Coronary Heart Disease Incidence in NIDDM Patients In The Helsinki Heart Study

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OBJECTIVE — To determine coronary heart disease (CHD) incidence among dyslipidemic subjects with non-insulin-dependent diabetes mellitus (NIDDM) and to assess the effect of lipid-modifying treatment on serum and lipoprotein lipids and the CHD incidence in these patients.

RESEARCH DESIGN AND METHODS — Of the 4081 men participating in the Helsinki Heart Study, a coronary primary prevention trial with gemfibrozil in middle-aged men with high non–high-density lipoprotein (HDL) cholesterol (>5.2 mM; 200 mg/dL), 135 had NIDDM at entry. The incidence of definite myocardial infarction and cardiac death and changes in serum and lipoprotein lipids were determined during the 5-yr trial in the NIDDM patients and compared with those observed in nondiabetic trial participants.

RESULTS — Compared with nondiabetic subjects, NIDDM patients had lower HDL cholesterol ($P < 0.001$), higher triglyceride concentration ($P < 0.0001$), and greater body mass index ($P < 0.001$), there were more hypertensive patients ($P < 0.001$) among them. The incidence of myocardial infarction and cardiac death was significantly higher among diabetic than nondiabetic participants (7.4 vs. 3.3%, respectively, $P < 0.02$). CHD incidence in the gemfibrozil-treated diabetic men ($n = 59$) was 3.4% compared with 10.5% in the placebo group (NS). In multivariate analysis, diabetes ($P < 0.05$), age ($P < 0.0001$), smoking ($P < 0.0001$), low HDL cholesterol ($P < 0.05$), and high low-density lipoprotein cholesterol ($P < 0.005$) were independently related to CHD incidence. Gemfibrozil-induced serum and lipoprotein lipid changes in diabetic patients were similar to those observed in nondiabetic subjects.

CONCLUSIONS — Compared with similarly dyslipidemic nondiabetic subjects, patients with NIDDM are at markedly increased risk of CHD. This elevated risk can be somewhat reduced by gemfibrozil.

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Prospective epidemiological and clinical studies have demonstrated that in most populations subjects with non-insulin-dependent diabetes mellitus (NIDDM) are at increased risk of premature coronary heart disease (CHD) (1–4). The reasons for the elevated risk have not been fully elucidated. Only part of the increment can be attributed to NIDDM-induced quantitative and qualitative abnormalities in serum lipids and lipoproteins, because at different lipid levels the CHD incidence in NIDDM patients seems to be two to three times that observed in nondiabetic subjects with similar dyslipidemias (5). Accordingly, other explanations for the excess CHD morbidity in NIDDM have been sought. It has been proposed that NIDDM and CHD share common, possibly genetic, antecedents (6). Resistance to insulin-stimulated glucose uptake with consequent hyperinsulinemia has been claimed as such an antecendent (7). Moreover, hyperinsulinemia, in addition to its effects on blood pressure and plasma lipids and lipoproteins, is independently related to increased incidence of CHD (8–10).

Because few prospective data exist on the incidence of myocardial infarction and cardiac death in dyslipidemic NIDDM patients, we analyzed the data of the diabetic patients participating in the Helsinki Heart Study, a placebo controlled coronary primary prevention trial with gemfibrozil among dyslipidemic men.

RESEARCH DESIGN AND METHODS

The Helsinki Heart Study tested the hypothesis that elevating high-density lipoprotein (HDL) cholesterol and simultaneously lowering low-density lipoprotein (LDL) cholesterol in men without evidence of CHD would decrease the incidence of coronary events over 5 yr. The design and main results have been described elsewhere (11–13). Briefly, the study population was derived from 23,531 men aged 40–55 yr who volunteered for the

study. They were employees of two state agencies and five private industrial companies. To be included in the trial, the subjects had to have non-HDL cholesterol (i.e., serum total cholesterol minus HDL cholesterol) ≥5.2 mM (200 mg/dL) at two screenings. Subjects with known CHD and those with changes in resting electrocardiogram suggestive of CHD were excluded, as were those with major illnesses, e.g., insulin-dependent diabetes mellitus (IDDM). However, men with NIDDM were allowed to participate.

Of the 18,966 men screened, 4081 fulfilled the inclusion criteria and were randomly allocated to receive either placebo (n = 2035) or gemfibrozil (n = 2046) in a double-blind fashion. These 4081 included 109 subjects who had previously diagnosed diabetes; the mean pretrial duration of diabetes was 4.5 yr. Sixteen diabetic patients were on hypoglycemic drug treatment (sulfonylureas in all cases), whereas in 96 men diabetes was controlled by diet alone. An additional 26 subjects were discovered to have fasting blood glucose ≥7.0 mM (125 mg/dL) on entry (14). Of 135 diabetic patients, 76 (mean age 50.1 ± 4.0 yr) were randomized to receive placebo and 59 (mean age 48.0 ± 4.7 yr) gemfibrozil. Of 76 subjects assigned to placebo, 11 were on hypoglycemic drugs; in 49 patients, diabetes was controlled by diet alone; and 16 patients had new-onset diabetes. The respective numbers in the gemfibrozil group were 5, 44, and 10.

All participants received dietary advice to reduce their fat intake from the prevailing levels of 37–40% total calories to 30–35% and to increase the polyunsaturated-saturated ratio from 0.2 to 0.3–0.5. Dietary counseling continued throughout the trial, and overweight and sedentary men were encouraged to start exercise programs. Treatment of diabetes was not part of this trial, and thus the diabetic patients were treated by family doctors. All cases of newly detected diabetes were also referred to family doctors for treatment. At the subsequent blood glucose measurements, 10 of 26 patients still had fasting blood glucose ≥7.0 mM (125 mg/dL); in 10 patients it was below this; and in 6 patients, no further blood glucose values were available.

Hypertension was defined as sitting blood pressure >170/100 mmHg or a diastolic pressure >105 mmHg at screening. It was also considered to be present in subjects already taking antihypertensive treatment. Fifteen percent of the hypertensive diabetic patients and 22% of nondiabetic patients were not on antihypertensive drugs. Smoking status was determined by direct questioning. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m).

Follow-up visits were made every 3 mo, during which blood was drawn for the determination of serum total and HDL cholesterol. During the second screening visit, and semiannually thereafter, a fasting blood sample was taken for serum triglyceride determinations. Blood glucose was determined during the second screening visit and annually thereafter. Electrocardiography was routinely performed at the annual medical examination to detect possible silent myocardial infarctions and also whenever subjects reported symptoms suggestive of myocardial infarction. All electrocardiograms were coded according to the Minnesota system (15). The trial end points were definite myocardial infarction and cardiac death, and the final end point assessments were made by a four-member safety committee without knowledge of the subject's treatment.

Laboratory methods

All lipid and glucose analyses were performed in a central laboratory. Total cholesterol concentration was determined from serum, and HDL cholesterol measured after dextran sulfate–magnesium chloride precipitation by an enzymatic method (kit 236691, Boehringer Mannheim, Mannheim, Germany). Serum triglycerides were measured as glycerol after enzymatic hydrolysis with lipase-esterase (kit 124966, Boehringer Mannheim). The Friedewald formula was used to calculate the LDL values (16).

Blood glucose was determined by the hexokinase method after deproteinization (Boehringer Mannheim).

Statistical methods

Differences between the diabetic subjects and the other participants, and also between placebo- and gemfibrozil-treated NIDDM patients, in continuous variables were tested by Student's t test and differences in frequencies by Fisher's exact test. Multiple logistic analysis was used to assess associations between the measured risk factors and the occurence of CHD events in the whole study population. The following were included in the model as continuous variables: age, BMI, LDL and HDL cholesterol, and triglycerides. Diabetes, smoking status, and hypertension were entered into the model as binary variables (yes or no). Results are means ± SD. $P < 0.05$ (2 tailed) was considered statistically significant.

RESULTS

Pretreatment data

NIDDM patients versus euglycemic participants. At entry, the blood glucose concentrations of the 16 diabetic subjects on oral hypoglycemic drugs, of the 93 patients on diet alone, and of the 26 patients with new-onset diabetes were 8.7 ± 2.6, 5.3 ± 1.5, and 10.1 ± 5.3 mM (155.4 ± 46.4, 94.6 ± 26.8, and 180.4 ± 94.6 mg/dl), respectively. The diabetic participants were older ($P < 0.001$), had a greater BMI ($P < 0.001$), and were more often hypertensive ($P < 0.001$) than the nondiabetic men. However, the proportion of smokers was higher among the nondiabetic subjects than the NIDDM patients ($P = 0.04$). Serum HDL cholesterol was significantly lower ($P < 0.001$) and triglycerides were significantly higher ($P < 0.0001$) in diabetic compared with nondiabetic partic-

Table 1—*Pretreatment characteristics and serum and lipoprotein lipid concentrations of patients with non-insulin-dependent diabetes mellitus (NIDDM) and other participants*

	NIDDM (N = 135)	OTHER (N = 3946)	P
AGE (YR)	49.2 ± 4.4	47.2 ± 4.6	0.001
HYPERTENSIVE (%)	30	14	0.001
SMOKER (%)	27	36	0.04
BODY MASS INDEX (KG/M^2)	28.5 ± 3.9	26.6 ± 3.0	0.001
TOTAL CHOLESTEROL (MM)	7.54 ± 0.92	7.48 ± 0.82	0.41
LOW-DENSITY LIPOPROTEIN (LDL) CHOLESTEROL (MM)	5.21 ± 0.86	5.34 ± 0.80	0.03
HIGH-DENSITY LIPOPROTEIN (HDL) CHOLESTEROL (MM)	1.18 ± 0.30	1.26 ± 0.29	0.001
LDL-HDL RATIO	4.7 ± 1.4	4.5 ± 1.3	0.08
TRIGLYCERIDES (MM)	2.69 ± 2.27	2.05 ± 1.32	0.0001

Values are means ± SD.

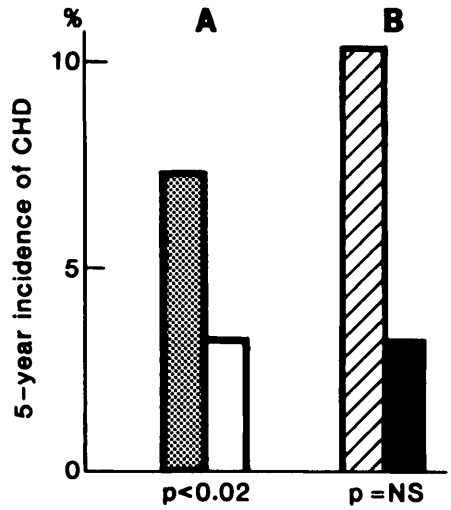

Figure 1—*Five-year incidence of myocardial infarction and death from coronary heart disease (CHD). A: non-insulin-dependent diabetes mellitus (NIDDM) patients (n = 135; stippled bar) and other subjects (n = 3946; open bar). B: NIDDM patients treated with either placebo (n = 76; hatched bar) or gemfibrozil (n = 59; solid bar).*

ipants. By contrast, LDL cholesterol levels were lower among the diabetic subjects (P = 0.04; Table 1).

Placebo- versus gemfibrozil-treated NIDDM patients. The pretreatment serum and lipoprotein lipid levels were not significantly different between the NIDDM patients treated with either placebo or gemfibrozil (Table 2).

The pretreatment serum and lipoprotein values in the patients with newly detected diabetes (n = 26) were as follows: serum total cholesterol was 7.81 ± 1.28 (302.2 ± 49.5), LDL cholesterol 5.04 ± 0.88 (194.7 ± 33.9), HDL cholesterol 1.08 ± 0.27 (41.6 ± 10.3), and triglycerides 4.29 ± 3.85 (379.7 ± 341.3) mM (mg/dl); the corresponding values in the group treated with drugs (n = 16) were 7.49 ± 0.62, 5.20 ± 0.73, 1.13 ± 0.18, and 2.54 ± 0.89 mM (2.89 ± 23.8, 200.7 ± 28.3, 43.7 ± 6.8, and 224.8 ± 79.0 mg/dl), respectively. In the patients who were on diet therapy already at the beginning of the trial (n = 93), the respective values were 7.49 ± 0.83, 5.26 ± 0.87, 1.22 ± 0.32, and 2.22 ± 1.48 mM (289.0 ± 32.3, 203.4 ± 33.7, 47.2 ± 12.5, and 196.2 ± 130.9 mg/dL).

Incidence of CHD in the study population

Figure 1 shows the frequencies of NIDDM patients and other participants who suffered myocardial infarction or cardiac death during the 5-yr follow-up period. Incidence among the diabetic participants was significantly higher than among the other subjects (7.4 vs. 3.3%; P < 0.02). Among the NIDDM patients, two on gemfibrozil (3.4%) and eight on placebo (10.5%) had a CHD event during the trial (P = 0.19; Fig. 1).

Logistic regression analysis showed that diabetes (P = 0.04), age (P < 0.0001), smoking (P < 0.0001), low HDL cholesterol (P = 0.04), and high LDL cholesterol (P = 0.003) levels were all independently related to the incidence of CHD, whereas triglycerides, hypertension, and BMI were not.

Treatment-induced changes in serum and lipoprotein lipids

The changes in serum and lipoprotein lipids among the NIDDM patients

Table 2—*Pretreatment blood glucose and serum and lipoprotein lipid concentrations in non-insulin-dependent diabetes patients assigned to either placebo or gemfibrozil*

	PLACEBO (N = 76)	GEMFIBROZIL (N = 59)
BLOOD GLUCOSE (MM)	7.0 ± 4.0	6.1 ± 2.3
CHOLESTEROL (MM)		
TOTAL	7.54 ± 0.84	7.54 ± 1.02
LOW-DENSITY LIPOPROTEIN (LDL)	5.23 ± 0.82	5.18 ± 0.91
HIGH-DENSITY LIPOPROTEIN (HDL)	1.18 ± 0.29	1.18 ± 0.32
LDL-HDL RATIO	4.7 ± 1.3	4.6 ± 1.6
TRIGLYCERIDES (MM)	2.90 ± 2.70	2.42 ± 1.53

Values are means ± SD

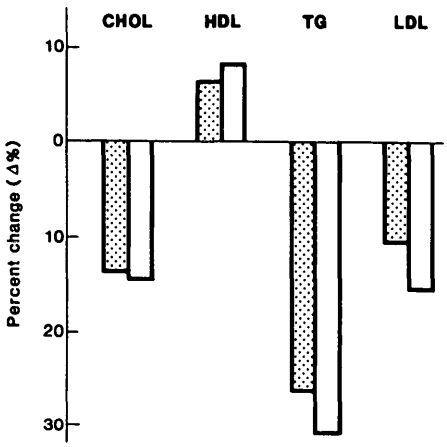

Figure 2—*Gemfibrozil-induced changes in serum and lipoprotein lipids in non-insulin-dependent diabetic patients (n = 59; stippled bars) and other subjects (n = 1987; open bars) averaged over 5 yr. CHOL, serum total cholesterol; HDL, high-density lipoprotein cholesterol; TG, serum triglycerides; LDL, low-density lipoprotein cholesterol.*

treated with gemfibrozil were similar, although somewhat smaller, to those seen in the other participants on gemfibrozil (Fig. 2). Among the placebo-treated NIDDM patients, the average serum cholesterol decrease was 5.9% compared with 5.4% among the euglycemic participants; LDL cholesterol decreased 6.1 and 6.0%, respectively. HDL cholesterol increased 0.9% in the NIDDM group and decreased 2.7% in the others; the decrease in the LDL-HDL ratio was 4.3 and 3.4%, respectively. Serum triglyceride level decreased 5.1% in the NIDDM patients during the trial, whereas it increased 6.8% in the euglycemic participants.

Blood glucose changes among NIDDM patients

The blood glucose concentrations before treatment in patients with NIDDM assigned to placebo or gemfibrozil were 7.0 ± 4.0 and 6.1 ± 2.3 mM (125.0 ± 71.4 and 108.9 ± 41.1 mg/dL), respectively (NS; Table 1). The glucose levels averaged over the 5-yr study were 6.1 ± 1.9 mM (108.9 ± 33.9 mg/dL) among the placebo-receiving patients and 5.8 ± 1.9 mM (103.6 ± 33.9 mg/dl) among those on gemfibrozil treatment (NS).

CONCLUSIONS — This 5-yr prospective study demonstrated that the incidence of CHD events among actively employed men with well-controlled NIDDM and dyslipidemia, but who were devoid of clinical evidence of CHD at entry, was significantly higher than that among nondiabetic men with comparable hypercholesterolemia. Indeed, the CHD incidence in diabetic men was more than double that of other participants.

Previous studies have produced similar findings, although none of them is entirely comparable with our study (1–4). The definition of diabetes and the inclusion of subjects have both varied, and no lipid-modulating drugs were used. The Framingham Study reported a 1.7 times greater age-adjusted incidence in CHD morbidity in diabetic men compared with euglycemic subjects (1). In that study, however, both IDDM and NIDDM patients were included. In the Whitehall Study, the men with NIDDM or glucose intolerance also had higher CHD morbidity than the other subjects (2). Based on the 15-yr mortality rates of that study, the relative risk of CHD in glucose intolerant and diabetic men compared to normoglycemic men ranged from 1.2 to 2.6 after controlling for other cardiovascular risk factors. In a population-based study of diabetic men in Sweden, those with a serum cholesterol concn >7.3 mM (282.3 mg/dl) had a significantly higher incidence of CHD during the follow-up (mean 7.1 yr) than those with cholesterol concn ≤5.5 mM (212.7 mg/dl) (28.3 vs. 5.4%), and in multivariate analysis, high serum cholesterol level was an independent predictor of CHD events (3). Unfortunately, no other lipids or lipoproteins were determined.

A well-controlled 5-yr prospective study of NIDDM patients (70 men) in Finland found that the incidence of myocardial infarction was 19.4% compared with 3.2% in the control subjects (4). However, most NIDDM patients already had clinical evidence of CHD at the beginning of the follow-up. Interestingly, apart from diabetes itself, none of the other risk factors studied, i.e., serum and lipoprotein lipids, BMI, blood glucose, and fasting and postglucose serum insulin, were significantly related to the CHD incidence.

Although all subjects of this study were selected on the basis of their high non-HDL cholesterol, a further clustering of the CHD-related risk factors, excluding smoking, was found among the NIDDM patients compared with the other participants. The diabetic men had lower HDL cholesterol and higher triglyceride levels, their BMI was greater, and there were more hypertensive subjects compared with the nondiabetic participants with similar non-HDL cholesterol. Although insulin concentrations were not determined, the other findings suggest that the diabetic men of this study may have included patients with the so-called "insulin-resistance syndrome" or "syndrome X" (7,17), which may explain the excess CHD morbidity among the diabetic patients.

The alterations in serum and lipoprotein lipids among diabetic patients on gemfibrozil treatment were comparable to those observed in the other participants of this study, although somewhat smaller. This finding coincides with previous studies in NIDDM patients showing reductions of total cholesterol and triglycerides of 6–14 and 17–58%, respectively, whereas HDL cholesterol increments varied between 6 and 24%, depending on the type of dyslipoproteinemia (18–20).

This study also suggested that the risk of myocardial infarction in NIDDM patients could be reduced by lipid-modifying treatment with gemfibrozil. However, caution should be used in drawing conclusions from the data because the number of diabetic men, and

hence also the number of events, were rather low and the difference in the CHD incidence between gemfibrozil- and placebo-treated diabetic patients was not statistically significant. Nevertheless, gemfibrozil's favorable effect on both HDL-LDL cholesterol ratio and hypertriglyceridemia suggests that the drug may offer protection from CHD, not only via its effects on atheroma development, but also because it corrects unfavorable hypertriglyceridemia-related influences in various hemostatic functions (22,23). Indeed, analyses relating the treatment effect to groups of participants with different lipoprotein patterns have indicated that the subjects who benefited most from gemfibrozil treatment were those with high level of both triglyceride and LDL-HDL ratio (24). Treatment with gemfibrozil did not significantly change blood glucose levels in the NIDDM patients, although other studies with gemfibrozil have shown either an increase (20) or no change (18,19,21) in fasting glucose levels of dyslipidemic NIDDM patients. Insulin levels have remained stable in diabetic patients receiving gemfibrozil (18,20). Some studies with other fibric acid derivatives have even found improved glycemic control in NIDDM patients (25), whereas a study reported marked deterioration of glycemic control during nicotinic acid treatment (26).

In conclusion, the incidence of CHD was significantly higher in diabetic compared with nondiabetic men in this high-risk population. The NIDDM patients had other risk factors that probably contributed to the excess morbidity, in addition to elevated non-HDL cholesterol. Gemfibrozil treatment reduced the incidence of myocardial infarction among the diabetic men and the other participants.

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