Lipoprotein Alterations in Hemodialysis: Differences Between Diabetic and Nondiabetic Patients

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Both renal failure and type 2 diabetes may contribute synergistically to the dyslipemia of diabetic renal failure with the development of atherosclerosis as the possible consequence. It has not yet been conclusively evaluated whether diabetic patients with end-stage renal failure under maintenance hemodialysis (HD) show accentuated alterations in plasma lipids and lipoproteins in comparison to nondiabetics under HD. These abnormalities would involve hepatic lipase activity and the regulation of triglyceride-rich lipoprotein metabolism. The purpose of the present study was to evaluate whether type 2 diabetic patients undergoing HD exhibited a lipid-lipoprotein profile different from that of nondiabetic hemodialyzed patients. We compared plasma lipids, apoprotein (apo) A-I and B, and lipoprotein parameters among 3 groups: 25 type 2 diabetics, 25 nondiabetics, both undergoing HD, and 20 healthy control subjects. Intermediate-density lipoprotein (IDL) and low-density lipoprotein (LDL) were isolated by sequential ultracentrifugation. Hepatic lipase activity was measured in postheparin plasma. Both groups of HD patients showed higher triglyceride and IDL cholesterol ($P < .001$), and lower high-density lipoprotein (HDL) cholesterol ($P < .01$) and apo A-I ($P < .001$) levels compared to the control group, even after adjustment for age and body mass index (BMI). However, no differences were found in lipid, lipoprotein, and apoprotein concentrations between diabetic and nondiabetic HD patients, except for high LDL triglyceride content of diabetic HD patients ($P < .01$). Nondiabetics undegoing HD also presented higher LDL triglyceride levels than controls ($P < .05$). LDL triglyceride correlated with plasma triglycerides ($r = 0.51$, $P < .001$). A lower LDL cholesterol/apo B ratio was found in each group of HD patients in comparison to controls ($P < .02$). Comparing the diabetic and nondiabetic patients, hepatic lipase activity remained unchanged, but significantly lower than control subjects ($P < .001$). Hepatic lipase correlated with log-triglyceride ($r = -0.31$, $P < .01$), IDL cholesterol ($r = -0.41$, $P < .001$), and LDL triglyceride ($r = -0.32$, $P < .01$). In conclusion, both diabetic and nondiabetic HD patients shared unfavorable alterations in lipid-lipoprotein profile not different between them but different from a healthy control group. The only difference between the groups of HD patients was a significant LDL triglyceride enrichment, which correlated negatively with hepatic lipase activity. Lipoprotein abnormalities in HD patients would enhance their risk for the development of atherosclerosis.

PATIENTS WITH chronic renal failure undergoing hemodialysis (HD) treatment are known to be at accelerated atherosclerosis risk and have a high incidence of death due to cardiovascular disease.[1] In diabetic patients under HD, morbidity and mortality are still higher compared to nondiabetic patients.[2]

Impaired lipoprotein metabolism is often observed in patients with chronic renal failure under HD.[3] Patients receiving maintenance HD exhibit potentially atherogenic patterns of lipid abnormalities, which are mainly characterized by hypertriglyceridemia and low levels of high-density lipoprotein (HDL). Generally, an increase in apolipoprotein (apo) C-III is associated with triglyceride levels, because it is an inhibitor of lipoprotein lipase.[3] Hepatic lipase activity is also involved in this metabolic pathway, having an impact on intermediate-density lipoprotein (IDL) levels and low-density lipoprotein (LDL) composition, especially on the LDL triglyceride content.

On the other hand, type 2 diabetes without chronic renal failure is also associated with an increased risk of coronary artery disease, which might be due, at least in part, to abnormalities in lipid and lipoprotein metabolism.[4] Diabetic dyslipemia consists of multiple lipoprotein disorders; the most typical findings are high triglyceride concentration and reduced HDL cholesterol. However, there may be other frequent abnormalities, such as IDL accumulation and atherogenic disturbances of LDL composition, not necessarily with elevated plasma lipid levels.[5] It was recently reconfirmed that IDL plays an important role in coronary artery disease in type 2 diabetic patients.[6]

A previous study[7] showed that type 2 diabetic patients undergoing HD have elevated serum apo B, prominent reduction in serum apo A-I, and a higher apo B/apo A-I ratio compared to nondiabetic HD patients, indicating that lipid abnormalities are accentuated in diabetic end-stage renal disease patients under HD. The study measured low hepatic lipase activity, but the investigators did not evaluate IDL or LDL in relation to enzyme activity. Another study found no differences in any of the lipid and lipoprotein variables studied between diabetic and nondiabetic patients undergoing maintenance HD; the type of diabetic patients included was not clear.[8]

It seems that both renal failure and type 2 diabetes may contribute synergistically to the dyslipemia of diabetic renal failure with the development of atherosclerosis as the possible consequence. It has not yet been conclusively determined whether diabetic patients with end-stage renal failure under

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Table 1. Clinical Characteristics of Diabetic and Nondiabetic Patients Undergoing HD and Healthy Controls

	Controls	Nondiabetic HD Patients	Diabetic HD Patients
No. of subjects (M/F)	20 (10/10)	25 (16/9)	25 (13/12)
Age (yr)	29 ± 1.83	41 ± 2.07†	59 ± 2.45†‡
Duration of HD treatment (mo)*	—	3.5 (1-48)	11 (2-55)
BMI (kg/m^2)	23.75 ± 0.74	21.87 ± 0.95	26.63 ± 0.84†‡
Serum glucose (mg/dL)	86.3 ± 1.9	89.2 ± 2.20	144.3 ± 7.49†‡
Serum albumin (g/dL)	4.43 ± 0.09	3.98 ± 0.06	3.65 ± 0.09
Serum creatinine (mg/dL)	0.96 ± 0.04	10.53 ± 0.53†	9.18 ± 0.55†
Serum urea (mg/dL)	34.1 ± 1.05	163.1 ± 8.67†	172.3 ± 10.87†

NOTE. Data are expressed as the mean ± SEM or median (range).
$P < .05$ †*v* controls and ‡*v* nondiabetic HD patients.

maintenance HD show accentuated alterations on lipid-lipoprotein profile in comparison to nondiabetics on HD.

The purpose of the present study was to evaluate plasma lipids, apoproteins, and lipoprotein concentrations in type 2 diabetic and nondiabetic patients undergoing HD. Because hepatic lipase plays an important role in regulating triglyceride-rich lipoprotein metabolism and in generating LDL with abnormal composition, we determined hepatic lipase activity and its relationship with LDL triglyceride content.

MATERIALS AND METHODS

We studied 50 Caucasian patients with end-stage renal disease receiving maintenance HD, 25 of whom suffered from type 2 diabetes, while the other 25 patients were nondiabetic. Diabetic nephropathy was diagnosed clinically when the following criteria were fulfilled: persistent albuminuria, presence of diabetic retinopathy, and no clinical or laboratory evidence of other kidney or renal tract disease. The nondiabetic patients with chronic renal failure had chronic glomerulosclerosis (n = 3), polycystic kidney disease (n = 5), interstitial nephritis (n = 4), nephrosclerosis secondary to hypertension (n = 5), and other unknown etiologies (n = 8).

Twenty nondiabetic subjects without renal disease and dyslipemia were studied as healthy controls. The clinical characteristics of patients and controls are shown in Table 1.

The patients were treated with antihypertensive drugs (angiotensin receptor blockers or calcium channel blockers, not with beta-blockers or adrenergic antagonist).

Fourteen diabetic patients were receiving insulin once or either twice daily (at 8 AM and 9 PM). Insulin dose was 10 to 35 IU; none of the patients were treated with oral hypoglycemic agents, because impaired renal function may result in greatly reduced excretion of these drugs, leading to drug accumulation and thus increasing the risk of hypoglycemia and other adverse events.

Patients followed a standard diet for HD treatment, containing 1.2 g proteins/kg body weight/d and 35 cal/kg/d, phosphate binders, and vitamins as appropriate. Healthy controls followed a varied diet with calorie intake according to individual body weight.

The patients were dialyzed with conventional low-flux HD treatment, for at least 4 hours, 3 times per week using bicarbonate-containing dialysis fluid. The blood flow, dialysate flow rate, dialyzer model, and treatment time were tailored to individual patients to achieve the target equilibrated urea KT/V of 1.20.

Exclusion criteria for both HD patients and controls were liver dysfunction, or thyroid or acute infectious diseases. None of the subjects received corticosteroids, immunosuppressive agents, or drugs known to influence lipid metabolism. In no case did alcohol consumption surpass 15 g/d; 5 patients and 4 controls consumed from 2 to 6 cigarettes per day, and the remaining subjects had been nonsmokers for the last 10 years. Patients and controls did not follow a regular exercise training program. Considering high blood pressure over 140/90 mm Hg, 13 of 25 nondiabetic HD and 19 of 25 diabetic HD patients showed increased blood pressure.

Informed consent was obtained from all participants. This study was approved by the Ethical Committee of the School of Pharmacy and Biochemistry of Buenos Aires University.

Blood Sampling

Blood samples were drawn after a 12-hour overnight fast by antecubital venipuncture. In the patient groups, blood was obtained after the longest interdialysis interval, prior to the initiation of HD. Serum was separated by centrifugation at 3,000 rpm for 15 minutes within 1 hour of having been extracted; disodium EDTA, 1.5 mg/mL of serum, and 0.1 mg/mL of sodium azide were added to inhibit lipoprotein peroxidative degradation and bacterial growth. Serum was kept at 4°C until its processing, within 48 hours.

After blood sampling, heparin (60 UI/kg body weight) was administered intravenously for the determination of hepatic lipase activity. Ten minutes later, blood obtained by venipuncture of the contralateral arm was collected in tubes on ice. Postheparin plasma was obtained by centrifugation at 2,500 rpm at 4°C for 10 minutes and kept at −70°C until its processing within 30 days.

Analytical Procedures

Total cholesterol and plasma triglycerides were determined in a Hitachi 727 autoanalyzer by enzymatic methods, standardized by Boehringer Mannheim (Mannheim, Germany), with standards and controls in each run. The intra-assay coefficient of variation (CV) of total cholesterol was 1.11% and the interassay CV, 2.10 %. Triglycerides intra-assay CV was 1.32% and interassay CV, 2.55%. LDL cholesterol and HDL cholesterol were determined by precipitation[9,10] and enzymatic measurement of cholesterol in the supernatant.

Serum apo B and A-I levels were measured by electroimmunoassay (Hidragel, Sebia, France).

IDL (d = 1.006 to 1.019 g/mL) and LDL (d = 1.019 to 1.063 g/mL) were isolated by sequential preparative ultracentrifugation in a Beckman XL-90 ultracentrifuge using a fixed-angle rotor type 70.1 Ti. Each run was performed at 105,000 × g, for 18 hours at 15°C. EDTA was present throughout all the steps of the isolation procedure. Purity of each lipoprotein fraction was tested by agarose gel electrophoresis. Cholesterol was assessed in IDL and LDL and triglyceride in LDL by the methods previously mentioned.

Enzyme Assay

Hepatic lipase activity in postheparin plasma was determined by measuring the oleic acid produced by the enzyme-catalyzed hydrolysis of a triolein emulsion carrying a [^{3}H]triolein radiolabel (Amersham

Table 2. Serum Lipid Analysis of HD Patients and Controls

	Controls	Nondiabetic HD Patients	Diabetic HD Patients
Triglycerides	79 ± 7.37	171 ± 16.19*	196 ± 21.32*
Cholesterol	192 ± 7.21	193 ± 9.86	202 ± 11.05
HDL cholesterol	54 ± 3.03	43 ± 2.76†	41 ± 3.11†
LDL cholesterol	119 ± 7.54	105 ± 6.61	117 ± 7.14
IDL cholesterol	4.0 ± 0.39	10.0 ± 0.88*	10.0 ± 1.06*

NOTE. Data are expressed in mg/dL of serum, mean ± SEM.

$P < .05$ *v controls by Kruskal Wallis ANOVA, †v controls by 1-way ANOVA and Dunnett; all adjusted for age and when necessary by BMI.

TRA.191; Amersham, Buckinghamshire, UK). To selectively measure the activity of hepatic lipase, lipoprotein lipase was inhibited by 1 mol/L NaCl as previously reported.[11] [^{3}H]oleic acid was quantitated using a Liquid Scintillation Analyzer (Packard 210TR; Packard Instruments, Meridian, CT), and expressed as micromoles of free fatty acids (FFA) per milliliter of postheparin plasma times hour. Using triplicate analysis, the intra-assay CV was 4% and observed interassay CV, 9%. Due to the complexity of this assay, the CV is considered to be satisfactory.

Statistical Analysis

Results are expressed as mean ± SEM and differences were considered significant at P less than .05. Differences between groups were tested using unpaired Student's t test or Mann-Whitney U test as appropriate. Correlations between variables were assessed using the Pearson or Spearman test. Mean differences among groups were performed by 1-way analysis of variance (ANOVA), and Kruskal Wallis ANOVA as required; when a statistically significance difference was noted, further evaluation was done with Tukey or Dunnett multiple comparison tests. Multiple regression analysis were performed to assess adjustments significance by age and body mass index (BMI). All analyses were performed using STATA software (Intercooler STATA 6 for Windows, STATA Corp, TX).

RESULTS

No differences were found in lipid-lipoprotein concentration between diabetic and nondiabetic HD patients. However, both groups of patients showed higher plasma triglyceride and IDL cholesterol ($P < .001$), and lower HDL cholesterol ($P < .01$) levels than the control group, even after adjustment for age and BMI (Table 2).

As shown in Table 3, there were no differences in apo A-I and apo B concentrations between HD patients, although apo A-I decreased and apo B/A-I ratio increased in patients in comparison to healthy controls ($P < .001$), even after controlling for age and BMI. Ratios of LDL cholesterol/apo B and HDL cholesterol/apo A-I were calculated as estimators of alterations in lipoprotein composition. A lower LDL cholesterol/apo B ratio was found in both groups of HD patients in comparison to controls ($P < .02$).

Table 3. Serum apo A-I and B, apo B/apo A-I, HDL Cholesterol/apo A-I, and LDL Cholesterol/apo B Ratios in HD Patients and Controls

	Controls	Nondiabetic HD Patients	Diabetic HD Patients
apo A-I	166 ± 9.39	128 ± 3.92*	135 ± 5.80*
apo B	79 ± 4.96	89 ± 5.12	93 ± 6.82
apo B/apo A-I	0.49 ± 0.03	0.70 ± 0.04*	0.69 ± 0.04*
HDL cholesterol/apo A-I	0.34 ± 0.03	0.34 ± 0.02	0.30 ± 0.02
LDL cholesterol/apo B	1.52 ± 0.28	1.21 ± 0.31*	1.27 ± 0.44*

NOTE. apo A-I and apo B are expressed in mg/dL, mean ± SEM.

*$P < .05$ *v* controls by 1-way ANOVA and Dunnett; all adjusted for age and when necessary by BMI.

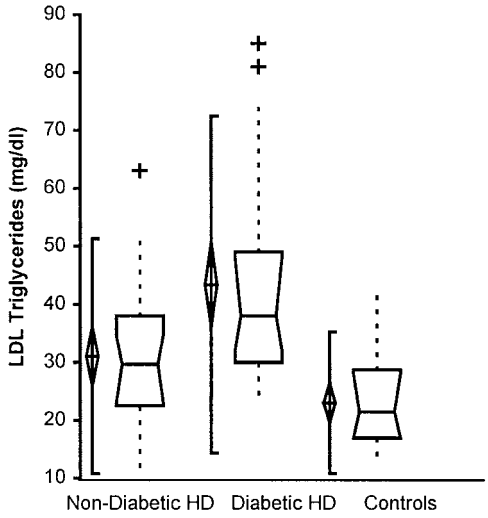

Fig 1. Box and whisker plot showing median, 25th to 75th percentile, and mean (diamond, 95% confidence interval) of LDL triglycerides in nondiabetic HD patients (n = 25), diabetic HD patients (n = 25), and controls (n = 20). Diabetic *v* nondiabetic HD patient, $P < .01$; diabetic HD patients *v* controls, $P < .0001$; and nondiabetic HD patients *v* controls, $P < .05$.

Regarding LDL composition, LDL isolated from diabetic HD patients showed higher triglyceride content, not only against controls ($P < .0001$), but also against nondiabetic HD patients ($P < .01$). On the other hand, nondiabetic HD patients also presented LDL triglyceride levels significantly higher than controls ($P < .05$) (Fig 1). These results indicate an LDL triglyceride enrichment, which remained high after controlling by multiple regression analysis. LDL triglyceride content correlated positively with plasma triglyceride concentration ($r = 0.51$, $P < .001$).

Between the diabetic and nondiabetic patients, hepatic lipase activity remained unchanged, but a statistically significant decrease was exhibited in comparison to enzyme activity of control subjects, $P < .001$ (Fig 2). Taking into account the 3 groups, linear regression analysis showed that hepatic lipase correlated negatively with log-transformed plasma triglycerides ($P < .01$), with IDL cholesterol ($P < .001$), and with LDL triglycerides ($P < .01$)(Fig 3). No correlation was found between hepatic lipase and HDL cholesterol ($r = 0.02$, $P = .86$), LDL cholesterol ($r = 0.06$, $P = .63$), nor HDL cholesterol/apo A-I ($r = -0.07$, $P = .5$) or LDL cholesterol/apo B ratios ($r = 0.16$, $P = .2$).

DISCUSSION

This study was designed to determine whether type 2 diabetic patients undergoing HD exhibited a plasma lipid-lipopro-

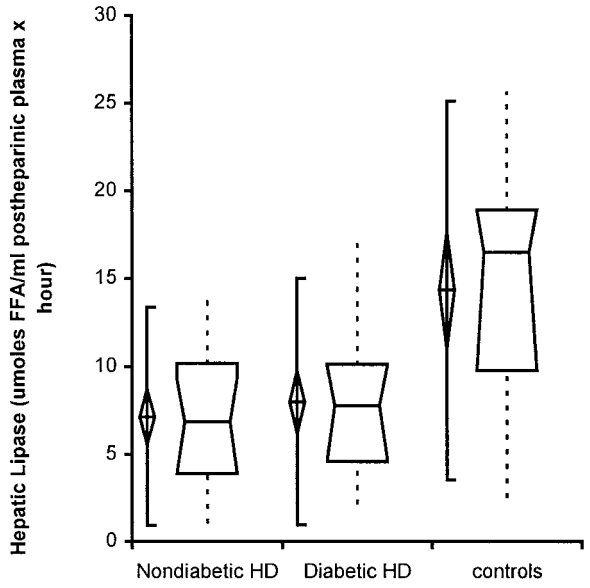

Fig 2. Box and whisker plot showing median, 25th to 75th percentile, and mean (diamond, 95% confidence interval) of hepatic lipase in nondiabetic HD patients (n = 25), diabetic HD patients (n = 25), and controls (n =20). Diabetic HD *v* nondiabetic HD patients, nonsignificant; diabetic and nondiabetic HD patients *v* controls, *P* < .001.

tein profile different from nondiabetic HD patients. Both groups of patients showed alterations not different between them but different from a healthy control group. One of our main findings is that the only difference between the groups of HD patients was a significant LDL triglyceride enrichment, which correlated negatively with hepatic lipase activity.

Given that the control group was younger than HD patients and that diabetic patients presented higher BMI, multiple regression analysis was performed to assess the influence of age and BMI on the variation of plasma lipids and lipoprotein concentration, when necessary.

As expected, HD patients showed higher triglyceride and lower HDL cholesterol concentrations,[3,7] prominent characteristics of lipid abnormalities associated with uremic patients. Beyond these parameters, IDL cholesterol was higher in HD patients than in controls, in accordance with the findings of others.[12,13] These investigators found that IDL cholesterol was elevated in uremic patients even independently of the presence of hyperlipemia. Elevated IDL level strongly correlates with the extent and progression of angiographically assessed coronary atherosclerosis.[14] Thus, the increased IDL cholesterol in the HD population constitutes an atherogenic lipoprotein change.

On the other hand, it is well known that IDL cholesterol is increased in nonuremic type 2 diabetic patients.[15] However, in the present study, nondiabetic patients undergoing HD also showed an increase in IDL cholesterol in comparison to healthy controls.

Taking into account that hepatic lipase plays an important role in regulating triglyceride-rich lipoprotein metabolism, we measured the enzyme activity and investigated its association with several lipoprotein parameters, such as IDL cholesterol. There is little information about the relationship between lipolytic enzymes and IDL cholesterol in HD patients. In this study, IDL cholesterol correlated inversely with hepatic lipase activity, consistent with previous findings obtained by Oi et al.[16]

Despite the increased hepatic lipase activity in type 2 diabetes, probably related to high insulin fasting levels,[17] our results demonstrated that both diabetic and nondiabetic HD patients showed a decrease in hepatic lipase activity. Although the

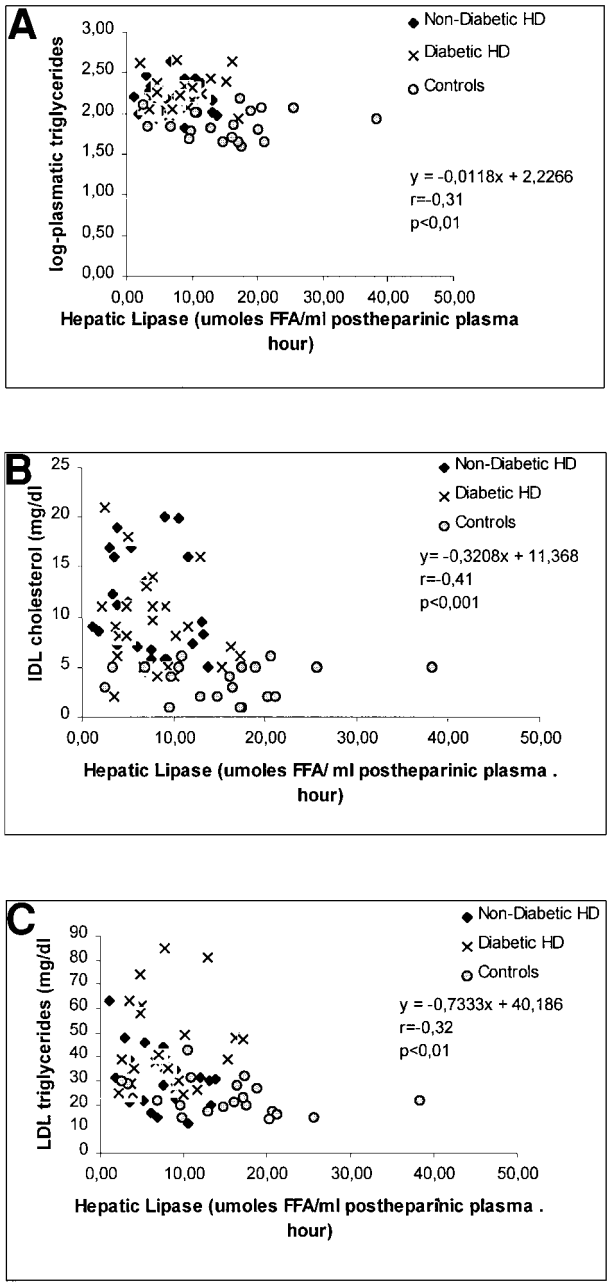

Fig 3. Correlation between hepatic lipase activity *v* (A) log-transformed plasmatic triglycerides, (B) IDL cholesterol, and (C) LDL triglycerides, in patients and controls (n = 70).

cause is not clear, Klin et al[18] have provided evidence that in chronic renal failure there is a downregulation of mRNA of the enzyme and impairment of hepatic lipase production, activity, and release. On the other hand, other investigators have suggested that low hepatic lipase activity is associated with metabolic alterations due to renal failure, such as impaired calcium metabolism,[19] or with the presence of plasma inhibitors.[20]

Another consequence of the decrease in hepatic lipase activity would be the abnormal composition characteristic of LDL, since LDL triglyceride content increased in HD patients. This feature was previously reported by Attman et al,[21] although they included type 1 diabetic patients. In our study, triglycerides LDL content correlated negatively with hepatic lipase activity. Some studies performed on patients with hepatic lipase deficiency showed high triglyceride in LDL enrichment.[22] Similarly, LDL produced in vitro by the action of muscular lipoprotein lipase but not hepatic lipase, on very-low-density lipoprotein (VLDL) or IDL, also showed an abnormal increase in triglycerides.[23] All of these data show the importance of hepatic lipase in the formation of typical LDL particles. In addition, Zambon et al[24] found a negative correlation between hepatic lipase activity and the presence of larger and more buoyant LDL particles, both in men with coronary artery disease and in normal subjects. As size particle was not measured, it cannot be stated whether the triglyceride-rich LDL from HD patients were large and buoyant or small and probably dense.

On the other hand, the increase in LDL triglyceride could also be attributed to triglyceride and cholesteryl esters exchange between LDL and HDL or VLDL, and this process has been shown to be accelerated in hypertriglyceridemia,[25] as seen in uremic patients. Thus, a significant positive correlation between LDL triglyceride and plasma triglycerides was observed in this study.

The high content of triglyceride in LDL is one of the factors known to change the spatial disposition of apo B epitopes, affecting the interaction with LDL receptors[26] and favoring the atherogenic properties of the lipoprotein. It is important to note that a qualitative alteration in LDL chemical composition such as LDL triglyceride enrichment was the only difference we found between the lipid-lipoprotein profile of diabetic and nondiabetic HD patients.

Profound alterations of lipoprotein profile and lipoprotein composition can also be frequently seen, including content of apoprotein A-I and B. Unlike others,[7] we have demonstrated that diabetic HD patients showed apo A-I and apo B concentrations similar to nondiabetic HD patients. However, apo A-I was lower and apo B/apo A-I ratio higher in both groups of patients in comparison to controls. The decrease in apo A-I and increase in apo B/apo A-I ratio were in accordance with the decrease in HDL cholesterol and, for this reason, HDL cholesterol/apo A-I ratio did not change. Nevertheless, based on these results, it is not possible to state that HDL from HD patients does not show an abnormal composition, not even among type 2 diabetic patients, already reported to have abnormalities in HDL composition.[27] HD patients may have an increase in triglyceride in their HDL,[19] which is greater in diabetic patients.[28] Quantitative and qualitative alterations in HDL particles may be directly related to the reduced catabolism of triglyceride-rich lipoproteins.

It is also important to note that HDL did not correlate inversely with hepatic lipase activity as expected. Most probably, uremic patients have delayed HDL metabolism with reduced formation and retarded maturation of HDL subfractions based on lower activity of lipoprotein-lipase rather than the activity of hepatic lipase on HDL particles.[19]

The results obtained when LDL cholesterol/apo B ratio was calculated revealed that LDL is not only trigliceride-rich but also cholesterol-depleted. This ratio is considered an estimator of the extent of small dense LDL particles. In this study, LDL cholesterol/apo B ratio was found to be lower in both groups of HD patients than in controls, probably due to the high plasma trigliceride levels in the patient groups. Other reports showed that small dense LDL predominated in chronic renal failure patients.[29] An increasing number of studies have shown a connection between small dense LDL subclass and coronary artery disease.[30]

It must be also taken into account that increased oxidative modification of LDL may be implicated in the etiology of accelerated atherosclerosis in chronic renal failure. However, based on the current data, it is unclear whether there are differences in the degree of oxidative modification of LDL from HD patients.[31,32]

Although diabetes itself may impair lipoprotein metabolism, the present findings did not allow us to conclude that type 2 diabetic patients with chronic renal failure undergoing HD presented more prominent abnormalities on their lipoprotein profile, except greater LDL triglyceride enrichment. Therefore, both diabetic and nondiabetic HD patients showed unfavorable changes in serum lipid-lipoprotein, which tend to be treated not only with diet, but also with drugs such as statins in order to lower the enhance risk of premature death from cardiovascular disease.

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