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EXPEDITED REVIEWS

The Reduction of Inflammatory Biomarkers by Statin, Fibrate, and Combination Therapy Among Diabetic Patients With Mixed Dyslipidemia

The DIACOR (Diabetes and Combined Lipid Therapy Regimen) Study

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OBJECTIVES The primary objective was to determine the effect of statin-fibrate combination therapy on inflammatory biomarkers in patients with diabetes.

BACKGROUND Atherosclerosis is a long-term, chronic inflammatory disease that is exacerbated in patients with diabetes.

METHODS Patients (n = 300) with type II diabetes, mixed dyslipidemia (2 or more of low-density lipoprotein ≥100 mg/dl, triglycerides ≥200 mg/dl, or high-density lipoprotein <40 mg/dl), and no history of coronary heart disease were randomly assigned to receive simvastatin 20 mg, fenofibrate 160 mg, or a combination of simvastatin 20 mg and fenofibrate 160 mg daily. At 12 weeks after randomization, we measured levels of high-sensitivity C-reactive protein (hsCRP) and lipoprotein-associated phospholipase A_2 (Lp-PLA_2).

RESULTS At 12 weeks, median hsCRP was significantly reduced (−14.6%, $p = 0.004$) from baseline, but the effect did not differ between treatments. The effect was greatest among patients with baseline hsCRP levels >2.0 mg/l (fenofibrate = −18.9%, $p = 0.002$ vs. baseline; simvastatin = −24.8%, $p < 0.0001$; combination = −27.3%, $p = 0.002$). Likewise, median Lp-PLA_2 levels in the overall study population were significantly reduced (−16.8%, $p < 0.0001$), and the effect did not differ among treatments. This effect also was greatest among patients with increased baseline levels of Lp-PLA_2 greater than the median of 320.9 ng/ml (fenofibrate = −41.3%, $p < 0.0001$; simvastatin = −47.5%, $p < 0.0001$; combination = −46.8%, $p < 0.0001$).

CONCLUSIONS Simvastatin, fenofibrate, and combination therapy each lowered hsCRP and Lp-PLA_2. These anti-inflammatory effects were most pronounced among patients with increased baseline levels. Combination therapy was no more effective than either form of monotherapy. (The DIACOR Study; http://www.clinicaltrials.gov/ct/show/NCT00309712?order=1) (J Am Coll Cardiol 2006;48:396–401) © 2006 by the American College of Cardiology Foundation

Diabetes mellitus confers a 2- to 4-fold increase in cardiovascular risk compared with the general population (1). Although microvascular complications of diabetes result in increased rates of morbidity, macrovascular complications, including coronary artery disease, often cause death (2). Cardiovascular disease and diabetes are both associated with elevated levels of inflammatory biomarkers, including C-reactive protein (CRP) (3). C-reactive protein is the most well-studied inflammatory marker of atherothrombotic risk (4) and is incremental to the Framingham Risk Score (5). Lipoprotein-associated phospholipase A_2 (Lp-PLA_2) is a newer inflammatory biomarker that has been proposed to be more specific to vascular inflammation.

Statin and fibrate therapy have been shown to variably lower levels of CRP (6,7), as well as levels of Lp-PLA_2 (8). However, the influence of a statin and fibrate combination on levels of inflammatory markers requires further investigation (9,10). Therefore, among patients with type II diabetes, we assessed the effect of statin, fibrate, and combination therapy on inflammatory biomarkers in the DIACOR (Diabetes and Combined Lipid Therapy Regimen) study.

METHODS

Patients. Patients with a clinical diagnosis of type II diabetes mellitus and biochemical evidence of mixed dyslipidemia were considered for enrollment in the study. The study protocol was approved by the institutional review board, and all patients provided written informed consent. Patients meeting prescreening criteria were required to undergo wash-

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Abbreviations and Acronyms

CRP = C-reactive protein
HDL-C = high-density lipoprotein cholesterol
hsCRP = high-sensitivity C-reactive protein
LDL-C = low-density lipoprotein cholesterol
Lp-PLA_2 = lipoprotein-associated phospholipase A_2

out if currently receiving lipid therapy. A complete list of inclusion/exclusion criteria is found in Table 1.

Protocol. We undertook a single-center, randomized, double-blind, and placebo-controlled 12-week study. Those participants satisfying all inclusion/exclusion criteria were assigned randomly to receive 1 of 3 daily oral treatments: simvastatin 20 mg taken in the evening/fenofibrate placebo taken in the morning with food, fenofibrate 160 mg taking in the morning with food/simvastatin placebo taken in the evening, or simvastatin 20 mg taken in the evening and fenofibrate 160 mg taken in the morning with food. Coordinators, investigators, statistical personnel, and patients remained blinded to patient treatment assignment.

Follow-up visits were scheduled 6 and 12 weeks after randomization, where assessment of adverse events and 12-h fasting laboratory measurements were made. A creatine kinase was drawn if the patient complained of any muscle aches at those visits or at any time throughout the study period.

Laboratory measurements. Laboratory samples were analyzed in an Intermountain Healthcare laboratory (LDS Hospital, Salt Lake City, Utah, or McKay Dee Hospital, Ogden, Utah). Total cholesterol and triglycerides were quantified using dry-slide measurement on the VITROS 950 Analyzer (Ortho Clinical Diagnostics, Raritan, New Jersey). High-density lipoprotein cholesterol (HDL-C) was

Table 1. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Controlled type II diabetes mellitus (hemoglobin A1C ≤9%)	Plasma creatine kinase levels >50% above the upper limit of normal (ULN)
If taking chronic hypoglycemic therapy including pioglitazone, rosiglitazone, metformin, sulfonlylureas, or insulin, alone or in combination, must be on a stable dosing regimen for the previous 3 months	Known history of coronary heart disease; myopathy, or rhabdomyolysis; active liver disease (positive antibodies to hepatitis B or C) or serum alanine aminotransferase or aspartate aminotransferase levels >30% above the ULN
If taking warfarin or warfarin-like anticoagulants, agree to have their anticoagulation levels drawn per standard of care for adjustment of anticoagulant dose	History of alcohol consumption: ≥2 drinks/day or ≥10 drinks/week
Documented post-washout dyslipidemia, defined as having at least two of the following: LDL ≥100 mg/dl, triglycerides ≥200 mg/dl, HDL <40 mg/dl	The use of lipid-lowering agents taken within 6 (bile acid sequestrants, statins, fish oil, nicotinic acid [doses >200 mg/day], or niacin) or 8 (fibrates) weeks prior to randomization assessment
Able to give voluntary informed consent	Serum creatinine >1.5 mg/dl (if between 1.2 and 1.49 mg/dl, the calculated creatinine clearance using the Crockcroft/Gault formula has to be >50 ml/min)
	Uncontrolled hypertension (systolic blood pressure >160 mm Hg or diastolic blood pressure >100 mm Hg)
	Proteinuria (dipstick >+1 or nephrotic syndrome)
	Hypothyroidism (thyroid-stimulating hormone >6 μU/ml)
	Concomitant use of cyclosporine, systemic itraconazole or ketoconazole, erythromycin or clarithromycin, nefazadone, HIV protease inhibitors, glucocorticoids, verapamil, or consumption of >1 quart of grapefruit juice per day
	Known hypersensitivity to statins or fibrates (elevated muscle or liver test, jaundice, hepatotoxicity, or myopathy)
	Partial ileal bypass
	Treatment with any other investigational drug within the previous 30 days
	Currently using illicit drugs or history of drug or alcohol abuse within the last 5 years
	Type I diabetes mellitus or diagnosis of homozygous familial hypercholesterolemia or types I or V hyperlipidemia
	Hyperlipidemic pancreatitis, or known presence of cholelithiasis
	Any therapy or condition that would pose a risk to the patient or make it difficult to comply with study requirements
	Pregnant and/or lactating women and women of child bearing potential not using acceptable means of contraception