Utility of Non–High-Density Lipoprotein Cholesterol in Hemodialyzed Patients

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Non–high-density lipoprotein-cholesterol (HDL-C) is proposed as a strong predictor of cardiovascular disease (CVD). Measuring non–HDL-C, as total cholesterol minus HDL-C, is convenient for routine practice because, among other advantages, fasting is not required. There are limited data of non–HDL-C in end-stage renal disease patients. We applied non–HDL-C calculation to 50 chronic renal patients receiving maintenance hemodialysis (HD) and 20 healthy subjects, apart from measurement of low-density lipoprotein (LDL), very–low-density lipoprotein (VLDL) HDL, intermediate-density lipoprotein-cholesterol (IDL-C), apoprotein (apo) B, and triglycerides. HD patients presented higher plasma triglycerides and IDL-C and lower HDL-C than the control group, even after adjustment for age ($P < .05$). VLDL-C increased in HD patients ($P < .001$) while differences in non–HDL-C did not reach significance ($P = .08$). To detect which parameter constitutes a better marker of CVD risk among HD patients, a receiver-operating characteristic (ROC) analysis was performed considering HD patients in the highest risk group for CVD. In the ROC graphic, the plots of VLDL and IDL-C exhibited the greater observed accuracy and the best performance, while non–HDL-C showed a curve close to the 45° line indicating that this parameter is a poor discriminator for evaluating CVD risk among HD patients. Non–HDL-C calculation, expressing all apo B-containing lipoproteins, may miss the significant contribution of each atherogenic lipoprotein, such as increase in IDL. This observation would not be in agreement with the currently proposed application of non–HDL-C a useful tool for risk assessment among HD patients.
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CARDIOVASCULAR DISEASE (CVD) is currently the primary cause of morbidity and mortality in patients with chronic renal failure under hemodialysis (HD). We have demonstrated recently that HD patients showed unfavorable alterations in the plasma lipid-lipoprotein profile, consisting of high triglycerides and intermediate-density lipoprotein-cholesterol (IDL-C), low high-density lipoprotein-cholesterol (HDL-C), and decreased hepatic lipase activity associated with low-density lipoprotein (LDL) triglyceride enrichment.[1] All of these alterations remained significant even after adjustment for age and body mass index (BMI).

After National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) recommendations,[2] very–low-density lipoprotein-cholesterol (VLDL-C) is also considered an important target of cholesterol-lowering therapy, and thus the sum of LDL-C + VLDL-C + IDL-C (termed non–HDL-C) constitutes a secondary target of therapy in persons with high triglycerides. Recently, The Strong Heart Study showed that non–HDL-C is a strong predictor of CVD in men and women with type 2 diabetes.[3]

Non–HDL-C can be calculated as total cholesterol minus HDL-C, constituting a practical advantage because of the possibility of being assessed in patients with triglyceride levels >400 mg/dL or in those who are not fasting. It must be taken into account that it is frequently difficult to obtain adequate fasting samples from patients under HD.

The finding of an increase prevalence of atherogenic lipoproteins in HD patients, even with normal LDL-C, leads us to consider non–HDL-C as a useful parameter for assessing CVD risk in this population. Recommendations for the use of non–HDL-C in HD patients arises from extrapolations from the general population, given that there are limited data of non–HDL-C in end-stage renal disease patients.

The purpose of this study was to evaluate the utility of non–HDL-C in predicting cardiovascular outcome in chronic renal patients receiving HD.

MATERIALS AND METHODS

We applied non–HDL-C calculation to 50 chronic renal patients receiving maintenance HD and 20 healthy subjects. The patients were dialyzed with conventional low-flux HD treatment for at least 4 hours, 3 times per week using bicarbonate-containing dialyzed fluid. HD patients showed high prevalence of CVD without presenting myocardial infarction or stroke. Table 1 gives characteristics of the subjects. There were no differences in BMI between patients and controls. Half of HD patients were type 2 diabetics, however no important differences were found in lipid, lipoprotein, and apoprotein concentrations between diabetic and nondiabetic HD patients.[1] The patients were treated with antihypertensive drugs (angiotensin receptor blockers or calcium channel blockers). Fourteen diabetic HD patients were receiving insulin (10 to 35 IU), but none was treated with oral hypoglycemic agents. Blood samples were drawn after a 12-hour overnight fast. In the patient groups, blood was obtained after the longest interdialysis interval, prior to the initiation of dialysis. Total cholesterol and triglycerides were determined in a Hitachi 727 autoanalyzer (Tokyo, Japan) by enzymatic methods, standardized by Boehringer-Mannheim (Mannheim, Germany). LDL-C and HDL-C were performed by precipitation,[4,5] VLDL-C was determined by substracting HDL-C from supernatant obtained after LDL precipitation and non–HDL-C was calculated by substracting HDL-C from total cholesterol. These parameters were determined under good quality control (coefficient of variation routinely <3%). IDL-C was measured after isolating IDL by ultracentrifugation (1.006 to 1.019 g/mL).

Statistical Analysis

Results are expressed as mean ± SEM and differences were considered significant at $P < .05$. Differences between groups were tested using unpaired Student′s t test for the clinical characteristics and analysis of covariance (ANCOVA) with age as covariate for the lipid-lipoproteins parameters. Receiver-operating characteristic (ROC) was

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

	Controls	HD Patients
Gender (M/F)	10/10	29/21
Age (yr)	29 ± 1.83	50 ± 1.89*
Duration of HD treatment (mo)	—	8 (1-55)
BMI (kg/m^2)	23.75 ± 0.74	24.20 ± 0.72
Serum albumin (g/dL)	4.4 ± 0.09	3.8 ± 0.06*
Serum creatinine (mg/dL)	0.96 ± 0.04	9.87 ± 0.39*
Serum urea (mg/dL)	34 ± 1.05	167 ± 6.88*

NOTE. Data are expressed as mean ± SEM or median (range).
Abbreviations: HD, hemodialysis, BMI, body mass index.
*$P < .0001$ *v* controls.

Table 2. Serum Lipid and Lipoproteins of HD Patients and Controls

	Controls	HD Patients
Triglycerides	79 ± 7.37	183 ± 13.20*
Cholesterol	192 ± 7.21	198 ± 7.27
HDL-C	54 ± 3.03	42 ± 2.04*
LDL-C	119 ± 7.54	111 ± 5.99
IDL-C	4 ± 0.39	10 ± 0.69*
VLDL-C	20 ± 1.54	45 ± 3.10*
Non–HDL-C	138 ± 7.69	156 ± 7.18

NOTE. Data are expressed in mg/dL of serum as mean ± SEM.
*$P < .05$ *v* controls, adjusted by ANCOVA with age as covariate.

performed; it is a graphic representation of the relationship between sensitivity and specificity for a diagnostic parameter, and it was drawn through potential points that represented different decision levels, considering the area under the ROC curve as a display of the performance of the test, with the larger the area the better the test. The curves of several lipid-lipoprotein parameters were plotted on the same graphic representation to allow comparison. The ROC analysis was based on the prediction of the HD versus control status of participants, assuming that HD status represents a high CVD risk condition.[6]

RESULTS AND DISCUSSION

As expected, Table 2 shows that HD patients presented higher plasma triglycerides and IDL-C and lower HDL-C than the control group, even after adjustment for age. VLDL-C increased in HD patients ($P < .05$), while differences in non–HDL-C did not reach significance ($P = .08$). However, significant correlations were found between non-HDL and LDL-C ($y = 0.745x + 0.8368$, $r = 0.89$), apoprotein B ($y = 0.3229x + 38.86$, $r = 0.54$), IDL-C ($y = 0.0571x - 0.3252$, $r = 0.52$), triglycerides ($y = 1.0538x - 5.2812$, $r = 0.53$), and VLDL-C ($y = 0.255x - 0.8368$, $r = 0.55$), $P < .001$ for all subjects.

To detect which of the studied parameters constitute a better marker of CVD risk among end-stage renal disease patients, a ROC analysis was performed. It is noteworthy that HD patients have a very high prevalence of CVD and, according to the recent guidelines of the National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (K/DOQI), patients with chronic kidney disease should be considered CVD equivalents for risk factor management.[6] Therefore, the ROC curves were plotted considering the 50 HD patients and the 20 healthy controls. In Fig 1, the plots of IDL-C, as well as VLDL-C, exhibited the greater observed accuracy and the best performance, while non–HDL-C showed a curve close to the 45° line indicating that this parameter is a poor discriminator for evaluating CVD risk among end-stage renal disease patients under HD.

Although non–HDL-C comprises all apoprotein B-containing triglyceride-rich lipoprotein particles, when calculated, non–HDL-C in HD patients did not allow appreciating the known lipoprotein variations, such as increases in VLDL-C or IDL-C. Moreover, non–HDL-C correlated best with LDL-C. This observation would not be in agreement with the currently proposed application of non–HDL-C as a useful tool for CVD risk assessment among HD patients.[7,8] Although significant

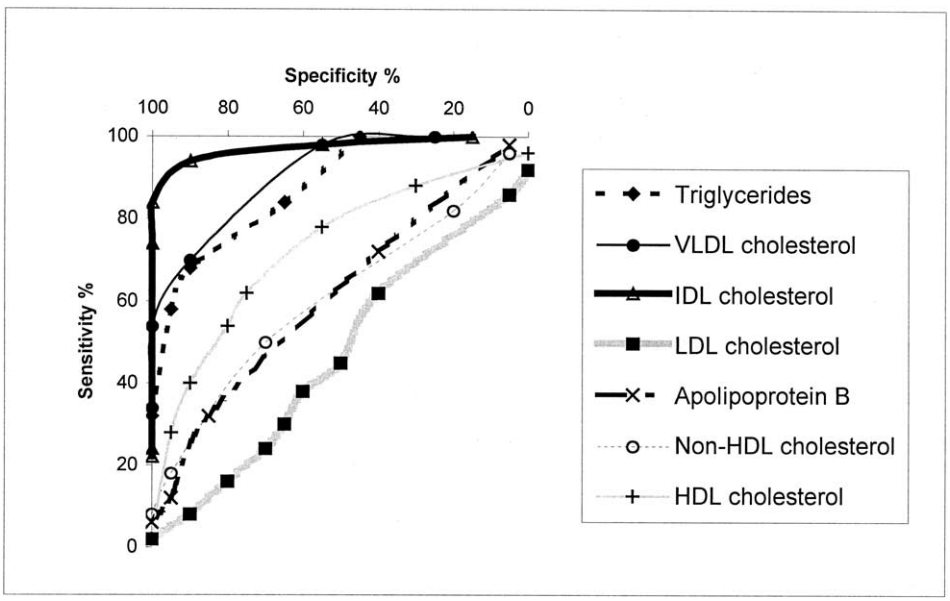

Fig 1. ROC curves for individual lipoprotein parameters based on 50 HD patients and 20 healthy controls.

differences in non–HDL-C were reported between end-stage renal disease patients and healthy controls, values were lower in the former, contrary to expectation.[9,10]

On the other hand, Nishizawa et al,[8] recently reported that non–HDL-C is an independent predictor of cardiovascular mortality by performing Kaplan-Meier curves in a cohort of HD patients, but they assumed that as they could not obtain sufficient information on cardiovascular morbidity at baseline, it was possible that preexisting CVD might have confounded the association between non–HDL-C and cardiovascular death during the follow-up.

Our results confirm the most characteristic feature of the dialysis-associated dyslipemia represented by an accumulation of heterogeneous triglyceride-rich lipoprotein particles including IDL. This lipoprotein, among other lipid-lipoprotein parameters, turned out to be an independent risk factor for atherosclerosis in the HD population.[11] On the other hand, VLDL-C also showed a good performance, and it can be assessed without ultracentrifugation methods, convenient for routine practice.

Non–HDL-C calculation, expressing all apoprotein B-containing lipoproteins, may miss the significant contribution of each atherogenic lipoprotein. Although it is convenient for routine practice, in part because overnight fasting is not required, non–HDL-C would represent mainly LDL-C, which is not the feature of lipid abnormalities in end-stage renal disease.

Perhaps, from a therapeutic point of view, considering the need of an aggressive treatment of lipoprotein abnormalities, establishing a non–HDL-C cut-off would be helpful to classify risk level and manage the dyslipemia.

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