Turk J Med Sci
33 (2003) 95-101
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Lecithin:Cholesterol Acyltransferase Activity and Cholesteryl Ester Transfer Rate in Patients with Diabetes Mellitus*

Received: August 08, 2002

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Abstract: Several factors may be responsible for the high prevalence of atherosclerosis in diabetes mellitus, including alterations in reverse cholesterol transport. In the present study, the activity of plasma lecithin:cholesterol acyltransferase (LCAT) and the cholesteryl ester transfer rate, and concentrations of lipids and lipoproteins were measured in 11 patients with insulin-dependent diabetes mellitus (type 1), 42 patients with noninsulin-dependent diabetes mellitus (type 2) and compared with those in age-matched control groups (Control I, n = 14; and Control II, n = 29, respectively). No statistically significant differences were observed in plasma total cholesterol, triglyceride, ester cholesterol or very low density lipoprotein (VLDL)-cholesterol concentrations between the diabetic and control groups. High density lipoprotein (HDL)- and HDL_2-cholesterol levels were significantly lower in the diabetic patients. Plasma free cholesterol and low density lipoprotein (LDL)-cholesterol concentrations were higher in the type 2 diabetics than in the control subjects. LCAT activity was significantly lower in both groups of diabetic patients than in the control groups. The mass of cholesteryl ester transferred from HDL to VLDL + LDL was significantly greater in the diabetic groups than in the controls. In conclusion, the decrease in LCAT activity and the increase in cholesteryl ester transfer observed with both type 1 and type 2 diabetics could affect the reverse cholesterol transport of HDL and contribute to the development of atherosclerosis in diabetes.

Key Words: Diabetes, Lecithin:cholesterol acyltransferase, Cholesteryl ester transfer, Reverse cholesterol transport

Introduction

Atherosclerosis is an important complication of diabetes mellitus (1). Why diabetes mellitus should be associated with an increased premature atherosclerosis risk is not clear, but it has been partly attributed to disturbances in reverse cholesterol transport (2). This is a multi-step process and includes the uptake of free cholesterol (FC) by high density lipoprotein (HDL) from cell membranes, the esterification of FC at the HDL surface by lecithin:cholesterol acyl transferase (LCAT), which is mainly activated by apolipoprotein (apo) A-I, and the transfer of esterified cholesterol (CE) to apo B-containing lipoproteins (low density lipoprotein, LDL; very low density lipoprotein, VLDL), which is catalyzed by the cholesteryl ester transfer protein (CETP). The rate of CE mass transfer depends not only on levels of CETP but also on the concentration and composition of the plasma lipoproteins involved in the transfer process (3).

HDL plays a central role in reverse cholesterol transport because it not only promotes the efflux of cholesterol from peripheral tissues but is also the major site for the esterification of cholesterol by LCAT. LCAT activity modulates cholesterol transfer from lipoproteins and cell membranes to HDL. Therefore, decreased activity of LCAT promotes the accumulation of FC at cell membranes, and of remnant lipoprotein in plasma, both factors being strongly related to atherosclerosis (4,5). Modifications in the cholesteryl ester transfer (CET) are potentially atherogenic if the compositional changes adversely affect the function of lipoproteins. The question of whether CET is a beneficial or deleterious process remains unresolved. If CET were inhibited because the efflux of cholesterol from arterial wall tissues were retarded, it could have potentially atherogenic consequences (6,7). On the other hand, it seems likely that when CET is accelerated, more atherogenic

* This work was supported by the Uludağ University Research Fund.

cholesteryl ester-enriched apo B-containing lipoproteins will be formed (8).

There has been considerable controversy concerning the process of the CET rate in diabetes mellitus. The objective of the present study was to measure cholesteryl ester transfer from HDL to apo B-containing lipoproteins in insulin-dependent (type 1) and noninsulin-dependent (type 2) diabetics, as compared to normal controls matched for age.

Materials and Methods

1. Subjects: Eleven subjects (six female, five male, aged 29 ± 11 years; mean ± SD) with insulin-dependent diabetes mellitus (IDDM) (duration 10 ± 8 years; mean ± SD) and 42 subjects (21 female, 21 male, aged 58 ± 11 years; mean ± SD) with noninsulin-dependent diabetes mellitus (NIDDM) (duration 8 ± 6 years; mean ± SD) were studied as outpatients. The classification of these patients was based on clinical criteria (9). At the time of the study all noninsulin-dependent diabetic patients were being treated with an oral sulfonylurea agent and diet. The insulin-dependent diabetic patients were in a stable metabolic condition (none had a history of ketoacidosis in the 3 months prior to the study) by the use of multiple daily insulin injections. The last administration of insulin was 12 h preceding the blood sampling. Age-matched control groups were formed for both IDDM and NIDDM groups [Control I (n = 14, six female and eight male, aged 27 ± 7 years) and Control II (n = 29, 11 female and 18 male, aged 51 ± 9 years), respectively]. All participants were non-smokers; none were receiving medications affecting the lipid metabolism, or had hepatic or renal disease. All patients and control subjects were informed volunteers.

2. Methods:

Chemicals: 5,5'-dithiobis(2-nitrobenzoic acid), polyvinyl sulfate-potassium salt, magnesium chloride and dextran sulfate (MW: 15,000) were purchased from Sigma. Dextran sulfate-sodium salt (MW: 500,000) and polyethylene glycol 350 monomethyl ether were obtained from Pharmacia Fine Chemicals and Fluka, respectively.

Sample preparation: Blood samples were drawn into tubes containing EDTA after fasting overnight. Plasma was separated by low-speed centrifugation (900 x g, for 10 min) and the parameters described below were analyzed immediately. Glucose was measured by the glucose oxidase method. Glycosylated hemoglobin was measured in fasting blood using a chromatographic kit (Boehringer, Germany). Plasma total cholesterol (TC) (Boehringer, Germany) and triglyceride (TG) (Chematil, Italy) were determined by enzymatic methods. The plasma HDL-cholesterol level was determined after precipitation of apo B-containing lipoproteins with dextran sulfate-magnesium chloride (10). HDL_2 was precipitated in the clear supernatant containing the HDL by using low-molecular weight dextran sulfate (MW: 15,000). After the precipitation of HDL_2, the cholesterol level was measured in the HDL_3 supernatant to determine the HDL_3-cholesterol level. The concentration of HDL_2-cholesterol was estimated as the difference between the HDL-cholesterol and HDL_3-cholesterol (11). Plasma FC was measured by an enzymatic kit (Boehringer, Germany), and the concentration of cholesteryl ester was calculated by subtracting FC from TC. The LDL-cholesterol concentration was determined after precipitating LDL with polyvinyl sulfate. The concentration of LDL-cholesterol was estimated as the difference between the total and the supernatant cholesterol values (12). Cholesterol and TG measurements were performed on a Shimadzu 1202 spectrophotometer (Japan).

LCAT activity measurement: Plasma LCAT activity was determined as a function of the decrease in FC, which is esterified during incubation at 37 ºC, as described by Hitz et al. (13). LCAT activity was expressed as the reduction in FC ($\mu mol/L^{-1}h^{-1}$) in the assay mixture.

CE transfer in plasma: The CE mass transfer, which measures the net transfer of preformed CE from HDL to the apo B-containing lipoproteins in intact plasma, was measured as described by Bagdade et al., in which freshly drawn plasma was incubated at 37 ºC in a shaking water bath in the presence of 5,5'-dithiobis (2-nitro-benzoic acid) (DTNB) (final concentration of DTNB was 1.5 mmol/L) to inhibit LCAT (14). Aliquot samples of plasma were removed after 2 and 4 h of incubation and chilled on ice, and VLDL + LDL were precipitated from plasma by using a combined dextran sulfate-magnesium chloride reagent (10 g dextran sulfate and 1.5 mol magnesium chloride/L) so that the final concentrations of the precipitant were 0.909 g/L dextran sulfate and 0.136 mol/L magnesium chloride. At each sampling interval the transfer of CE from HDL to apo B-containing lipoproteins

was determined by measuring the decrease in the mass of CE (mg/L) present in the supernatant containing HDL. The LCAT activity and CE transfer assays were performed in duplicate. The within-day coefficients of variation were 5.5% and 7.0% for LCAT and CE transfer rate, respectively.

Statistical analysis: Quantitative variables are expressed as mean ± SD. The data obtained for diabetics and controls were compared by Student's t-test. Pearson's correlation coefficients were used to test for relationships between variables. A p value of less than 0.05 was considered significant.

Results

The clinical features of the IDDM, NIDDM and control subjects are shown in Table 1. As expected, both fasting glucose and glycated hemoglobin (Hb A1c) levels were significantly increased in the diabetics.

Table 2 shows plasma lipid and lipoprotein concentrations in diabetic patients and healthy individuals. The plasma TC level of the diabetic patients was not statistically different from those of the control subjects. The plasma TG concentration was slightly higher in the diabetic groups compared with the respective control groups, but the differences were not statistically significant. Plasma HDL-cholesterol and HDL_2-cholesterol were significantly lower in IDDM patients compared with their control subjects. Plasma levels of FC and LDL-cholesterol were significantly higher ($p < 0.001$ and $p < 0.05$, respectively), while plasma HDL-cholesterol was significantly decreased ($p < 0.01$) in NIDDM patients compared to Control II subjects. This decrease occurred in both HDL subfractions. Plasma LCAT activity was reduced in IDDM and NIDDM patients ($p < 0.001$ for both), compared with their controls (Table 2).

CET responses of NIDDM subjects differed significantly from those of the non-diabetic controls. In the Control-II group, 21.6 ± 6.8 and 64.3 ± 20.6 mg of CE was transferred to VLDL and LDL at the 2 h and 4 h intervals, respectively. In the NIDDM group, however, the CE transfer rates under the same conditions were 27.0 ± 8.9 and 80.9 ± 20.1 mg of CE transferred to VLDL and LDL, significantly greater at both sampling intervals ($p < 0.05$ and $p < 0.01$, respectively) than that found in the Control-II group (Figure 1). CE transfer to VLDL + LDL was also altered in the IDDM patients. In the Control-I group, 19.8 ± 7.7 and 50.2 ± 10.5 mg of CE was transferred to VLDL + LDL at the 2 h and 4 h intervals, respectively. In the IDDM group, the CE transfer rates were 21.6 ± 10.3 and 68.9 ± 30.0 mg/L. The net mass of CE transferred from HDL to VLDL + LDL was significantly greater than that in the Control-I group at 4 h ($p < 0.05$). The CE mass transferred at 2 h in the IDDM group was slightly higher than that in the Control-I group but the difference was not statistically significant ($p < 0.05$) (Figure 2).

Correlation analyses: The CE mass transferred at 4 h was correlated significantly with age ($r = 0.359$, $p < 0.05$) and HDL_2-C levels ($r = -0.320$, $p < 0.05$) in control subjects. In diabetic subjects, both plasma FC and VLDL-C were positively correlated with CE transfer rate at 4 h ($r = 0.338$, $p < 0.05$; $r = 0.337$, $p < 0.05$, respectively). LCAT activity was found to negatively correlate with plasma glucose concentration in diabetic patients ($r = -0.310$, $p < 0.05$).

Table 1. Characteristics of patients and control subjects.

Parameter	IDDM patients (n = 11)	Control I (n = 14)	p value	NIDDM patients	Control II (n = 42)	p value (n = 29)
Age (years)	28.0 ± 10.9	26.8 ± 7.1	-	58.0 ± 10.7	50.8 ± 8.9	-
Gender (F/M)	6/5	6/8	-	21/21	11/18	-
BMI (kg/m^2)	20.9 ± 1.8	23.0 ± 3.0	<0.05	26.4 ± 4.0	25.9 ± 2.6	NS
Glucose (mg/dL)	233 ± 88	83 ± 5	<0.001	193 ± 64	87 ± 8	<0.001
HbA1c, %	10.6 ± 3.6	5.2 ± 0.5	<0.001	8.7 ± 2.2	5.0 ± 0.6	<0.001

BMI: Body mass index, HbA1c: Hemoglobin A1c, NS: Non-significant
Data are expressed as mean ± S.D.

Table 2. Plasma lipids in diabetics and control subjects.

Parameter	IDDM patients	Control I	p value	NIDDM patients	Control II	p value
TC (mg/dL)	170 ± 31	178 ± 33	NS	196 ± 35	186 ± 34	NS
FC (mg/dL)	43.6 ± 10.0	49.0 ± 14.4	NS	55.6 ± 12.7	47.1 ± 7.6	<0.001
CE (mg/dL)	126.7 ± 21.9	128.7 ± 20.9	NS	140.4 ± 25.3	138.7 ± 28.3	NS
FC/CE	0.344 ± 0.04	0.377 ± 0.07	NS	0.396 ± 0.07	0.347 ± 0.05	<0.001
HDL-C (mg/dL)	43.0 ± 7.7	50.6 ± 10.7	<0.05	44.3 ± 9.5	50.1 ± 9.9	< 0.01
HDL_2-C (mg/dL)	15.4 ± 3.3	19.8 ± 3.5	<0.01	16.8 ± 3.9	18.9 ± 3.3	<0.01
HDL_3-C (mg/dL)	27.6 ± 6.2	30.9 ± 8.1	NS	27.5 ± 6.4	31.2 ± 7.5	<0.05
LDL-C (mg/dL)	93 ± 27	103 ± 28	NS	117 ± 27	104 ± 29	<0.05
VLDL-C (mg/dL)	28 ± 10	24 ± 10	NS	34 ± 23	31 ± 14	NS
TG (mg/dL)	142 ± 48	121 ± 52	NS	170 ± 114	153 ± 69	NS
LCAT (μmol/L/h)	28.5 ± 14.8	59.5 ± 25.4	< 0.001	28.4 ± 14.9	46.8 ± 21.5	<0.001

Data are expressed as mean ± S.D.
TC: Total cholesterol, FC: Free cholesterol, CE: Cholesterol ester, HDL-, LDL-, VLDL-C: High, low, very low density lipoprotein-cholesterol, TG: Triglycerides, LCAT: Lecithin: cholesterol acyltransferase
NS: Non-significant

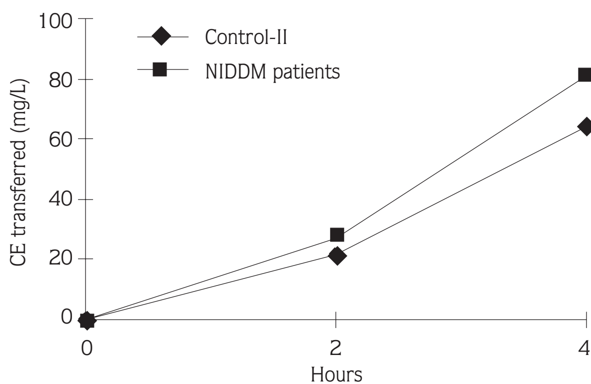

Figure 1. Mass of cholesterol ester (CE) transferred in plasma from HDL to VLDL + LDL in noninsulin dependent diabetes mellitus (NIDDM) patients and control subjects during a 4-h incubation at 37 °C.

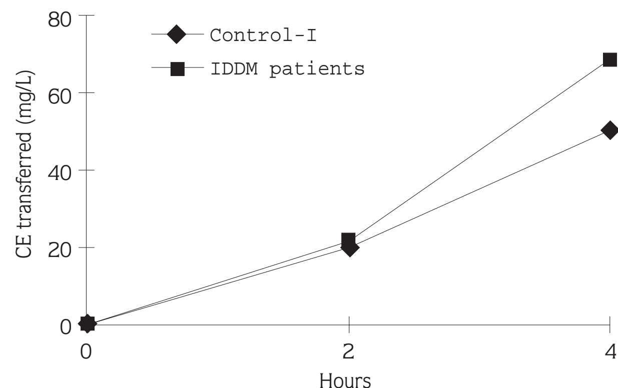

Figure 2. Mass of cholesterol ester (CE) transferred in plasma from HDL to VLDL + LDL in insulin dependent diabetes mellitus (IDDM) patients and control subjects during a 4-h incubation at 37 °C.

Discussion

Reverse cholesterol transport is a multi-step process including lipoproteins, enzymes and transport proteins. HDL plays a central role in this process. Free cholesterol taken up by HDL from peripheral tissue is esterified by LCAT. Thus, LCAT contributes to maintaining a concentration gradient of free cholesterol between peripheral tissues and HDL, and promotes cholesterol movement from tissue to HDL.

CETP mediates the transfer of CE and triglyceride between HDL and apolipoprotein B-containing lipoproteins. Inhibition of the transport may be atherogenic because the efflux of cholesterol from tissues would be retarded. On the other hand, promotion of this process is probably proatherogenic because CETP may lead to enrichment of apo B-containing lipoproteins with CE (15). An increased rate of CE transport has been postulated to be responsible for the higher risk of

atherosclerosis by various investigators (16-19). CETP activity has been reported to be normal or lower in diabetic patients (6,20). However, studies reporting the accelerated transfer of CE from HDL to apolipoprotein B-containing lipoproteins seem to be more common (14,15,21-25). The higher CE transfer rate observed in both types of diabetic patients in the present study is in agreement with the latter studies. This functional alteration was attributed to abnormalities in the concentration and composition (apolipoprotein E, FC and phospholipid, free fatty acid) of apo B-containing lipoproteins (26-30). Among other possible explanations are glycation of lipoproteins involved in CE transfer (31) and increased CETP mass at elevated plasma glucose concentrations (21,32). Several investigators have reported that high CE transfer protein activity is related to low plasma HDL-C levels in various conditions (16, 33-35) and may lead to the development of atherosclerosis. In the present study, we have demonstrated that cholesterol levels in HDL fraction and HDL_2 and HDL_3 subfractions were significantly lower in diabetic groups than in their respective controls ($p > 0.05$ in HDL_3 subfraction between type 1 diabetics and Control I). Although a decrement in HDL_2-C levels has been postulated to be responsible for the lower risk of coronary heart disease (CHD), it has been recently suggested that low levels of HDL_3 may also be associated with higher CHD risk (36).

Alterations in the reverse cholesterol transport have been described in a number of conditions carrying a high risk of atherosclerosis, such as diabetes. Chronic hyperglycemia in diabetic patients leads to nonenzymatic glycation of proteins including apo A-I (37). This modification of apo A-I results in a decrease of LCAT activity (38,39). It has been shown by Fournier et al. that LCAT reactivity decreased in both native diabetic HDL and in vitro glycated HDL (40).

There has been considerable controversy concerning the activity of LCAT in diabetes mellitus. Mattock et al. described increased activity of LCAT in diabetics (41), whereas Fielding et al. found decreased activity (42). On the other hand, Misra and Schernthaner reported that the LCAT activities of diabetic patients were similar to those found in controls (43,44). Weight and coworkers reported that although LCAT activity did not differ between poorly controlled type 1 diabetic patients and control subjects, a significant increase was observed in plasma LCAT activity with an improvement in metabolic control (45). In this study, we have demonstrated that LCAT activity was lower in both IDDM and NIDDM patients than in the control subjects. The discrepancies among the studies suggest that, in diabetes, HDL particles may be submitted to complex alterations, including compositional modifications. Results on compositional alterations in diabetic HDL are conflicting (14,40,46). Alterations in HDL lipid composition could have effects on LCAT activity, because it has been well established that the chemical and physical properties of the particle are critical in determining the enzymatic reaction rate (40).

In conclusion, the decrease in LCAT activity and the increase in CE transfer observed with both type 1 and type 2 diabetics may be associated with a reduction in reverse cholesterol transport and contribute to the development of atherosclerosis in patients with diabetes mellitus.

Acknowledgment

This work was supported by the Uludağ University Research Fund.

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