

Serum Lipids and Lipoproteins in Insulin-treated Diabetes

Demonstration of Increased High Density Lipoprotein Concentrations

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SUMMARY

In view of the high incidence of coronary heart disease in insulin-dependent diabetes, we determined cholesterol and triglyceride concentrations in serum and in three major lipoprotein fractions of 170 nonuremic middle-aged diabetic patients who had been treated with insulin for a minimum of 10 years. In addition, postheparin plasma lipoprotein lipase activity was measured in a subsample of the diabetic subjects. The diabetics had serum cholesterol and triglyceride concentrations similar to those of nondiabetic control subjects of the same age and sex. However, the concentration of high density lipoprotein (HDL)-cholesterol was significantly higher in both male and female diabetic patients than in respective controls ($P < 0.001$). Male patients with poor diabetic control or with overweight had elevated triglyceride and very low density lipoprotein (VLDL)-triglyceride concentrations, whereas the patients with good diabetic control had significantly lower triglyceride and VLDL-triglyceride concentrations than did nondiabetic subjects. Overweight diabetic patients also had elevated serum

cholesterol and LDL-cholesterol concentrations. The HDL-cholesterol of diabetic subjects, on the other hand, was not dependent on the degree of diabetic control or on the relative body weight. Diabetic patients had higher lipoprotein lipase activity in postheparin plasma than did normal subjects of corresponding age and sex. The HDL-cholesterol concentration showed a significant positive correlation with postheparin plasma lipoprotein lipase activity.

We conclude that the average serum lipid and lipoprotein pattern of insulin-treated chronic diabetic patients is not more atherogenic than that of nondiabetic subjects of similar age and sex. On the contrary, the increase of HDL-cholesterol observed in the diabetic subjects should make them less liable to develop coronary heart disease. Thus, the excess cardiovascular disease that is associated with insulin-dependent diabetes must be accounted for by other factors. *DIABETES* 27:1078-86, November, 1978.

Patients with diabetes mellitus have more coronary atherosclerosis^{1,2} and a higher incidence of clinical coronary heart disease than does the nondiabetic population of similar age.³⁻⁵ The increased risk of developing ischemic heart disease is evidently related to the duration and severity of diabetes but it is less clear as

to whether the risk is similar for patients with juvenile and for those with adult-type diabetes. The insulin-treated patients have a higher relative total mortality than other diabetics,^{6,7} and in the Framingham cohort the insulin-treated diabetic women showed the greatest relative mortality from coronary heart disease.⁴ These data suggest that the insulin-dependent type of diabetes is associated with particularly high risk of coronary heart disease.

The factors that dispose a diabetic patient to early coronary disease are not well understood. The possibility that elevated serum lipid levels could be responsible was raised already in the early report of Root et al.,¹ and it is further supported by more recent data indicating increased prevalence of hyperlipidemia in

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diabetic patients.⁸⁻¹³ However, most studies of plasma lipids and lipoproteins in diabetes have been confined to either patients with adult-type diabetes or children and adolescents with the juvenile-type disease, while little is known about the frequency of hyperlipoproteinemia in long-term, insulin-treated diabetic patients at middle age. We have, therefore, determined serum lipids and lipoproteins in a population of middle-aged, insulin-dependent diabetic patients who had been on regular insulin treatment for a minimum of 10 years. Furthermore, lipoprotein lipase activity was measured in postheparin plasma in some of the patients.

PATIENTS AND METHODS

Patients

The patients recruited for the study had to meet the following three criteria: (1) insulin-dependent diabetes detected before the age of 40 years, (2) regular use of insulin for a minimum of 10 years, and (3) age at examination of between 35 and 55 years. In order to find a study population that was representative enough of middle-aged, insulin-dependent diabetes the subjects were obtained from the register of the local diabetes association and from Helsinki health centers. Primarily, no exclusion was made on the basis of possible presence of any diabetic complications or cardiovascular disease, but, in this report, the 12 patients who had elevated serum creatinine or gross proteinuria have been omitted, since these conditions are known to influence plasma lipid concentrations irrespective of the diabetes.

After the exclusions, the patient population comprised 170 diabetics, of which 84 were men and 86 were women. The mean age was 46.5 years, 75 patients being between 35 and 44 years and 95 patients from 45 to 55 years of age. The mean age at the onset of diabetes was 26.0 years in men (range, eight to 40 years) and 24.2 years in women (range, one to 40 years). The diabetes had been detected before age 30 in 65 per cent and before age 20 in 29 per cent of cases. The average duration of the disease was 19.8 years, with a range of 10 to 40 years. The daily insulin dose at the time of the study varied from 16 to 102 U. (mean, 45 U.).

The fasting blood glucose concentrations in the diabetic patients ranged from 34 to 408 mg. per deciliter with a mean of 167 mg. per deciliter. Four subjects had ketonuria detectable with Ketostix. Control of diabetes was estimated as good (fasting blood glucose 100 mg. per deciliter or less) in 26 per cent of

cases and as poor (fasting blood glucose exceeding 250 mg. per deciliter) in 20 per cent of the cases. The mean relative body weight of diabetic men was 109 per cent and that of diabetic women 113 per cent. Obesity (relative body weight 120 per cent) was present in 13.1 per cent of the men and in 30.2 per cent of the women.

All subjects had been advised to be on sugar-free diets, but the actual dietary habits were not evaluated. None of the diabetics received lipid-lowering drugs.

Control Subjects

The control group for the lipoprotein study was formed from nondiabetic siblings of the diabetic patients. The control subjects were accepted only when their fasting blood glucose was less than 90 mg. per deciliter, the oral glucose tolerance was normal (one-hour value: 160 mg. per deciliter), and there was no evidence of any acute illness. Exclusions on other grounds were not made. Altogether, 90 subjects (41 men and 49 women) fulfilled these criteria. The age distribution (mean 45.9 years) of the control subjects was similar to that of the patients. The mean relative body weight of the male and female controls was 113 and 112 per cent, respectively, i.e. virtually identical to that of the patients. The control subjects were on a free diet, the composition of which was not evaluated. None was receiving lipid-lowering drugs.

The normal values for the lipoprotein lipase assays were obtained from our earlier study of normolipidemic healthy subjects.¹⁴

Procedures

The patients and controls came to the examination without any adjustment of their diet or their insulin dose. Blood samples were taken after an overnight fast and before injection of the morning insulin dose. Postheparin plasma for the assay of lipoprotein lipase activity was obtained five minutes after intravenous injection of 1 mg. per kilogram of heparin (Virtum).¹⁵ Blood samples were collected on ice, and plasma was separated immediately in refrigerated centrifuge. Samples for measurement of postheparin plasma lipases were frozen and stored at -20° C. until assay.

Serum lipoproteins were separated with preparative ultracentrifuge (Beckman Spinco Model L-50, titanium angle rotor). Six milliliters of serum was overlaid with 5 ml. of saline (density 1.006) and spun for 18 hours at 40,000 rpm. Very low density lipoproteins (VLDL) were sliced from the top layer, and the remainder was mixed with a salt solution¹⁶ to give a density of 1.063. This mixture was centrifuged

for 20 hours at 40,000 rpm and the low density lipoprotein (LDL) was sliced from the top. The infranatant was used for analysis of high density lipoproteins (HDL) without further fractionation. Whole serum and each of the three lipoprotein fractions were analyzed for cholesterol¹⁷ and triglyceride.¹⁸ The recovery rate of both lipids in lipoproteins ranged from 87 to 100 per cent. Appropriate corrections for recovery were made.

Lipoprotein lipase activity of postheparin plasma was determined by a selective method,¹⁵ which is based on inactivation of the hepatic triglyceride lipase by a specific antiserum prepared against purified hepatic lipase of postheparin human plasma. The substrate was a 3-mM emulsion of ¹⁴C-labeled triolein (Radiochemical Centre, Amersham, England) containing 5 per cent gum arabic in Tris buffer, pH 8.6. Details of the preparation of substrate and of the assay system have been described.¹⁵

RESULTS

Serum Lipids and Lipoproteins

The serum total cholesterol and LDL-cholesterol concentrations were similar in diabetics and controls (table 1). Only the younger (35 to 44 years) female diabetics had slightly higher serum cholesterol (259 mg. per deciliter versus 228 mg. per deciliter, P < 0.05) and LDL-cholesterol (181 mg. per deciliter versus 154 mg. per deciliter, P < 0.05) than did non-

diabetic women of same age. The mean HDL-cholesterol concentration, on the other hand, was significantly higher in both male and female diabetics than in their respective control subjects (table 1). This difference was present in all age groups although it was least in younger diabetic women (P < 0.05). As shown in figure 1, there was a definite shift of the HDL-cholesterol values of both male and female diabetics towards the upper range of respective non-diabetic control subjects. Seventeen per cent of the diabetic patients had an HDL-cholesterol concentration above the highest level of the respective control group.

The mean serum total triglyceride concentrations of both male and female diabetics were similar to those of comparable nondiabetic subjects. The diabetic men, on the other hand, had significantly lower triglyceride levels in the VLDL than did the control men of similar age (table 1). The difference was due to a shift from medium range values towards low normal range, whereas the frequency of high VLDL-triglyceride values was similar in diabetic and non-diabetic men (figure 2). The distribution of the values was log-normal with one mode. No difference was present between the VLDL-triglyceride values of diabetic and normal women.

Serum total triglyceride and VLDL-triglyceride concentrations correlated positively with fasting blood glucose in diabetic men (r = +0.50, P < 0.01, for

TABLE 1

Cholesterol and triglyceride concentrations (mean ± S.D.) in whole plasma and in very low density (VLDL), low density (LDL), and high density (HDL) lipoproteins in insulin-treated diabetic patients and in controls

	Diabetic (N = 84)	Control (N = 41)	Significance of difference,* P
Men			
Total cholesterol (mg./dl.)	259 ± 46	259 ± 50	N.S.
VLDL-cholesterol	22 ± 19	22 ± 13	N.S.
LDL-cholesterol	178 ± 46	181 ± 46	N.S.
HDL-cholesterol	59 ± 15	50 ± 12	<0.001
Total triglyceride (mmol/L.)	1.38 ± 0.87	1.48 ± 0.65	N.S.
VLDL-triglyceride	0.75 ± 0.69	0.92 ± 0.56	<0.01
LDL-triglyceride	0.46 ± 0.19	0.42 ± 0.13	N.S.
HDL-triglyceride	0.17 ± 0.10	0.15 ± 0.08	N.S.
Women	N = 86	N = 49	
Total cholesterol (mg./dl.)	278 ± 58	262 ± 54	N.S.
VLDL-cholesterol	14 ± 13	17 ± 12	N.S.
LDL-cholesterol	197 ± 58	185 ± 54	N.S.
HDL-cholesterol	68 ± 15	58 ± 12	<0.001
Total triglyceride (mmol/L.)	1.15 ± 0.64	1.07 ± 0.56	N.S.
VLDL-triglyceride	0.37 ± 0.49	0.50 ± 0.36	N.S.
LDL-triglyceride	0.45 ± 0.19	0.40 ± 0.20	N.S.
HDL-triglyceride	0.18 ± 0.10	0.17 ± 0.11	N.S.

N, number; N.S., not significant.

*Log values used in calculations of triglyceride values.

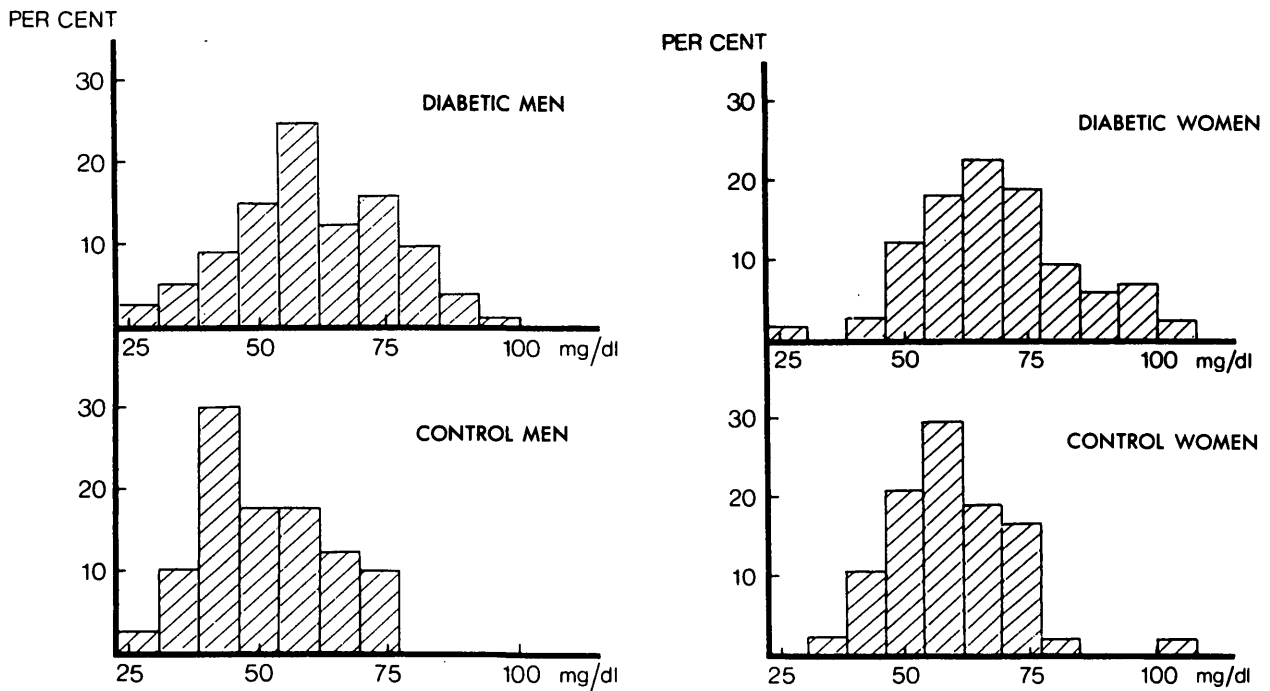


FIG. 1. Distribution of plasma HDL-cholesterol concentrations in insulin-treated diabetic men (left) and women (right) and in their respective nondiabetic control subjects.

triglyceride and $r = +0.42$, $P < 0.01$, for VLDL-triglyceride). This relationship was not present in diabetic women. Table 2 presents the serum lipid and lipoprotein values in patients with good control of

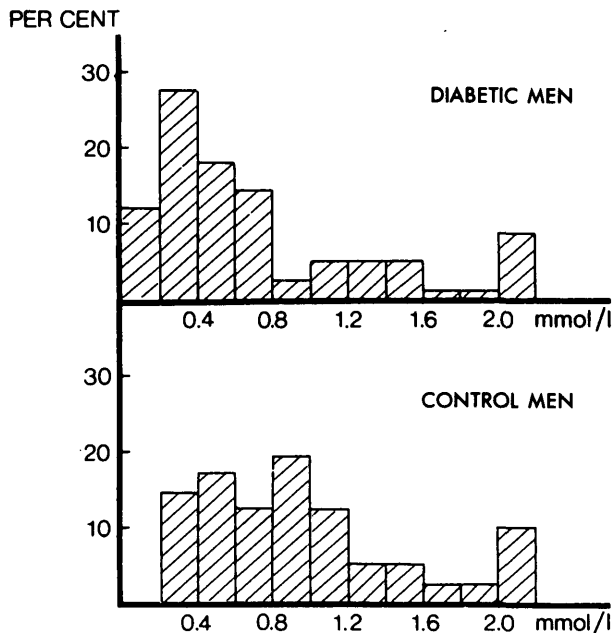


FIG. 2. Distribution of plasma VLDL-triglyceride concentrations in insulin-treated diabetic men and in control subjects. Note the shift of the peak in diabetics to lower values.

diabetes (defined as fasting blood glucose of 100 mg. per deciliter or less) in comparison with those of poor control (defined as fasting blood glucose of 250 mg. per deciliter or more). As expected, the triglyceride concentrations in whole serum and in VLDL were significantly lower in the well controlled diabetics than in patients with poor diabetic control. What is remarkable, however, is that diabetic patients with good glucose control had mean triglyceride and VLDL levels below even those of nondiabetic subjects. It thus appears that strict control of diabetes can reduce effectively the serum VLDL level. On the other hand, the LDL-cholesterol and HDL-cholesterol concentrations were not influenced by the degree of diabetic control (table 2).

Another factor that appeared to have an influence on serum lipid and lipoprotein levels of diabetic subjects was body weight. Table 3 shows the lipid values of diabetic patients allocated by relative body weight into lean, normal, and obese. The average degree of control was similar in all three groups, as indicated by the fasting blood glucose values. In spite of this, the obese diabetic men had significantly higher mean levels of total cholesterol and triglyceride, of LDL-cholesterol, and of VLDL-triglyceride than did the nonobese male patients. Remarkably, these differences were not present in diabetic women, even

TABLE 2

Influence of good versus poor control of diabetes on cholesterol and triglyceride concentrations (mean ± S.D.)

	Good control (fB-glucose < 100 mg./dl.)	P*	Poor control (fB-glucose > 250 mg./dl.)
Men	N = 25		N = 15
Total cholesterol (mg./dl.)	242 ± 30	<0.05	271 ± 50
VLDL-cholesterol	12 ± 4	<0.001	36 ± 10
LDL-cholesterol	167 ± 27	N.S.	176 ± 46
HDL-cholesterol	63 ± 12	N.S.	59 ± 15
Total triglyceride (mmol/L.)	0.83 ± 0.39†	<0.001	1.91 ± 0.87‡
VLDL-triglyceride	0.40 ± 0.28†	<0.001	1.14 ± 0.79
Women	N = 19		N = 18
Total cholesterol (mg./dl.)	257 ± 47	N.S.	270 ± 50
VLDL-cholesterol	10 ± 4	N.S.	16 ± 6
LDL-cholesterol	176 ± 47	N.S.	184 ± 44
HDL-cholesterol	71 ± 13	N.S.	70 ± 13
Total triglyceride (mmol/L.)	0.89 ± 0.44	<0.01	1.43 ± 0.73‡
VLDL-triglyceride	0.34 ± 0.25‡	<0.02	0.61 ± 0.41

fB-glucose = fasting blood glucose.

*Log values used in calculations of triglyceride values.

†P < 0.001, ‡P < 0.05, for difference from nondiabetic controls (table 1).

though the obese female patients showed a tendency to high LDL-cholesterol levels. Lowest VLDL and LDL levels among diabetics of both sexes were present in the lean patients. In contrast to the other lipoproteins, HDL-cholesterol concentrations were not influenced by degree of body fatness.

The serum lipid levels were not related to the duration of diabetes or to the daily insulin dose.

Lipoprotein Lipase Activity of Postheparin Plasma

The mean activities of lipoprotein lipase in post-

heparin plasma were significantly increased in both male and female diabetic patients as compared with corresponding values of age-matched normal subjects (table 4). The difference between the diabetic and control subjects was least in the group of younger women. The lipoprotein lipase activity did not correlate with fasting blood glucose level or with daily insulin dose. However, diabetic men with poor control of diabetes (blood glucose > 250 mg. per 100 ml.) had slightly lower lipoprotein lipase activity than

TABLE 3

Influence of relative body weight on the degree of glucose control and on plasma cholesterol and triglyceride concentrations in insulin-treated diabetic patients (mean ± S.D.)

	Relative body weight		
	<100% (A)	100-120% (B)	>120% (C)
Men	N = 21	N = 52	N = 11
Glucose (mg./dl.)	145 ± 79	176 ± 88	150 ± 85
Total cholesterol (mg./dl.)	242 ± 40	259 ± 48//	301 ± 44‡
LDL-cholesterol	161 ± 38	178 ± 44§	209 ± 53†
HDL-cholesterol	60 ± 16	61 ± 17	54 ± 14
Total triglyceride (mmol/liter)	1.01 ± 0.49**	1.38 ± 0.85§	2.16 ± 1.68†
VLDL-triglyceride	0.48 ± 0.35**	0.76 ± 0.67§	1.40 ± 1.22†
LDL-triglyceride	0.40 ± 0.16	0.45 ± 0.18//	0.60 ± 0.22†
Women	N = 17	N = 43	N = 26
Glucose (mg./dl.)	175 ± 86	170 ± 94	178 ± 86
Total cholesterol (mg./dl.)	254 ± 50	276 ± 49	291 ± 65*
LDL-cholesterol	175 ± 55	193 ± 49	206 ± 61
HDL-cholesterol	69 ± 11	65 ± 13	73 ± 19
Total triglyceride (mmol/liter)	0.97 ± 0.45	1.22 ± 0.74	1.22 ± 0.49
VLDL-triglyceride	0.41 ± 0.29	0.62 ± 0.55	0.52 ± 0.36
LDL-triglyceride	0.40 ± 0.17	0.44 ± 0.16§	0.53 ± 0.21*

N, number.

Significance of the differences for A versus C: *P < 0.05, †P < 0.01, ‡P < 0.001; for B versus C: §P < 0.05, //P < 0.01; and for A versus B: **P < 0.05.

TABLE 4

Postheparin plasma lipoprotein lipase activity (mean \pm S.D.) in insulin-treated diabetic patients and in normal subjects

Group	Age (yr.)	N	Lipoprotein lipase activity ($\mu\text{mol FFA/ml}\cdot\text{hr.}$)	P
Diabetic men	35-44	17	32.6 \pm 7.7	<0.001
Control men	35-44	12	20.3 \pm 4.8	
Diabetic men	45-55	24	29.3 \pm 8.5	<0.001
Control men	45-55	22	15.8 \pm 5.6	
Diabetic women	35-44	19	34.3 \pm 8.9	<0.05
Control women	35-44	11	27.0 \pm 9.8	
Diabetic women	45-55	26	37.9 \pm 10.0	<0.001
Control women	45-55	16	22.8 \pm 7.7	

N, number; FFA, free fatty acid.

did men with good control (26.6 versus 32.9 $\mu\text{mol FFA} \cdot \text{hr.}^{-1} \cdot \text{ml.}^{-1}$, $P < 0.05$). In diabetic patients there was a high degree of positive correlation between the postheparin plasma lipoprotein lipase activity and the HDL-cholesterol concentration (figure 3). On the other hand, a slight but significant negative correlation was present between lipoprotein lipase activity and the VLDL-triglyceride concentration ($r = -0.42$, $P < 0.01$, for diabetic men and $r = -0.27$, $P < 0.05$, for diabetic women).

DISCUSSION

A variety of the known risk factors of coronary heart disease (for example, hypertension, hyperlipoproteinemia, obesity, and smoking) have been reported to be slightly more common among diabetics than in the general population.^{19,20} Yet, taken together they do not seem to account for the excess of coronary heart disease that is associated with diabetes.^{4,21} Furthermore, analysis of the coronary risk factors in diabetic patients usually has been made without sharp separation of the two clinical subtypes of diabetes. Thus, there is little previous knowledge on the prevalence of these risk factors among insulin-dependent diabetics who have reached the coronary-prone age. It is well known that insulin-treated juvenile diabetics have higher cardiovascular morbidity,⁴ mortality,^{4,6,7} and case fatality rates⁴ than the patients suffering from adult-onset diabetes.

Serum lipid concentrations are known to be elevated in a high proportion of patients with untreated or poorly controlled diabetes.^{12,22,23} A rise of plasma total triglyceride and VLDL-triglyceride is the most common abnormality, but elevations of LDL-cholesterol have also been reported.^{22,23} Data on the treated adult diabetics were shown to have lower

plasma lipid and lipoprotein concentrations in insulin-treated, juvenile-type diabetics have usually been obtained in children or adolescents, and they have given somewhat contradictory results. Raised mean levels of total cholesterol,^{9,10,13,24-26} total triglyceride,^{8,10,13} VLDL or S_f 12-100-lipoprotein,²⁴ and of LDL^{13,22} have been reported in insulin-treated juvenile diabetics, but there are also studies in which normal values were observed.^{9,25,27} To our knowledge, there is only one study¹⁰ in which the plasma lipid levels of middle-aged, insulin-treated diabetics have been compared with those of nondiabetic controls of similar age. It was found that at any relative body weight, the diabetics had higher plasma triglyceride and cholesterol concentrations than the nondiabetic subjects. In two other studies,^{11,28} insulin-treated adult diabetics were shown to have lower

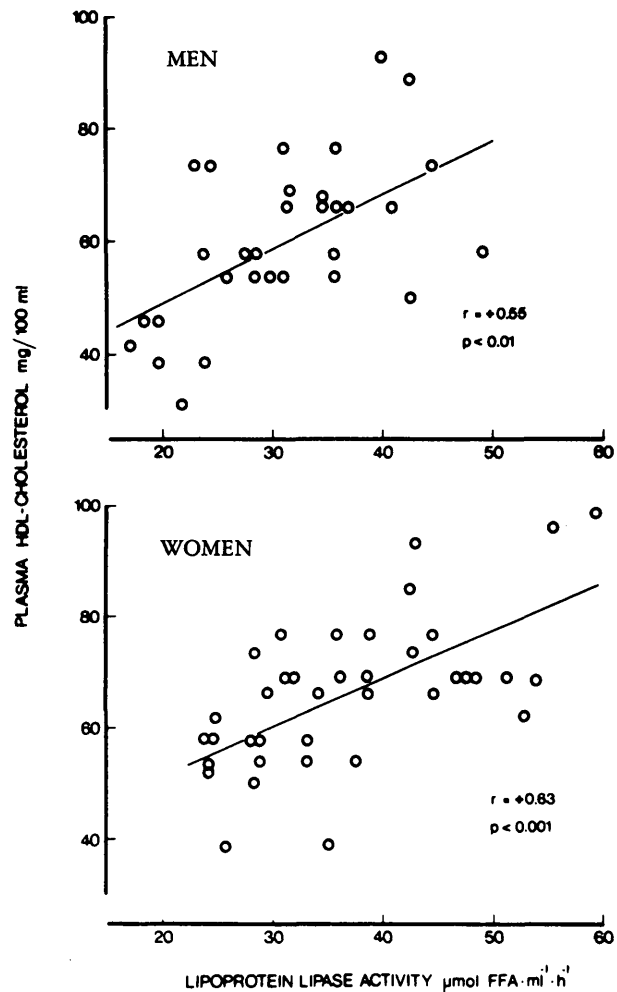


FIG. 3. Correlation between high density lipoprotein (HDL)-cholesterol concentration in fasting plasma and lipoprotein lipase activity of postheparin plasma in insulin-treated diabetic patients.

plasma triglyceride levels than the diabetic patients treated by diet or oral hypoglycemic agents. Santen et al. analyzed this difference also after adjustment for ponderal index, and they could demonstrate that, independent of body weight, diabetic patients treated with insulin had lower serum triglyceride mean levels than the group treated with orally administered agents.¹¹ Administration of insulin to patients with adult-onset diabetes is followed by reduction of serum triglyceride, cholesterol, and LDL-cholesterol concentrations.²³ On the other hand, decreased HDL-cholesterol levels have been reported recently in a group of insulin-treated adult-onset diabetics.²⁹

Our present diabetic material is thought to be representative of middle-aged, insulin-dependent diabetic patients who undergo routine ambulatory treatment. Apart from exclusion of patients who had renal failure or gross proteinuria, no intentional case selection was made. Nondiabetic siblings of the patients were studied as a control group in order to exclude the influence of possible familial hyperlipoproteinemias. It was expected that, if present, the familial disorders of lipid metabolism could express themselves independently of diabetes³⁰ and be manifest in the nondiabetic siblings with similar likelihood as in the diabetic patients.

In contrast to many previous observations the present study showed that insulin-treated diabetics on an average do not differ from age-matched nondiabetics in regard to serum cholesterol, triglyceride, VLDL, or LDL concentrations. The only consistent and most significant finding was an increase of mean HDL-cholesterol level in both male and female diabetics. Since HDL-cholesterol is known to be related inversely to the risk of coronary heart disease³¹⁻³³ and to correlate positively with life expectancy,³⁴ the raised HDL levels should protect diabetics from atherosclerotic complications. Those diabetic patients who were well controlled by insulin had low concentrations of serum triglyceride and VLDL as additional coronary antirisk factors.

The only subgroups of diabetics who showed an atherogenic plasma lipoprotein pattern were the obese men having markedly increased concentrations of both LDL and total cholesterol and of VLDL and total triglyceride. Poor control of diabetes was also associated with increased levels of triglycerides and VLDL. It is remarkable that the lipoprotein concentrations of the women were much less influenced by body weight or by the degree of control of the diabetes than those of the men.

It is thus evident that some other risk factors of coronary heart disease must be associated with insulin-treated diabetes. It is well known that hyperglycemia and hyperinsulinemia may cause arterial disease by several mechanisms that do not include plasma lipoprotein abnormalities.³⁵⁻³⁷ Another possibility is that all excess cases of coronary heart disease among diabetics occur in the high-risk groups, viz. in patients with obesity, poor control, or renal failure.

The mechanisms responsible for the observed alterations of plasma lipoprotein levels in insulin-treated diabetes are not clear. The tendency to subnormal concentrations of triglyceride in whole plasma and in VLDL, particularly in the diabetics who have good control of hyperglycemia, might be due to the high lipoprotein lipase activity of tissues and subsequent increase in the rate of removal of triglyceride-rich lipoproteins from the blood. The present study confirmed our preliminary observation³⁸ that the lipoprotein lipase activity of postheparin plasma is often elevated in insulin-treated diabetes. Since this enzyme is known to be highly sensitive to insulin, it is possible that the rise in the activity is a consequence of high insulin levels at peripheral tissues.⁴¹ These excessive insulin concentrations in the peripheral blood are probably necessary in a diabetic patient in order to achieve even near-physiologic insulin levels in the portal vein and the liver, which under normal conditions is perfused by blood in which insulin concentrations are two to three times higher than in the peripheral blood.⁴⁰ If, on the other hand, the insulin dose results in normal insulin concentrations in the peripheral plasma, these must be unphysiologically low in portal blood, and this presumably leads to a reduction of hepatic secretion of VLDL.⁴¹ In a way, this situation is opposite to that present in adult-onset diabetes, where the liver is perfused by high insulin concentrations and the peripheral tissues are resistant to the action of insulin.

The present study demonstrated that in diabetes there is a close association between the concentration of HDL-cholesterol and the postheparin plasma lipoprotein lipase activity. Parallel variations in these two parameters are known to occur also in some other conditions. Women have higher HDL-cholesterol levels³¹⁻³² and lipoprotein lipase activities¹⁴ than men. In uremic patients, both HDL-cholesterol and the lipoprotein lipase activity are subnormal.⁴² Furthermore, we have recently shown that in normal subjects there is a highly significant correlation between the serum HDL-cholesterol level and the adipose tis-

sue lipoprotein lipase activity.⁴³ This relationship could be due to part of the HDL being a product of the catabolism of triglyceride-rich lipoproteins,⁴⁴⁻⁴⁶ but the possibility cannot be excluded that the activity of lipoprotein lipase is stimulated by HDL apoproteins.

We wish to emphasize that the increases of HDL-cholesterol and of postheparin plasma lipoprotein lipase activity were observed only among insulin-treated diabetic patients, but they are not found in adult-onset diabetes or in untreated juvenile-onset diabetes.⁴⁰ It is of interest, however, that high levels of HDL have been previously detected in streptozotocin-diabetic (insulin-deficient) rats⁴⁷ and in some patients with adult-onset diabetes.⁴⁸ The mechanism of these forms of hyperlipoproteinemia remains to be established.

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