0.1
After 60 days	7.0 ± 0.2***†	6.2 ± 0.1***†††	6.7 ± 0.2***††	6.1 ± 0.1***†††	7.3 ± 0.2***	5.1 ± 0.2
Total cholesterol (mg/dl)						
Baseline	226.5 ± 4.1***	229.3 ± 3.2***	228.1 ± 4.2***	232.1 ± 3.6***	228.8 ± 5.4***	162.0 ± 4.2
After 30 days	224.4 ± 4.2***	228.3 ± 2.5***	216.6 ± 3.2***	221.1 ± 3.5***	230.1 ± 3.4***	160.0 ± 3.2
After 60 days	229.3 ± 5.0***	223.6 ± 4.0***	188.3* ± 4.5***†††	183.8 ± 4.0***††††	231.1 ± 2.3***	159.9 ± 2.3
LDL cholesterol (mg/dl)						
Baseline	148.2 ± 2.3***	150.3 ± 2.6***	149.0 ± 3.2***	150.6 ± 2.6***	151.1 ± 3.5***	108.1 ± 2.8
After 30 days	148.1 ± 2.4***	147.0 ± 3.1***	139.8 ± 4.1***	142.2 ± 2.0***	147.4 ± 2.8***	110.4 ± 2.6
After 60 days	145.0 ± 3.0***	140.9 ± 3.5***	115.1 ± 3.2††††	113.4 ± 1.9†††††	145.4 ± 3.7***	110.7 ± 2.7
HDL cholesterol (mg/dl)						
Baseline	40.1 ± 1.0***	39.5 ± 1.1***	40.4 ± 1.1***	39.2 ± 1.0***	39.9 ± 1.1***	47.8 ± 0.7
After 30 days	41.8 ± 0.7***	40.1 ± 0.3***	40.6 ± 0.6***	41.5 ± 0.4**	39.0 ± 1.3***	48.0 ± 0.6
After 60 days	42.1 ± 0.6***	41.0 ± 0.3***	43.2 ± 0.5***†	43.7 ± 0.3***†	39.2 ± 0.6***	47.1 ± 0.5
Triglycerides (mg/dl)						
Baseline	206.8 ± 6.4***	219.6 ± 5.2***	214.8 ± 6.8***	215.9 ± 5.5***	214.4 ± 8.8***	122.4 ± 3.2
After 30 days	193.8 ± 6.8***	198.6 ± 5.1***	204.8 ± 5.3***	190.6 ± 4.5***	212.5 ± 8.0***	121.1 ± 4.0
After 60 days	181.5 ± 8.2***†	184.5 ± 6.0***†	166.8 ± 7.8***†††	142.2 ± 8.2†††	210.0 ± 7.8***	120.4 ± 4.6
hsCRP (mg/l)						
Baseline	3.0 ± 0.2***	2.9 ± 0.2***	2.8 ± 0.2***	2.9 ± 0.2***	2.8 ± 0.1***	1.0 ± 0.1
After 30 days	2.8 ± 0.3***	2.5 ± 0.2***	2.5 ± 0.2***	2.7 ± 0.2***	2.8 ± 0.2***	1.0 ± 0.2
After 60 days	2.8 ± 0.3***	2.2 ± 0.1***†	1.9 ± 0.4***†	2.0 ± 0.2***†††	2.7 ± 0.2***	1.1 ± 0.1
Fibrinogen (mg/dl)						
Baseline	455.0 ± 48.1***	474.1 ± 32.9***	453.5 ± 37.6***	469.9 ± 18.3***	474.2 ± 32.1***	296.5 ± 22.0
After 30 days	467.8 ± 45.1***	440.2 ± 49.0***	465.1 ± 35.4***	443.1 ± 54.2***	486.0 ± 21.0***	285.1 ± 23.4
After 60 days	460.5 ± 51.6***	436.4 ± 29.5***	391.2 ± 36.7***††	346.3 ± 48.9***†††	475.1 ± 27.5***	290.3 ± 19.8
PAI-1 (ng/ml)						
Baseline	101.5 ± 4.1***	99.4 ± 3.9***	102.0 ± 4.8***	95.7 ± 3.6***	101.1 ± 5.2***	49.6 ± 6.2
After 30 days	100.6 ± 6.1***	94.8 ± 3.8***	94.8 ± 5.1***	92.0 ± 2.7***	102.4 ± 4.4***	48.1 ± 4.2
After 60 days	103.3 ± 5.7***	92.1 ± 4.0***	73.9 ± 4.6***†††	69.8 ± 4.5***††††	100.8 ± 4.6***	48.9 ± 5.1
TNF-α release (pg/ml)						
Baseline	1,530.0 ± 68.1***	1,453.5 ± 42.1***	1,511.2 ± 64.5***	1,449.8 ± 53.2***	1,489.1 ± 71.1***	901.7 ± 46.6

Table 1—Continued

	Type 2 diabetic patients with mixed dyslipidemia complying with lifestyle intervention				Patients not complying with lifestyle intervention	
	Placebo + placebo	Metformin + placebo	Placebo + fenofibrate	Metformin + fenofibrate	Diabetic dyslipidemia	Control subjects [¶]
After 30 days	1,486.6 ± 70.8***	1,382.4 ± 35.1***	1,332.4 ± 53.2**	1,028.9 ± 87.3*†	1,523.1 ± 68.2***	895.3 ± 38.2
After 60 days	1,484.2 ± 56.7***	1,108.9 ± 52.0**†	830.1 ± 69.0††	620.1 ± 35.9†††††	1,510.8 ± 36.4***	908.2 ± 44.5
Interleukin-1 β release (pg/ml)						
Baseline	132.5 ± 5.2***	136.3 ± 6.8***	136.5 ± 7.0***	138.8 ± 7.1***	135.0 ± 4.0***	86.1 ± 6.5
After 30 days	146.8 ± 7.3***	139.0 ± 5.9***	125.8 ± 8.0**	139.5 ± 6.4***	138.4 ± 3.9***	90.2 ± 5.4
After 60 days	145.2 ± 3.8***	126.8 ± 7.3***	90.3 ± 5.6†††††	92.5 ± 7.0†††††	130.1 ± 6.8***	87.5 ± 3.2

Data are means \pm SEM. * P < 0.05, ** P < 0.01, *** P < 0.001 vs. control subjects; † P < 0.05, †† P < 0.01, ††† P < 0.001 vs. baseline values, ‡ P < 0.05, ‡‡ P < 0.01, ‡‡‡ P < 0.001 vs. values after 30 days of treatment. ^{||}Type 2 diabetic patients with mixed dyslipidemia. [¶]Subjects without carbohydrate and lipid abnormalities.

differences in lipid profile and glucose metabolism markers, the presence of diabetes and dyslipidemia was associated with higher plasma levels of hsCRP, fibrinogen, and PAI-1 and the increased release of both cytokines (see the supplemental Table, available in the online appendix). No serious adverse effects were observed throughout the study, and 188 patients completed the study (see the supplemental Results, available in the online appendix). Fenofibrate, administered alone or added to metformin, alleviated diabetic dyslipidemia-induced changes in plasma hsCRP, fibrinogen, and PAI-1 and in monocyte cytokine release. In turn, metformin or lifestyle intervention improved mainly glucose and lipid metabolism (Table 1). Metformin + fenofibrate were superior to 1) placebo + placebo in affecting fasting glucose, HOMA, A1C, total, LDL, and HDL cholesterol, triglycerides, hsCRP, fibrinogen, PAI-1, and monocyte cytokine release; 2) metformin + placebo in affecting HOMA, total, LDL, and HDL cholesterol, triglycerides, fibrinogen, PAI-1, and cytokine release; and 3) placebo + fenofibrate group in affecting fasting glucose, HOMA, A1C, triglycerides, fibrinogen, and TNF- α release. Placebo + fenofibrate were superior to 1) placebo + placebo in reducing total and LDL cholesterol, HOMA, hsCRP, fibrinogen, PAI-1, TNF- α , and interleukin-1 β release; 2) metformin + placebo group in reducing total, LDL, and HDL cholesterol, fibrinogen and PAI-1, and monocyte release of both cytokines; but 3) inferior to the latter group in reducing plasma fasting glucose, HOMA, and A1C. Metformin + placebo were superior to placebo + placebo in changing fasting glucose, HOMA, A1C,

and TNF- α release. At baseline, there was a weak correlation between plasma hsCRP and baseline cytokine release; between HOMA and plasma hsCRP, fibrinogen, and PAI-1; as well as well as between HOMA and cytokine release (r values between 0.42 and 0.51; P < 0.001). Treatment-induced changes in plasma hsCRP correlated weakly with the changes in TNF- α and interleukin-1 β release (r values from 0.45 to 0.59; P < 0.001). No other correlations were found in both baseline conditions and after treatment (see the supplemental Results, available in the online appendix).

CONCLUSIONS— This prospective partially double-blind placebo-controlled randomized study has shown that fenofibrate exhibited a stronger effect than metformin and nonpharmacological intervention on systemic inflammation, hemostasis, and monocyte secretory function, disturbed by the presence of type 2 diabetes and mixed dyslipidemia. This multidirectional action of fenofibrate, which was lipid independent and unrelated to the improvement in insulin sensitivity, may contribute to the beneficial action of PPAR- α activators on the reduction of cardiovascular events observed in some (8,9), but not other (10), clinical trials. A weaker than anticipated (11) action of metformin may be, at least in part, explained by all treated subjects complying with lifestyle modification, because placebo-treated patients following the latter strategy were superior to not complying patients in reducing plasma glucose, HOMA, A1C, and triglycerides. In our study, the treatment-induced changes in glucose and lipid metabolism, and in low-grade inflammation, hemosta-

sis, and monocyte cytokine release, were strongest in patients treated with both of these agents. Considering that the assessed markers are regarded as cardiovascular risk factors (12–14), the obtained results suggest bringing by metformin-fenofibrate combination some additional benefits to patients with diabetic dyslipidemia. Taking into account that statins markedly reduce cardiovascular risk and, if tolerated, should be given to all type 2 diabetic patients (15), administration of metformin with fenofibrate may be considered an alternative treatment option in subjects in whom statin therapy is either contraindicated or results in adverse effects, including drug interactions.

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No potential conflicts of interest relevant to this article were reported.

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