Treatment of Hypercholesterolemia and Combined Hyperlipidemia With Simvastatin and Gemfibrozil in Patients With NIDDM

A multicenter comparison study

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OBJECTIVE—To compare the lipid-lowering efficacies of simvastatin and gemfibrozil in NIDDM patients with combined (mixed) hyperlipidemia (CHL) or isolated hypercholesterolemia (IHC).

RESEARCH DESIGN AND METHODS— Patients with primary dyslipidemia and NIDDM were recruited for this double-blind, double-dummy comparison study from 10 Finnish centers. After a 4-week placebo run-in period, they were randomly assigned to simvastatin or gemfibrozil. The simvastatin group (n = 47) received 10 mg once nightly for 8 weeks, 20 mg for the next 8 weeks, and 40 mg for the third 8-week period. The gemfibrozil group (n = 49) received 600 mg twice daily throughout the 24 weeks. The lipid-lowering efficacies of both drugs were compared in all patients as well as separately in patients with CHL and IHC.

RESULTS— In all patients, simvastatin reduced LDL and total cholesterol and the LDL-to-HDL cholesterol ratio more effectively, whereas gemfibrozil was more effective in elevating HDL cholesterol and decreasing triglyceride levels. The drug effects differed according to lipid phenotype at baseline. Simvastatin decreased LDL cholesterol levels by 30–40% in both phenotypes. Gemfibrozil caused a 15% reduction in LDL cholesterol in IHC but no change in CHL patients. Simvastatin produced 15–30% reductions in triglyceride levels in CHL but no change in IHC patients. Gemfibrozil caused reductions in triglycerides in CHL (50% and more) and in IHC (40%) patients, with 12–18% increases in HDL cholesterol in these groups.

CONCLUSIONS— Simvastatin is useful in both CHL and IHC patients, whereas gemfibrozil can be used in patients with high triglyceride and low or normal LDL cholesterol levels.

NIDDM is associated with a markedly increased risk for all manifestations of atherosclerotic vascular disease (1). Among the factors contributing to this increased risk are various forms of dyslipidemia (2). Poor glycemic control worsens lipid abnormalities associated with NIDDM. In addition, diabetic nephropathy and obesity contribute to adverse changes in the plasma lipid pattern. Although the multiplicity of effects involved may result in difficulty defining individual lipid phenotypes, studies in different populations indicate that the most characteristic lipid abnormality in NIDDM is elevated plasma triglyceride levels associated with a low HDL cholesterol concentration (3). In contrast, although high LDL cholesterol is not uncommon in NIDDM patients, its occurrence appears to reflect the prevalence of hypercholesterolemia in the background population and is not a characteristic finding in NIDDM. For example, Finnish investigators reported a 53% prevalence of hypercholesterolemia (plasma cholesterol >6.5 mmol/l) in an NIDDM cohort, which was similar to the prevalence in the corresponding nondiabetic population (4).

On the basis of the inherently increased risk of macrovascular complications in NIDDM, the role of lipid-lowering treatment in dyslipidemic patients with this disorder has gained much attention, and international treatment recommendations have been published (5,6). Two major classes of lipid-lowering agents, the statins (3-hydroxy-3-methylglutaryl coenzyme A [HMG CoA] reductase inhibitors) and fibrates (fibric acid derivatives), are available. Nicotinic acid, because of its deleterious effect on glucose tolerance, and bile acid binding resins, because of their triglyceride-elevating properties, are not first-choice agents in patients with NIDDM. To compare the efficacies of two major representatives of statins and fibrates, we designed a study to investigate the effects of simvastatin and gemfibrozil in Finnish NIDDM patients with dyslipidemia expressed as isolated hypercholesterolemia or combined (mixed) hyperlipidemia.

RESEARCH DESIGN AND METHODS

— Patients with primary dyslipidemia and NIDDM treated with oral hypoglycemic agents and insulin, alone or in combination, were recruited from 10 Finnish centers participating in the study. Patients had to be between the ages of 35 and 70 years, with LDL cholesterol levels >4.0 mmol/l, total triglycerides normal or

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Abbreviations: CARE, Cholesterol and Recurrent Events; 4S, Scandinavian Simvastatin Survival Study.

moderately elevated (up to 4.5 mmol/l), fasting blood glucose <12 mmol/l, and HbA_{1c} <11%.

The diagnosis of NIDDM was based on World Health Organization criteria (5). C-peptide levels were determined in all patients, and individuals with possible insulin deficiency (fasting C-peptide <0.33 nmol/l or <0.66 nmol/l after stimulation with glucagon 1 mg i.v.) were excluded. Other exclusion criteria were impaired mental function, history of alcohol or drug abuse, liver disorder or liver transaminase levels increased ≥20% above normal, and concurrent use of drugs affecting lipid levels. Oral hypoglycemic agents, insulin, and other chronic treatments, such as antianginal, antihypertensive, thyroxine, and estrogen replacement therapy, were permitted, provided that the dosage was kept constant throughout the study period. Further exclusion criteria were symptoms of unstable angina, ventricular arrythmias, and occurrence of myocardial infarction or coronary bypass surgery within the 3 preceding months. Finally, premenopausal women without reliable contraceptive practice were excluded.

Patients screened for this double-blind double-dummy parallel comparison study received counseling for the American Heart Association Phase I diet at least 6 weeks prior to starting the study. Eligible patients were entered into a 4-week placebo run-in period after giving informed consent, and they started receiving placebo matching both simvastatin and gemfibrozil. The patients who met the inclusion criteria and none of the exclusion criteria during the placebo run-in period were randomized into one of the active treatment groups: simvastatin 10 mg once nightly or gemfibrozil 600 mg twice daily. Active treatment was administered with the placebo of the other treatment. The dose of simvastatin (or its placebo) was doubled to 20 mg once nightly after 8 weeks and to 40 mg after 16 weeks in all patients. The dosage of gemfibrozil (or its placebo) was maintained unchanged throughout the 24 weeks of active therapy.

The main efficacy variable was LDL cholesterol, the others being total plasma cholesterol, LDL-to-HDL cholesterol ratio, and triglyceride and HDL cholesterol concentrations.

Laboratory safety monitoring included determination of serum liver enzyme activities, creatinine kinase, HbA_{1c}, and blood glucose. Patient compliance was monitored by tablet counting and interviews, and no patients were excluded on this basis. Five patients in the simvastatin and four in the gemfibrozil group discontinued the study; one patient was lost to follow-up, and the others withdrew because of adverse clinical experiences.

Blood was drawn after a 10- to 12-h fast for determination of lipid levels and safety monitoring at baseline and at clinical visits at weeks 8, 16, and 24. Cholesterol and triglyceride concentrations were determined by standard enzymatic methods (Boehringer Mannheim, Germany), and HDL cholesterol concentrations were measured after precipitation of VLDL and LDL with sodium phosphotungstate and $MgCl_2$ (7). LDL cholesterol was calculated using the Friedewald approximation (8).

Table 1—*Clinical patient characteristics at baseline*

	Simvastatin	Gemfibrozil
n	47	49
Mean age (years)	59	57
Men (%)	40.4*	69.4*
Body weight (kg)	79.3	81.5
Insulin use (%)	44.7	34.7
Ischemic heart disease (%)	21.3	24.5
Hypertension (%)	61.7	44.9
Prior lipid-lowering treatment (%)	21.3	22.4
Hypercholesterolemia (%)	44.7	42.9
Combined (mixed) hyperlipidemia (%)	55.3	57.1

*P = 0.01.

Statistical analysis

The comparability of treatment groups at baseline was assessed by means of analysis of variance on the ranked values of the efficacy variables. Comparisons of treatment responses (percentage changes from baseline) between treatment groups were made using an analysis of variance on the ranks. Within-group comparisons were made at each visit using the Wilcoxon signed-rank test.

RESULTS — The baseline characteristics of the study population are given in Table 1. Except for the smaller proportion of men in the simvastatin group, the two treatment groups did not differ significantly from each other. The simvastatin group included 26 patients (55.3%) and the gemfibrozil group 28 patients (57.1%) with combined (mixed) hyperlipidemia based on triglyceride level exceeding 2.3 mmol/l. The remaining patients with normal triglyceride levels, 21 (44.7%) in the simvastatin and 21 (42.9%) in the gemfibrozil groups, were designated as the hypercholesterolemia group.

The baseline plasma levels and the percentage changes in efficacy parameters at treatment weeks 8, 16, and 24 for the whole study population are summarized in Table 2. Significant differences were observed in all efficacy parameters between simvastatin and gemfibrozil. Simvastatin was more effective in lowering LDL cholesterol, total cholesterol, and the LDL-to-HDL cholesterol ratio, whereas gemfibrozil was more effective in elevating HDL cholesterol and decreasing triglyceride concentrations (Table 2).

To evaluate the effects of simvastatin and gemfibrozil in patients with differing plasma lipid phenotypes at baseline, the results in patients with hypercholesterolemia and combined (mixed) hyperlipidemia were analyzed separately (Figs. 1 and 2). As indicated in Fig. 1, plasma LDL cholesterol levels responded by similar 30–40% decreases during simvastatin administration, regardless of whether patients were classified as belonging to the hypercholesterolemia or combined hyperlipidemia groups. Conversely, gemfibrozil caused an ~15% reduction in LDL cholesterol in the hypercholesterolemia group but no change in the group with combined hyperlipidemia.

Gemfibrozil caused median reductions in plasma triglyceride levels, ranging from ~40% in the hypercholesterolemic patients with initially normal triglyceride levels (<2.3 mmol/l) to 50% or more in patients with combined hyperlipidemia (Fig. 2). On the other hand, simvastatin did not reduce triglyceride levels in the hypercholesterolemia group, but caused reductions ranging from 15 to 30%, depending on the dose, in the combined hyperlipidemia group. Gemfibrozil increased HDL choles-

terol concentrations significantly by 10–12% in the hypercholesterolemic group and by 12–18% in patients with combined hyperlipidemia. Nonsignificant increases in HDL cholesterol with simvastatin by 1–5% were observed in both phenotype groups (data not shown).

Glycemic control was monitored by measuring blood glucose and HbA_{1c} levels during the baseline and active treatment periods (Table 3). Increased blood glucose and HbA_{1c} levels were observed at all visits relative to baseline during simvastatin treatment. For gemfibrozil, a significant increase in blood glucose occurred at week 16, and HbA_{1c} levels were elevated relative to baseline during the whole treatment period. The variation of the increases in these glycemic control parameters was large and increased further toward the end of the study. Mean body weight was slightly reduced by week 24 in both the simvastatin (−0.3 kg) and gemfibrozil group (−0.8 kg; $P < 0.05$). Serum glutamic-oxalacetic transaminase (SGOT) levels exceeded upper normal limits by more than 50% in three patients receiving simvastatin and in three receiving gemfibrozil; corresponding increases were recorded for serum glutamic-pyruvic transaminase (SGPT) in five patients on simvastatin and four patients on gemfibrozil. Serum creatinine kinase level increased by >50 U/l in four patients on simvastatin and three patients on gemfibrozil.

CONCLUSIONS — Direct comparison studies involving gemfibrozil and simvastatin (9–11) and gemfibrozil and lovastatin (12) have yielded results comparable to those reported in the current study for the study population as a whole. Thus, in all four studies, statins were powerful cholesterol-lowering agents, in contrast to gemfibrozil, which was markedly effective in decreasing triglyceride and elevating HDL cholesterol concentrations and ineffective in lowering LDL cholesterol levels. However, these studies did not report data on the number of patients with different lipid phenotypes at baseline, i.e., isolated hypercholesterolemia or combined hyperlipidemia, nor on treatment responses in such phenotypes. In view of the fact that hypertriglyceridemia is a typical characteristic of dyslipidemia in NIDDM, we did additional analyses separately on the patient groups with combined hyperlipidemia and pure hypercholesterolemia. The results revealed different plasma lipid responses in the two types of dyslipidemia for both tested agents.

Table 2—*Mean serum lipid and lipoprotein percentage change from baseline in patients treated with simvastatin and gemfibrozil*

	Simvastatin	Gemfibrozil	Between-treatment *P* value
n	42	45	—
LDL cholesterol			
Baseline (mmol/l)	4.53 ± 0.77	4.57 ± 0.71	—
Week 8	−31.2*	−7.2*	≤0.01
Week 16	−36.9*	−0.6	≤0.01
Week 24	−41.6*	−6.5*	≤0.01
Total cholesterol			
Baseline (mmol/l)	6.94 ± 0.93	7.00 ± 1.01	—
Week 8	−21.6*	−10.2*	≤0.01
Week 16	−25.7*	−6.1*	≤0.01
Week 24	−30.2*	−10.0*	≤0.01
HDL cholesterol			
Baseline (mmol/l)	1.26 ± 0.32	1.19 ± 0.31	—
Week 8	1.9	14.3*	≤0.01
Week 16	3.3	12.0*	≤0.01
Week 24	4.0	13.7*	≤0.01
LDL:HDL cholesterol			
Baseline (mmol/l)	3.80 ± 1.13	3.99 ± 0.91	—
Week 8	−31.8*	−17.1*	≤0.01
Week 16	−37.3*	−8.6*	≤0.01
Week 24	−43.0*	−14.5*	≤0.01
Triglyceride			
Baseline (mmol/l)	2.46	2.54	—
Week 8	−2.2	−43.0*	≤0.01
Week 16	−13.5*	−42.5*	≤0.01
Week 24	−15.4*	−45.2*	≤0.01

Simvastatin was given at a dose of 10 mg once nightly during weeks 1–7, 20 mg nightly during weeks 8–15, and 40 mg nightly during weeks 16–24. Gemfibrozil was given at a dose of 600 mg twice daily throughout the study (weeks 1–24). Triglyceride levels and changes are median levels and median % changes, respectively. *$P \leq 0.01$ vs. baseline.

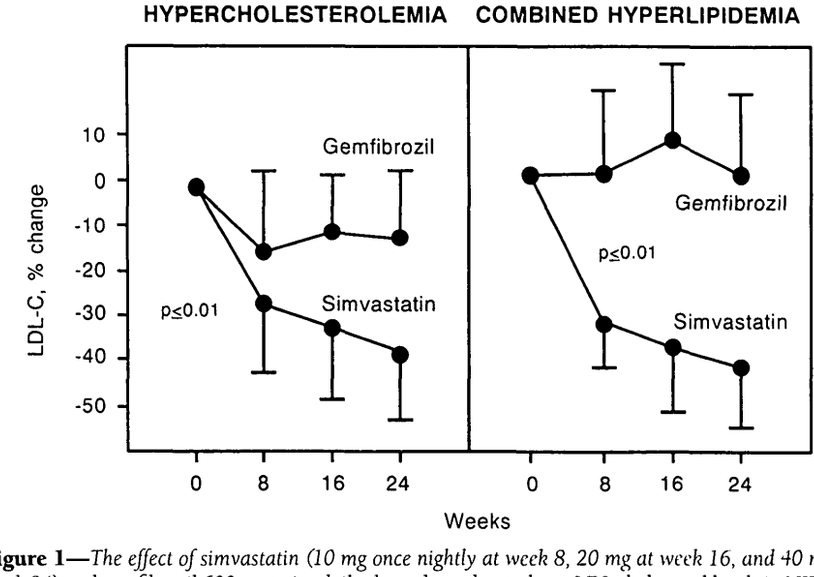

Figure 1—*The effect of simvastatin (10 mg once nightly at week 8, 20 mg at week 16, and 40 mg at week 24) and gemfibrozil 600 mg twice daily throughout the study on LDL cholesterol levels in NIDDM patients with hypercholesterolemia (LDL cholesterol >4.0 mmol/l, triglyceride ≤2.3 mmol/l) and combined hyperlipidemia (LDL cholesterol >4.0 mmol/l, triglyceride >2.3 mmol/l). Values are mean percentage changes, and vertical bars indicate SDs.*

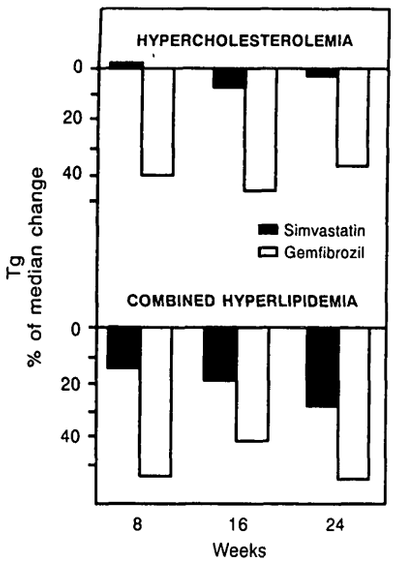

Figure 2—*The effect of simvastatin (10 mg once nightly at week 8, 20 mg at week 16, and 40 mg at week 24) and gemfibrozil 600 mg twice daily throughout the study on serum triglyceride levels in NIDDM patients with hypercholesterolemia (LDL cholesterol >4.0 mmol/l, triglyceride ≤2.3 mmol/l), and combined hyperlipidemia (LDL cholesterol >4.0 mmol/l, triglyceride >2.3 mmol/l). Values are median percentage decreases.*

Simvastatin caused similar LDL cholesterol reductions in both, with moderate reductions in triglyceride levels in combined hyperlipidemia alone. Gemfibrozil had a moderate LDL cholesterol–lowering effect in hypercholesterolemic patients but no effect in patients with combined hyperlipidemia, although it demonstrated markedly beneficial effects on triglyceride and HDL cholesterol in both phenotype groups.

Our findings for both drugs in NIDDM resemble those reported previously by us in nondiabetic subjects in combined hyperlipidemia and isolated hypercholesterolemia (13–15). These results provide a basis for recommendation of phenotype-specific treatments for dyslipidemia in NIDDM. Both statins and fibrates have properties that are seemingly beneficial for these patients. The primary role of statins in patients with elevated total and LDL cholesterol rests on a theoretically strong basis. According to current concepts, LDL particles start the atherogenic process by entering the arterial intima, where they become oxidized and degraded, and then deposit cholesterol, initiating formation of the lipid core of the lesion. For several reasons, LDL particles of NIDDM patients may be particularly atherogenic, partly because of the common occurrence of elevated triglyceride levels accompanied by LDL particles characterized by small size and increased density. Small, dense LDL may penetrate the arterial endothelium more avidly than normal-sized LDL and may be more susceptible to oxidation and glycation of apolipoprotein, all of which may add to their atherogenicity (16). From a theoretical point of view, reductions of circulating LDL should be beneficial in NIDDM, almost regardless of plasma cholesterol level. This view has received support from the Scandinavian Simvastatin Survival Study (4S) in hypercholesterolemic coronary patients (17) and in the Cholesterol and Recurrent Events (CARE) study in normocholesterolemic patients (18) that showed a decrease in coronary heart disease events in NIDDM patients of at least similar magnitude to that in nondiabetic subjects.

Gemfibrozil and other fibrates are markedly effective in lowering triglyceride and elevating HDL cholesterol concentrations, including patients with NIDDM (19). These changes are accompanied by a shift in LDL particle density toward lower density, probably causing a reduction in the number of atherogenic small, dense LDL particles (20). These effects could, in theory, have antiatherogenic potential despite the inefficacy in LDL cholesterol lowering, and even LDL cholesterol elevation (19), exhibited by gemfibrozil. This possibility has received attention after publication of a study in nondiabetic subjects receiving bezafibrate that showed reduced angiographic progression of atherosclerosis despite no reduction in LDL cholesterol (21). Moreover, a 34% reduction in coronary heart disease was observed with gemfibrozil in the Helsinki Heart Study, despite a modest 8.4% decrease in LDL cholesterol (22). Some patients could benefit from combined treatment with statin and fibrate (23). The risk of myopathy associated with combination therapy (24) appears to be smaller than initially believed (25). However, there is insufficient experience in diabetic patients, who could be excessively susceptible to complications because of nephropathy, impaired resistance to infections, and numerous concomitant medications. Treatment trials in specialized centers are needed before statin-fibrate combination therapy in diabetic patients can be recommended.

Table 3—*Mean changes in fasting blood glucose and HbA_{1c} during lipid-lowering treatment*

	Blood glucose (mmol/l)		HbA_{1c} (%)	
Week	Simvastatin	Gemfibrozil	Simvastatin	Gemfibrozil
Baseline	8.77	8.67	8.60	8.29
8	+0.74*	+0.32	+0.42†	+0.74†
16	+0.70†	+0.83*	+0.79†	+0.75†
24	+1.34†	+0.45	+0.93†	+0.67†

*$P < 0.05$ vs. baseline; †$P < 0.01$ vs. baseline.

Our study was not designed to assess the treatment effects on glycemic control, but we monitored fasting blood glucose and HbA_{1c} levels. The elevating effect of both treatments on these parameters is difficult to explain. In any case, it could not be explained by changes in body weight, which did not increase during the study. One study using the hyperinsulinemic euglycemic clamp method reported reductions in insulin sensitivity with both simvastatin and gemfibrozil (11); another study claimed no effect (25). Other studies have reported varying degrees of elevation in plasma glucose and HbA_{1c} levels (9,10,12). In view of a number of confounding factors, such as possible modification in dietary habits of NIDDM patients receiving pharmacological therapy for dyslipidemia, the question regarding diabetic control remains uncertain for the time being. In any case, the recent 4S (17) and CARE (18) trials employing statin treatment showed reductions in coronary heart disease endpoints similar to those achieved in nondiabetic subjects, suggesting that significant impairment of glycemic control probably did not occur.

In conclusion, simvastatin can be recommended for treatment of combined (mixed) hyperlipidemia and isolated hypercholesterolemia in NIDDM patients, as it had powerful LDL cholesterol– and total cholesterol–lowering efficacy in both plasma lipid phenotypes. The use of gemfibrozil, which had no effect on LDL cholesterol in combined hyperlipidemia but effectively lowered triglyceride levels, is limited to patients with high triglyceride and normal or low LDL cholesterol levels.

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