A Comparison Between the Effects of Gemfibrozil and Simvastatin on Insulin Sensitivity in Patients With Non–Insulin-Dependent Diabetes Mellitus and Hyperlipoproteinemia

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In a double-blind, randomized crossover study, 29 patients with non–insulin-dependent diabetes mellitus (NIDDM) and hyperlipoproteinemia were treated with gemfibrozil (1,200 mg/d) or simvastatin (10 mg/d) for 4 months. After gemfibrozil treatment, the insulin concentration was increased during the major part of the intravenous glucose tolerance test (IVGTT) and during the hyperinsulinemic euglycemic clamp. Similar but less pronounced elevations were caused by simvastatin. Insulin sensitivity decreased by 27% and 28% during gemfibrozil and simvastatin treatment, respectively. Low-density lipoprotein (LDL) cholesterol was decreased with simvastatin treatment by 24%. The LDL cholesterol level was not changed by gemfibrozil, but very–low-density lipoprotein (VLDL) cholesterol was reduced by 40%. The VLDL triglyceride concentration was reduced to a significantly greater extent by gemfibrozil. After gemfibrozil treatment, lipoprotein(a) [Lp(a)] was decreased by 24%, and the plasma free fatty acid (FFA) concentration was increased by 20% and skeletal muscle lipoprotein lipase activity (LPLA) by 37%. Although simvastatin more effectively decreased LDL cholesterol levels and the LDL to high-density lipoprotein (HDL) ratio, it cannot be claimed unreservedly that this drug is necessarily preferable in NIDDM patients. Gemfibrozil improved triglyceride removal and decreased VLDL concentrations, with qualitative changes in LDL. The apparent effects on insulin sensitivity are difficult to evaluate and need further study.

PATIENTS WITH non–insulin-dependent diabetes mellitus (NIDDM) have a high incidence of coronary heart disease.[1] The diabetic state is characterized by peripheral insulin insensitivity and an unfavorable serum lipoprotein profile with high concentrations of triglycerides and low concentrations of high-density lipoprotein (HDL) cholesterol.[2] These changes may contribute to the development of atherosclerosis, and it is therefore important to improve the insulin sensitivity and normalize the lipid levels.

Gemfibrozil has been proved in the Helsinki Heart Study to be an efficient and safe lipid-lowering drug.[3] In that study, the incidence of myocardial infarction was reduced by 34% in the gemfibrozil-treated group as compared with the placebo group. Much of this effect was related to an increase in HDL cholesterol, whereas an observed reduction in serum triglycerides was not significantly related to the decrease in risk. The best effect of gemfibrozil treatment on the risk for ischemic heart disease was found in patients who displayed a type IIB or type IV lipoprotein pattern. During treatment with clofibrate, another fibrate derivative, an increase in lipoprotein lipase activity (LPLA) in skeletal muscle was demonstrated.[4] This improvement was related to the simultaneous change in the serum insulin concentration.[5] Since insulin concentrations reflect insulin sensitivity, these data may imply that treatment with clofibrate is associated with improved insulin sensitivity. However, no studies of the direct effects of gemfibrozil treatment on insulin sensitivity have been reported.

Simvastatin, a 3-hydroxy-3-methyl glutaryl coenzyme A (HMG CoA) reductase inhibitor, is effective in decreasing the serum cholesterol concentration, mainly by decreasing low-density lipoprotein (LDL) cholesterol. In addition to decreasing LDL, it has also been found to reduce plasma triglyceride concentrations by approximately 25% and to increase HDL cholesterol by approximately 10%.[6]

Patients with NIDDM usually have high levels of triglycerides, mainly due to high levels of very–low-density lipoprotein (VLDL). Access to abundant substrate in skeletal muscle, as well as in the liver, resulting in an increased lipid oxidation may cause a reduction of glucose oxidation, as suggested by Randle,[7] with a following decrease of insulin sensitivity. Consequently, a reduction of serum lipid levels by lipid-lowering drugs could conceivably contribute to an improved insulin sensitivity. The principal aim of this study was to compare the effects of simvastatin and gemfibrozil on insulin sensitivity as measured by a hyperinsulinemic euglycemic clamp in subjects with NIDDM and hyperlipidemia, and to relate these to other effects on glucose and lipid metabolism.

SUBJECTS AND METHODS

Twenty-nine patients (20 men and nine women) with a mean age of 63.7 years (range, 48 to 78 years) and with NIDDM and hyperlipoproteinemia or dyslipoproteinemia (LDL > 5 mmol/L and/or HDL < 1 mmol/L and/or triglycerides > 2.3 mmol/L) treated with dietary therapy alone or combined with oral hypoglycemic agents took part in this double-blind, randomized crossover study. Nine patients were treated with sulfonylurea, four with metformin, and eight with a combination of these. No patients with other major diseases or with a history of hepatic, renal, coronary, or cerebral disease during the preceding 6 months were included in the study, nor were any patients with plasma alanine aminotransferase concentrations above 0.8 μkat/L. Of the 29 participants, seven were treated with β-blockers because of hypertension and/or stable ischemic heart disease. Another seven participants had

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hypertension and were treated with calcium blockers, angiotensin-converting enzyme inhibitors, or combinations of these agents. The medication regimen was unchanged during the study.

Three patients were excluded during the course of the study: one because of surgical treatment for a fracture of the femoral neck, one because of muscle pains, and one because he had lost his tablets. One patient could not participate in the final tests because of depression, and two had problems with compliance and were excluded from the second period of active treatment. Twenty-five patients completed the gemfibrozil treatment period, and 24 completed the simvastatin treatment period.

Informed consent was obtained from all subjects after the nature, purpose, and possible side effects of the study had been fully explained. The study protocol was approved by the Human Ethics Committee of the Medical Faculty of Uppsala University.

Protocol

A placebo run-in period of 4 to 6 weeks was followed by randomization to treatment with either gemfibrozil 600 mg twice daily or simvastatin 10 mg once daily in each group, together with placebo tablets that had the appearance of the alternative drug. The first phase of active treatment lasted 4 months and was followed by crossover to the alternative medication and placebo formulation for another 4 months. At the end of the run-in phase and at the end of each of the active treatment periods, a metabolic investigation was performed. All patients were studied after an overnight fast and without taking their morning medication. The insulin response to an intravenous glucose tolerance test (IVGTT) and insulin sensitivity were evaluated on 2 separate days. The participants were informed not to change their diet or activity level in connection with the study. At the end of the formal study, four patients who continued with gemfibrozil treatment (1,200 mg/d) once again underwent a metabolic investigation including a euglycemic clamp to investigate whether the significant increase of free fatty acids (FFAs) in the gemfibrozil group depended on a lack of suppression of lipolysis, since the tests were performed before the morning medication was taken. However, on this last occasion, they took their tablets 1 to 2 hours before the tests were performed.

Laboratory Tests

The euglycemic hyperinsulinemic clamp technique according to the method of DeFronzo et al[8] was performed as recently described in detail.[9] The insulin (Actrapid R Human; Novo, Copenhagen, Denmark) infusion rate during the clamp study was 56 $mU/m^2/min$, resulting in a mean plasma insulin concentration of approximately 120 mU/L. The target level of plasma glucose during the clamp study was maintained by measuring the plasma glucose level (Beckman Glucose Analyzer II, Beckman Instruments, Fullerton, CA) every 5 minutes and adjusting the rate of infusion of the 20% glucose solution accordingly. The desired plasma glucose level was attained within 60 minutes from the start of the insulin infusion.

The IVGTT was performed as recently described in detail,[9] with injection of 300 mg/kg body weight of glucose (Opotimate; Ames-Gilford, Elkhart, IN). The plasma glucose level was measured by the glucose oxidase method. Immunoreactive insulin was assayed in plasma using a commercial radioimmunoassay kit (Phadeseph Insulin RIA, Pharmacia, Uppsala, Sweden). Glucose tolerance was expressed as the *K* value as described by Ikkos and Luft.[10] The peak insulin response was defined as the mean of values obtained at 4, 6, and 8 minutes after the start of the glucose injection, and the insulin index was defined as the ratio between peak and basal plasma insulin values (mean of values at −10, −5, and 0 minutes). The areas under the curves for glucose and insulin during the IVGTT were calculated as the deviations from the basal value integrated over the sampling time.

Lipoprotein lipid concentrations in serum were determined. VLDL, LDL, and HDL were isolated with a combination of preparative ultracentrifugation[11] and precipitation with a sodium phosphotungstate and magnesium chloride solution.[12] VLDL was isolated as the top fraction after preparative ultracentrifugation at a density of 1.006. LDL was precipitated from the bottom fraction, and HDL lipid concentrations were determined in the supernatant. Triglyceride and cholesterol concentrations were measured in serum and in isolated lipoprotein fractions by enzymatic methods using the IL Test Cholesterol Trinder's Method 181618-80 and IL Test Enzymatic-Colorimetric Method 181709-00 for use in a Monarch apparatus (Instrumentation Laboratories, Lexington, MA).

Needle-biopsy specimens of subcutaneous adipose tissue[13] were taken from a site midway between the umbilicus and the ilial part of the pelvis, and the adipose tissue LPLA was assayed as described in detail previously.[14] Skeletal muscle tissue specimens were taken from the vastus lateralis muscle of the right leg in a subsample of the participants ($n = 11$),[15] and skeletal muscle tissue LPLA was measured as described in detail earlier.[16] One to 2 mL lidocaine (Xylocaine 1%; Astra, Södertälje, Sweden) was used to anesthetize the skin.

The lipoprotein(a) [Lp(a)] level was measured by the Pharmacia apo(a) radioimmunoassay method (Pharmacia, Uppsala, Sweden). This is based on the direct sandwich technique in which two monoclonal antibodies are directed against separate antigenic determinants on the apolipoprotein(a) in the sample. The concentration is expressed in units per liter. One unit of apolipoprotein(a) is approximately equal to 0.7 mg Lp(a) according to the manufacturer.

Statistics

An ANOVA model with factors for treatment, time, and patient was used. Results are presented as the least-square mean instead of as mean values, to balance and compensate for missing values. No carryover effects from treatment period 1 to period 2 were detected, and thus, results of the two periods were combined. Comparisons were made between the effects of the two drugs and also between the effects of each individual drug and the results at the end of the run-in placebo period. An analysis of covariance with change in body weight as a covariate was performed to separate the effects of treatment from those of changes in body weight. For variables with a skewed distribution, logarithmic transformation was performed. All data processing was accomplished with statistical program package SAS version 6.04 for personal computers (SAS Institute, Cary, NC).

RESULTS

Clinical Characteristics

The mean body weight before the study was 85.2 kg. The weight decreased by 0.7 kg during gemfibrozil treatment and increased by 0.6 kg during simvastatin treatment ($P = .0016$ for the difference between regimens).

Effects on Glucose Tolerance and Peripheral Insulin Sensitivity

The mean fasting blood glucose concentration before treatment was 8.6 mmol/L (Table 1). This concentration was significantly and equally elevated by both treatment regimens by 1.6 mmol/L (~ 18%). Blood glucose concentrations during the IVGTT were elevated by 10% to 19% by

Table 1. Glucose/Insulin Data (least-square mean ± SD) on Admission, After Gemfibrozil, and After Simvastatin

	At Admission (n = 26)	After Gemfibrozil (n = 25)	After Simvastatin (n = 24)	*P* (gemfibrozil *v* simvastatin)
Mean fasting plasma glucose (mmol/L)	8.6 ± 2.23	10.2 ± 2.94*	10.2 ± 3.09*	.9
Mean fasting plasma insulin (mU/L)	12.9 ± 6.27	16.7 ± 8.26*	15.6 ± 5.86†	.5
MCR (clamp)	2.8 ± 1.39	2.4 ± 1.25†	2.3 ± 1.19*	.7
MCR/I (clamp)	2.76 ± 1.87	2.01 ± 1.24*	1.99 ± 1.22*	.9

Abbreviations: MCR, metabolic clearance rate of glucose; I, insulin response.

*$P < .01$ *v* at admission.

†$P < .05$ *v* at admission.

both agents (Fig 1). Fasting insulin (mean value of 2 days) was increased by 30% ($P = .002$) and 21% ($P = .01$) by gemfibrozil and simvastatin treatment, respectively. The difference between the drugs in this respect was not significant (Fig 2). Compared with the values on admission, insulin concentrations during the IVGTT were significantly increased by gemfibrozil treatment at all points in time except 6 to 10 minutes after glucose infusion. After simvastatin treatment, the only significant increase in the insulin concentration was noted at 4 minutes after infusion of glucose. However, because of the simultaneous increase in fasting insulin, the increment above the fasting insulin concentration after glucose infusion was not significantly affected by either treatment. The *K* value at IVGTT was not significantly changed by either medication.

The mean glucose concentration before the hyperinsulinemic clamp studies was 8.9 mmol/L at the end of the placebo phase, 10.1 mmol/L after gemfibrozil treatment, and 10.3 mmol/L after simvastatin treatment. The preclamp insulin concentration at baseline was 13.7 mU/L and significantly increased (23%, $P = .04$) after the gemfibrozil period, but was not significantly altered by simvastatin

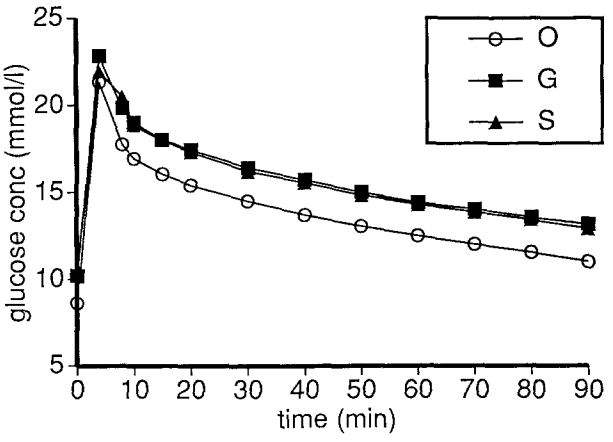

Fig 1. Plasma glucose responses to an IVGTT on admission (O), after gemfibrozil (G), and after simvastatin (S) treatment.

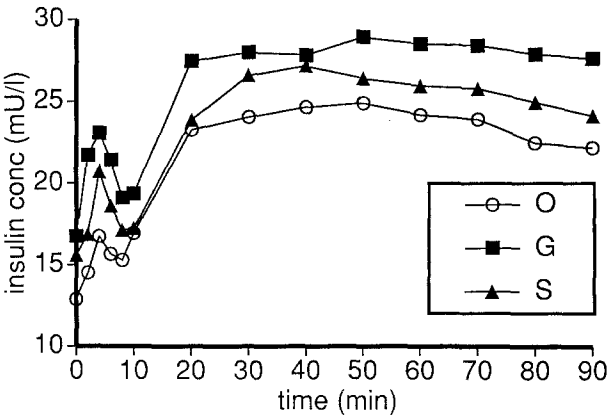

Fig 2. Plasma insulin responses to an IVGTT on admission (O), after gemfibrozil (G), and after simvastatin (S) treatment.

treatment. There was no significant difference between the drugs. Also during the clamp, insulin concentrations were higher after both active regimens than with placebo, more markedly so after gemfibrozil treatment. There were significant differences between the drugs at the beginning and end of the clamp investigation. After the gemfibrozil period, the mean insulin increase amounted to 15%.

The metabolic clearance rate of glucose was significantly decreased after both treatments, and compared with the value after the placebo period, insulin sensitivity (metabolic clearance rate divided by insulin response) was reduced by 27% after the gemfibrozil regimen and by 28% after treatment with simvastatin, with both changes significant on the .003 level. Adjustment for changes in body mass index did not affect these results.

There were no significant differences in insulin, glucose, or clamp data between patients with or without hypertension or between patients with or without treatment with β-blockers.

Effects on Serum Lipids and Lipoproteins

The mean serum cholesterol concentration before treatment was 6.00 mmol/L and was not significantly reduced by gemfibrozil (Table 2). Simvastatin treatment decreased the total cholesterol concentration by 18%. The greatest difference between the two medications concerned the concentration of LDL cholesterol, which decreased by 24% during the simvastatin period but was not altered by treatment with gemfibrozil. However, VLDL cholesterol was reduced by 40% ($P = .0001$) after the gemfibrozil period and by 27% ($P = .026$) after treatment with simvastatin. HDL cholesterol increased significantly by 9% during both regimens. The LDL/HDL cholesterol ratio was significantly decreased after simvastatin, but not after gemfibrozil treatment.

The serum triglyceride concentration was reduced to a significantly greater extent by gemfibrozil than by simvastatin. VLDL triglycerides were decreased by 32% after the gemfibrozil period, but were not significantly altered after treatment with simvastatin. The triglycerides in LDL were significantly decreased by both gemfibrozil and simvastatin. Although LDL cholesterol levels were not changed signifi-

Table 2. Concentrations (least-square mean ± SD) of Cholesterol and Triglycerides in Serum, VLDL, LDL, and HDL (mmol/L), and the Lp(a) Level (U/L) on Admission and After Gemfibrozil and Simvastatin Treatment

	At Admission (n = 26)	After Gemfibrozil (n = 25)	After Simvastatin (n = 24)	P (gemfibrozil v simvastatin)
Cholesterol				
Serum	6.00 ± 1.04	5.77 ± 0.99	4.94 ± 0.98‡	.0002
VLDL	1.15 ± 0.62	0.70 ± 0.48‡	0.84 ± 0.29*	.026
LDL	3.95 ± 1.12	4.00 ± 0.98	3.02 ± 0.88‡	.0001
HDL	0.95 ± 0.18	1.04 ± 0.23†	1.03 ± 0.21*	.77
Triglycerides				
Serum	3.00 ± 1.36	2.17 ± 1.28‡	2.64 ± 0.74	.003
VLDL	2.38 ± 1.25	1.62 ± 1.24‡	2.13 ± 0.75	.0006
LDL	0.55 ± 0.16	0.48 ± 0.11*	0.45 ± 0.11‡	.14
HDL	0.13 ± 0.09	0.10 ± 0.05	0.14 ± 0.08	.04
Triglyceride/ cholesterol				
VLDL	2.14 ± 0.49	2.36 ± 0.55*	2.65 ± 0.61‡	.0027
LDL	0.15 ± 0.07	0.13 ± 0.04*	0.16 ± 0.04	.0003
LDL/HDL ratio	4.20 ± 1.11	3.97 ± 1.07	2.99 ± 0.90‡	.0001
LDL + VLDL/HDL cholesterol	5.47 ± 1.10	4.47 ± 1.39†	3.86 ± 0.89‡	.0001
Lp(a)	407 ± 590	307 ± 473‡	353 ± 511	.03

*$P < .05$ v at admission.
†$P < .01$ v at admission.
‡$P < .001$ v at admission.

cantly after the gemfibrozil period, the ratio between triglycerides and cholesterol was significantly reduced, indicating an altered lipoprotein composition.

The Lp(a) concentration was significantly reduced by gemfibrozil (−24%), but not by simvastatin. The difference was statistically significant ($P = .03$).

The plasma FFA concentration was significantly increased by gemfibrozil (20%), but was unaffected by simvastatin (Table 3). Even when the gemfibrozil tablets were taken 1 to 2 hours before sampling, at the reinvestigation of the four subjects who continued with gemfibrozil treatment the FFA concentration remained significantly increased.

Effects of Body Weight Changes on Serum Lipids and Insulin Sensitivity

There was a significant difference in mean body weight during the two treatment periods. Since it is possible that some of the effects on lipoproteins and insulin sensitivity were due to the body weight difference as such rather than to the different treatments, an analysis of covariance with the change in body weight as a covariate was performed to separate the effects of treatment from those of the change in body weight. With regard to the effects on serum lipids and lipoproteins and variables for glucose sensitivity, the results remained virtually unchanged after adjustments for the body weight difference, indicating that the effects on these variables were in fact caused by the treatments.

Table 3. LPLA (mU/g) in Adipose and Skeletal Muscle Tissue, Serum FFA (mmol/L), and Plasma Fibrinogen (g/L) on Admission and After Gemfibrozil and Simvastatin Treatment

	At Admission (n = 26)	After Gemfibrozil (n = 25)	After Simvastatin (n = 24)	P (gemfibrozil v simvastatin)
LPLA				
Adipose	214 ± 72	206 ± 82	178 ± 106	.62
Muscle	46 ± 19	63 ± 36*	51 ± 24	.13
FFA	0.64 ± 0.27	0.78 ± 0.32*	0.67 ± 0.22	.057
Fibrinogen	3.6 ± 0.93	3.8 ± 0.70	3.6 ± 1.05	.30

*$P < .05$ v at admission.

Effects on LPLA and Plasma Fibrinogen Concentrations

Skeletal muscle LPLA was significantly increased by 37% after gemfibrozil treatment, but was not significantly changed by simvastatin. LPLA in adipose tissue did not change significantly during either of the two treatment periods (Table 2). The fibrinogen concentration was not significantly affected by treatment with either drug. There was a significant inverse correlation between the changes in the serum triglyceride and muscle LPLA concentrations ($r = -.6, P = .04$; Fig 3).

DISCUSSION

Insulin and Glucose

Insulin sensitivity did not differ between the two treatment periods. However, an unexpected finding of the study was that treatment both with simvastatin and with gemfibrozil was associated with a statistically significant decrease in the insulin sensitivity index in this group of patients with NIDDM. The diet or physical activity were not changed during the treatment periods, and the weight difference did not influence the results in this random crossover study, indicating that the impairment in insulin sensitivity may be associated with the effects of these drugs. The change in sensitivity to insulin-mediated glucose uptake was associated with a significant increase in the fasting blood glucose concentration by 18% by both drugs. In a study of 102

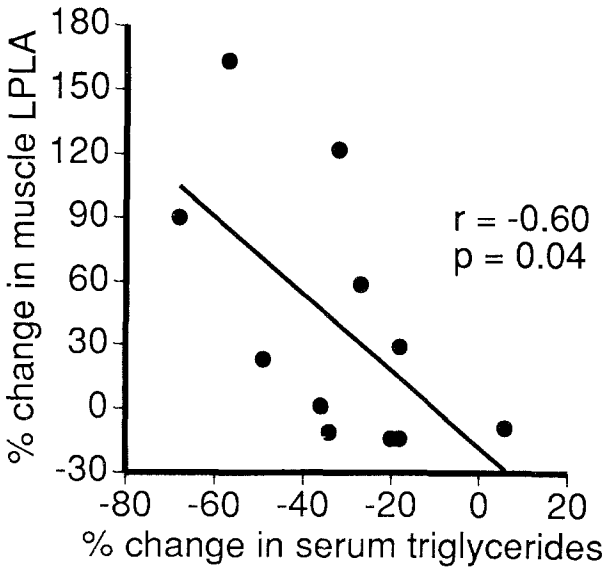

Fig 3. Linear regression of change in muscle LPLA after gemfibrozil treatment in relation to the corresponding change in serum triglyceride concentration.

hyperlipidemic NIDDM patients, Goldberg et al[17] found a significant increase in the fasting blood glucose concentration of 11.5% during gemfibrozil treatment, but no significant change during treatment with lovastatin. On the other hand, patients with NIDDM in a study by Mathur et al[18] showed an improvement in diabetic control with a small decrease in fasting blood glucose when treated with bezafibrate. In our study, the areas under the curves of glucose and insulin were significantly increased by both drugs as compared with baseline values. These results are consistent with our clamp data and may imply that the impairment of insulin sensitivity is followed by a compensatory increase in insulin concentration, but not to a sufficient extent to maintain blood glucose at a low level. Thus, hyperglycemia worsens.

The decrease in the insulin sensitivity index was approximately 20% and of similar magnitude for both drugs. The glucose infusion rate was reduced by 9% and 11% (NS) after the gemfibrozil and simvastatin periods, respectively, but the prevailing insulin concentration during the clamp was increased to a significantly greater extent by gemfibrozil than by simvastatin treatment, despite similar insulin infusion rates. This is consistent with the hypothesis that hepatic insulin clearance is more impaired by gemfibrozil than by simvastatin. In this context, it is of interest that the plasma FFA concentration increased by 20% ($P = .016$) during the gemfibrozil period but was not significantly altered by simvastatin ($P = .058$ for between-drug comparison). A positive correlation between the circulating nonesterified fatty acid concentration and the degree of fasting hyperglycemia has been found in patients with NIDDM.[18] It has been suggested that the increases in fasting blood glucose and plasma FFA in patients with NIDDM are due to insulin-related resistance in the liver and adipose tissue.[19] Elevated FFA levels may also independently increase fasting blood glucose by stimulating hepatic glucose production.[20]

A recent study[21] in 12 Taiwanese diabetic patients showed that insulin sensitivity was unchanged by gemfibrozil treatment, whereas the fasting glucose concentration increased. When that group of patients was divided into two subgroups, it was found that those with the poorest metabolic control, ie, those with a fasting blood glucose exceeding 9 mmol/L, benefitted more than the other group from treatment with this drug. Their glucose, insulin, plasma FFA, and serum triglyceride concentrations were significantly reduced by gemfibrozil treatment. When our present study group was subdivided according to the same criterion, no corresponding differences were observed. The reason for this discrepancy is not clear. Genetic and environmental differences cannot, of course, be ruled out. It should also be noted that the larger number of subjects in our study, 29 as compared with 12 in the Taiwanese study, favors statistical stability and decreases the risk of chance findings.

Serum Lipids and Lipoproteins

Serum total and LDL cholesterol were significantly reduced by simvastatin treatment. The cholesterol concentration was decreased proportionately more than the triglyceride concentration. Neither adipose nor skeletal muscle tissue LPLA changed during the simvastatin regimen. These results are compatible with the concept that simvastatin treatment acts by inhibiting HMG CoA reductase activity, resulting in decreased hepatic cholesterol synthesis, and by enhancing LDL removal by upregulation of LDL receptors.

During gemfibrozil treatment there was a reduction in the serum triglyceride concentration, reflecting significant decreases in triglycerides in VLDL and LDL. In a previous study of nondiabetic patients, no changes in triglycerides or phospholipids were observed in the VLDL fraction after gemfibrozil therapy.[22] In that study, gemfibrozil treatment caused LDL to shift to larger and less-dense subspecies. In the present study, there was a significant change in the ratio between the triglycerides and cholesterol of LDL, which became less triglyceride-enriched during gemfibrozil (but not during simvastatin) treatment. These alterations are probably largely explained by the observed significant increase in muscle LPLA.

The LPLA in muscle tissue is rate-limiting for the hydrolysis of triglycerides and is low in insulin-resistant states.[23] Insulin sensitivity and muscle LPLA are positively correlated in untreated subjects.[4] In contrast, during gemfibrozil treatment the muscle LPLA increased despite a decrease in peripheral insulin sensitivity, indicating that the improvement of LPLA after gemfibrozil treatment was not mediated via or associated with effects on insulin sensitivity.

Small, dense, triglyceride-rich LDLs are risk factors for development of atherosclerosis.[24] In a recent study, the LDL triglyceride concentration best correlated a number of quality characteristics to the proneness of lipoproteins to become oxidized.[25] It is of interest in this context that the LDL triglyceride concentration in the present study was inversely correlated to the muscle LPLA before treatment ($r = -.4, P = .08$).

The Lp(a) concentration was significantly decreased by gemfibrozil, but not by simvastatin. It has been reported that HMG CoA reductase inhibitors appear not to reduce Lp(a) levels.[26-28] Davies et al[29] have shown that among subjects with impaired glucose tolerance, there is a fivefold increase in the risk for developing coronary heart disease in those with Lp(a) concentrations above 300 mg/L. This may be one explanation for the increased incidence of coronary heart disease among subjects with impaired glucose tolerance. In a study by Bell and Wagenknecht,[30] gemfibrozil caused no significant change in Lp(a) in 47 patients with NIDDM. A reduction of Lp(a) during treatment with gemfibrozil has not been reported previously and may in part explain the decreased risk for coronary heart disease found in the Helsinki Heart Study.[3]

The pronounced decrease in LDL cholesterol caused by simvastatin should probably decrease the risk for coronary heart disease. However, the impressive 70% reduction in this risk in the subgroup with high triglycerides and a high LDL/HDL ratio in the Helsinki Heart Study[31] indicates that shortening the life span of triglyceride-rich lipoproteins by increasing the capacity for hydrolysis with gemfibrozil treatment may indeed be as effective in reducing the risk as decreasing the serum cholesterol concentration in subjects with this lipoprotein abnormality, which is not uncommon in NIDDM patients. Preliminary data from the Helsinki Heart Study[32] have indicated that treatment with

gemfibrozil reduced the incidence of coronary heart disease in NIDDM patients to at least the same extent as in those without diabetes, although the results were not statistically significant because of the limited number of participants suffering from NIDDM.

Conclusions

Both simvastatin and gemfibrozil improved the lipoprotein composition in patients with NIDDM. Although simvastatin more effectively decreased the LDL cholesterol concentration and the LDL/HDL ratio, it is difficult to claim that simvastatin is necessarily preferred in NIDDM patients. Gemfibrozil improved triglyceride removal and decreased the VLDL concentration, with qualitative changes in LDL and significantly reduced Lp(a). On the other hand, both drugs apparently impaired peripheral insulin sensitivity, and it would be interesting to compare gemfibrozil with other fibrates in this respect. Further studies are needed to evaluate the relative importance of changes in the lipoprotein composition on one hand and those in glucose/insulin homeostasis on the other for the risk of developing coronary heart disease.

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