Association of HDL cholesterol and triglycerides with mortality in patients with heart failure

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It has been demonstrated that there is an association between serum lipoproteins and survival rate in patients with ischemic cardiomyopathy, as well as in patients with non-ischemic causes of heart failure. We tested the hypothesis of an association between serum lipoprotein levels and prognosis in a cohort of outpatients with heart failure, including Chagas' heart disease. The lipid profile of 833 outpatients with heart failure in functional classes III and IV of the New York Heart Association, with a mean age of 46.9 ± 10.6 years, 655 (78.6%) men and 178 (21.4%) women, was studied from April 1991 to June 2003. The survival rate was estimated by the Kaplan-Meyer's method and the Cox proportional hazards models. Etiology of heart failure was ischemic cardiomyopathy in 171 (21%) patients, Chagas' heart disease in 144 (17%), hypertensive cardiomyopathy in 136 (16%), and other etiologies in 83 (10%). In 299 (36%) patients, heart failure was ascribed to idiopathic dilated cardiomyopathy. Variables significantly associated with mortality were age (hazard ratio, HR = 1.02; 95%CI = 1.01-1.03; P = 0.0074), male gender (HR = 1.77; 95%CI = 1.2-2.62; P = 0.004), idiopathic dilated cardiomyopathy (HR = 1.81; 95%CI = 1.16-2.82; P = 0.0085), serum triglycerides (HR = 0.97; 95%CI = 0.96-0.98; P < 0.0001), and HDL cholesterol (HR = 0.99; 95%CI = 0.99-1.0; P = 0.0280). Therefore, higher serum HDL cholesterol and higher serum triglycerides were associated with lower mortality in this cohort of outpatients with heart failure.

Introduction

Serum lipid and lipoprotein abnormalities have been reported in patients with heart failure (1-5). Low serum total cholesterol is associated with increased mortality in patients with systolic heart failure (6,7). A trend towards a significant relationship between higher serum lipoprotein levels and higher survival rate was suggested (3), but not confirmed (4). Specifically, HDL cholesterol was suggested to have antioxidant, anti-inflammatory and antithrombotic properties that would counteract pro-inflammatory activity in patients with heart failure (8-10).

We measured serum cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides in a cohort of outpatients with heart failure of different etiologies, including Chagas'

heart disease, followed from 1991 to 2003. This study was designed to test the hypothesis of an association between serum lipid protein profile and prognosis during a long-term follow-up and if high levels of HDL cholesterol and triglycerides can be protective in these patients.

Patients and Methods

Patients

We studied the lipid profile of 833 outpatients with heart failure referred for evaluation and ambulatory treatment of heart failure to the outpatient clinic of a tertiary care reference university public hospital, selected among 1400 referred patients (mean ± SD left ventricle ejection fraction on echocardiography 33.4 ± 4.6%; mean left ventricle

ejection fraction on radioisotopic ventriculography 22.3 ± 8.1%) in order to identify potential candidates for heart transplantation.

Inclusion criteria were patients under 75 years of age with a diagnosis of functional class III or IV (NYHA) heart failure due to systolic dysfunction. Exclusion criteria were patients with hypertrophic cardiomyopathy, chronic obstructive pulmonary disease, recent myocardial infarction, and unstable angina. In addition, patients with severe renal or hepatic dysfunction, severe peripheral arterial disease, cerebrovascular disease, insulin-dependent diabetes mellitus with end-organ damage, active infection, coexisting neoplasm, and active peptic ulcer disease were also excluded, as were patients with severe co-morbidities that would make them ineligible for surgery or heart transplantation (11).

Definitions

Diagnosis of heart failure was made according to the Framingham criteria (12). Diagnosis of the etiology of cardiomyopathy followed previously published criteria (13, 14). Chagas' heart disease was defined as patients with heart failure due to left ventricular systolic dysfunction and positive serologic tests. The association of etiologies such as ischemic and hypertensive cardiomyopathy was considered to be ischemic cardiomyopathy.

Clinical assessment protocol. Patients were referred to the outpatient clinic after diagnosis and stabilization of heart failure. After clinical evaluation, serum cholesterol was evaluated in 833 (59.5%) patients, HDL cholesterol in 722 (51.5%), LDL cholesterol in 720 (51.4%), VLDL cholesterol in 720 (51.4%), and serum triglycerides in 828 (59.1%).

Medical treatment was further optimized with medical advice regarding everyday living and drug therapy, including captopril and enalapril, furosemide and digoxin available at the Hospital Outpatient Clinic pharmacy. Carvedilol was progressively introduced after 1998. Statin therapy was not routinely administered.

Follow-up

Follow-up was assessed on the occasion of the last outpatient medical visit or by telephone contact. Patients with missed appointments at the outpatient clinic were actively contacted by means of telephone calls. In addition, the mortality database of the São Paulo City Authority was also scrutinized to determine patient deaths (ProAim - Programa de Aprimoramento de Informações de Mortalidade do Município de São Paulo). During the 10-year follow-up period of the study, 80 patients (7%) underwent the first clinical evaluation and eventually were lost to follow-up.

For the purpose of this study, death was considered to be an event, and heart transplantation and other surgical interventions were defined as censored observations.

Statistical analysis

After exploratory analysis to identify variables associated with mortality, survival was estimated for each demographic, clinical and laboratory variable in order to identify variables significantly associated with the probability of survival. Unadjusted Kaplan-Meier curves were constructed (15) and survival probabilities were compared using log-rank and Breslow methods. For continuous variables, patients were divided into three balanced groups according to the terciles of distribution in order to avoid pre-established categorizations. In the next step, Cox proportional hazards models (16) were fitted to each variable.

The estimated hazard ratios (HR) were then obtained. Because of missing values, the sample considered was not the same for all models. The results are presented as number of cases, events and censored data, P values, HR and 95% confidence intervals (95%CI).

Ethics. The protocol was approved by the Institution Ethics Committee. Written informed consent was obtained from the patients after identification of potential candidates for heart transplantation.

Results

The etiology of heart failure was ischemic cardiomyopathy in 171 (20.5%) patients, Chagas' heart disease in 144 (17.3%), hypertensive cardiomyopathy in 136 (16.3%), and other etiologies in 83 (9.9%). In 299 (35.8%) patients, heart failure was ascribed to idiopathic dilated cardiomyopathy. Mean patient age was 46.9 ± 10.6 years; 655 (78.6%) were men and 178 (21.4%) were women. Ten patients were younger than 20 years, 58 were 20 to 30 years old, 140 were 30 to 40 years old, 295 were 40 to 50 years old, 69 were 60 to 70 years old, and 3 were 70 to 71 years old.

The mean (± SD) duration of symptoms before entry in the study was 49.1 ± 48.3 months, the mean duration of follow-up was 658.8 days (median 462, SD = 654.8, range 3-3584) for patients who died and 1202.8 days (median 1043.5, SD = 959.3, range 1-4801) for patients who survived the last contact.

Baseline characteristics relative to the etiologies of heart failure are shown in Table 1. Statistically significant differences were observed in relation to duration of the symptoms, age, heart rate, creatinine, body mass index, gender, serum glucose, and death. In the ischemic cardio-

myopathy group, the patients were older, they had a higher body mass index, lower duration of symptoms, and lower heart rate. In the group of patients with hypertensive cardiomyopathy, we observed fewer males and deaths. There was a significantly lower body mass index in patients with Chagas' cardiomyopathy compared with patients with heart failure of other etiologies (P = 0.0003). The other variables compared between Chagas' and non-Chagas' heart disease were not statistically different.

The highest mean values of serum HDL cholesterol, LDL cholesterol and serum triglycerides were observed in patients with hypertensive cardiomyopathy. The lowest mean values of HDL cholesterol were observed in patients

with heart failure due to ischemic cardiomyopathy and the lowest mean values of LDL cholesterol and serum triglycerides were observed in patients with heart failure due to all other etiologies. However, there were no statistical differences between the etiologies. Serum glucose was higher than 126 mg/dL in 137 patients (16.4%), and between 100 and 126 mg/dL in 247 patients (29.6%).

Subsequently, clinical variables and serum lipoprotein variables were tested relative to mortality using a Cox univariate model. The clinical variables associated with mortality were diastolic blood pressure (P = 0.0082), serum sodium (P < 0.0001), serum leukocyte count (P < 0.0001), serum creatinine (P < 0.0001), and serum uric

Table 1. Clinical characteristics of the patients relative to the etiology of heart failure.

Variable	Chagas' disease (N = 144)		Idiopathic (N = 299)		Hypertensive (N = 136)		Ischemic (N = 171)		Other (N = 83)		P
	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD	
Duration of symptoms (days)	106	1486±1277	228	1703±1666**	95	1238±1161*	131	1183±1174*	67	1567±1642	**0.008**[1]
Age (years)	144	46.2±10.5	299	45.9±10.5	136	47.7±0.1	171	49.6±10.2	83	45.2±11.4	**0.002**[1]
Gender											
Male	114		232		97		147		65		**0.040**[2]
Female	30		67		39		24		18		
Deaths	51	(35.4%)	114	(38.1%)	32	(23.5%)	67	(39.2%)	27	(32.5%)	**0.031**[2]
Body mass index (kg/m²)	63	23.2±3.5	163	24.7±4.4	83	25.2±4.4	106	25.9±4.7	36	23.8±5.0	**0.002**[1]
Systolic blood pressure (mmHg)	47	123.6±23.0	79	114.8±21.4	36	114.2±20.0	47	115.6±19.8	26	114.8±16.7	0.155[1]
Diastolic blood pressure (mmHg)	47	85.3±20.3	79	78.2±16.8	36	82.1±16.5	48	75.0±21.1	26	76.4±15.9	0.054[1]
Heart rate (bpm)	55	79.2±13.9	126	82.5±15.9	35	85.5±4.4	61	79.9±13.9	30	89.6±13.8	**0.007**[1]
Serum sodium (mmol/L)	140	138.7±3.6	286	138.7±3.7	130	139.2±3.5	160	139.0±3.5	79	138.9±3.1	0.679[1]
Hemoglobin (g/dL)	141	14.5±1.6	287	14.5±1.8	135	14.6±1.9	168	14.6±1.6	80	14.8±1.5	0.705[1]
Hematocrit (%)	141	43.6±4.8	287	44.2±5.7	135	44±5.9	168	44.3±4.8	80	44.4±4.7	0.756[1]
Leukocyte count per mm³	125	7617±2142	252	8048±2635	116	7699±2205	144	8230±2708	71	7831±2054	0.205[1]
Platelets (x 1000/mm³)	110	226.0±68.3	221	226.8±74.2	104	218.0±61.7	122	215.9±69.7	60	209±59.6	0.308[1]
Serum cholesterol (mg/dL)	144	194.1±46.6	299	195.6±46.9	136	201.6±46.4	171	199.8±42.2	83	190.6±51	0.360[1]
Serum triglycerides (mg/dL)	143	137.2±135.5	296	132.4±94.2	133	139.7±95.6	170	138.2±91.9	83	126.4±75.9	0.856[1]
HDL cholesterol (mg/dL)	129	41.8±13.3	257	41.4±14.8	116	42.4±13.7	144	38.8±12.7	76	42.9±15.6	0.175[1]
LDL cholesterol (mg/dL)	129	127.1±38.9	257	128.8±39	116	132.6±40.5	142	131±37	75	123.8±40.4	0.557[1]
VLDL cholesterol (mg/dL)	129	26±20.6	257	25.6±16.6	116	27.3±17.9	142	27.9±19	76	26.5±16	0.767[1]
Serum glucose (mg/dL)											
<100	72		141		65		79		52		
100-126	36		103		35		54		19		**0.016**[2]
>126	31		38		31		28		9		
Serum creatinine (mg/dL)	141	1.3±0.6	293	1.2±0.4	136	1.2±0.4	169	1.3±0.3	82	1.2±0.3	**0.026**[1]
Serum uric acid (mg/dL)	90	8.1±2.2	184	8.1±2.5	79	7.9±2.3	91	8.1±2.9	50	8.6±2.6	0.652[1]

Data are reported as number of patients and means ± SD. Measurements were made anytime during the transplant evaluation. Patients were followed for 905 + 846 days. P values in bold indicate statistically significant differences. [1]ANOVA and [2]chi-square test were used for statistical analysis.

acid (P < 0.0001) (Table 2). Lipid profile variables significantly associated with mortality were serum cholesterol (P < 0.0001), serum triglycerides (P = 0.045), HDL cholesterol (P < 0. 0001), and LDL cholesterol (P = 0.0075) (Table 2).

Lipid profile variables, gender, age, and etiology were submitted to multivariate analysis using a Cox proportional hazards model. The associations that remained significantly associated with mortality were HDL cholesterol (P =

0.0280), triglycerides (P < 0.0001), VLDL cholesterol (P = 0.0074), age (P = 0.0074), gender (P = 0.0040), and idiopathic dilated cardiomyopathy relative to hypertensive cardiomyopathy (P = 0.0085), which was the etiology associated with the lowest mortality (Table 3).

For each 1 mg/dL increase of HDL cholesterol there was a 1% decrease in mortality, and for each 1 mg/dL increase of triglycerides there was a 4% decrease in mortality.

Discussion

Our data demonstrated that higher serum HDL cholesterol and triglycerides were associated with lower mortality in a cohort of outpatients with symptomatic heart failure of different etiologies. Previous reports in the literature with small samples, a predominance of patients with ischemic etiologies of heart disease and different statistical analysis of serum cholesterol and lipoproteins did not detect a significant relationship between HDL cholesterol and survival rate of patients with heart failure including Chagas' heart disease (3,4,6,7,17).

In fact, a protective role for HDL cholesterol in patients with heart failure observed in our patients may be explained on the basis of the endotoxin-lipoprotein hypothesis, which suggests that serum lipoproteins modulate inflammatory immune function (6) and that HDL cholesterol has antioxidant, anti-inflammatory and anti-thrombotic properties (10,18).

The hypothesis that HDL cholesterol can be a marker of coronary artery disease might influence our findings was evaluated by adjusting etiologies and testing for interaction between covariates such as HDL cholesterol relative to ischemic heart disease. Higher mean serum HDL cholesterol was observed in patients with hypertensive cardiomyopathy and in patients with heart failure grouped as other etiologies (valvular cardiomyopathy, alcoholic cardiomyopathy, peripartum cardiomyopathy, myocarditis, adriamycin toxicity, endomyocardial fibrosis, late postoperative aortic dissection). The lowest mean serum HDL cholesterol was detected in patients with heart failure due to ischemic cardiomyopathy. First-order interactions of etiology with the other covariates including HDL cholesterol were tested in the final model and revealed a non-significant interaction at the 5% level of significance (P = 0.2512).

Table 2. Univariate survival analysis.

Univariate analysis	Number of cases	P	Hazard ratio	95%CI
Duration of symptoms (days)	625	0.3100	1.00	(1.00-1.00)
Age (years)	829	0.0360	1.01	(1.00-1.02)
Body mass index (kg/m^2)	449	0.6500	0.99	(0.96-1.02)
Systolic blood pressure (mmHg)	233	0.9500	1.00	(0.99-1.01)
Diastolic blood pressure (mmHg)	234	0.1600	0.99	(0.97-1.00)
Heart rate (bpm)	307	0.8100	1.00	(0.99-1.01)
Serum sodium (mEq/L)	791	<0.0001	0.92	(0.88-0.95)
Hemoglobin (g/dL)	807	0.8700	1.00	(0.94-1.08)
Hematocrit (%)	807	0.0510	1.02	(1.00-1.05)
Leukocytes (/mm^3)	704	<0.0001	1.00	(1.00-1.00)
Platelets (1000/mm^3)	616	0.7800	1.00	(0.99-1.00)
Serum cholesterol (mg/dL)	829	<0.0001	0.99	(0.99-0.99)
Serum triglycerides (mg/dL)	821	0.0450	0.99	(0.99-1.00)
HDL cholesterol (mg/dL)	719	<0.0001	0.97	(0.96-0.98)
LDL cholesterol (mg/dL)	716	0.0075	0.99	(0.99-0.99)
VLDL cholesterol (mg/dL)	717	0.0550	0.99	(0.98-1.00)
Serum glucose (mg/dL)	789	0.5700	1.00	(0.99-1.00)
Serum creatinine (mg/dL)	817	<0.0001	1.59	(1.32-1.92)
Serum uric acid (mg/dL)	490	0.0001	1.11	(1.05-1.18)

After exploratory analysis, clinical variables and serum lipoprotein variables were analyzed using univariate Cox proportional hazards model.

Table 3. Multivariate survival analysis.

Multivariate analysis	Coefficient (beta)	P	Hazard ratio	95%CI
Age (years)	0.0170	0.0074	1.02	(1.00-1.03)
Gender (female/male)	0.5727	0.0040	1.77	(1.20-2.62)
Chagas' disease/hypertensive	0.3993	0.1200	1.49	(0.90-2.45)
Idiopathic/hypertensive	0.5950	0.0085	1.81	(1.16-2.82)
Ischemic/hypertensive	0.4292	0.0780	1.54	(0.95-2.48)
Others/hypertensive	0.2469	0.4000	1.28	(0.72-2.26)
Serum cholesterol (mg/dL)	-0.0034	0.0930	0.99	(0.99-1.00)
Serum triglycerides (mg/dL)	-0.0334	<0.0001	0.97	(0.95-0.98)
HDL cholesterol (mg/dL)	-0.0043	0.0280	0.99	(0.99-1.00)
LDL cholesterol (mg/dL)	-0.0003	0.9700	1.00	(0.98-1.02)
VLDL cholesterol (mg/dL)	0.0170	0.0074	1.01	(1.00-1.03)

Gender, age, and etiology were fitted and lipid profile variables were analyzed using multivariate Cox proportional hazards model.

By contrast, in this study, serum cholesterol and LDL cholesterol did not remain significantly associated with mortality after multivariate analysis, as reported recently in a study of 422 patients with heart failure due to idiopathic dilated cardiomyopathy (17). The statistical treatment of serum cholesterol and lipoproteins as continuous variables in the present study might be responsible for this result. On the other hand, in previous experiences, serum cholesterol and LDL cholesterol were evaluated in quintiles (3), or serum cholesterol was evaluated in quartiles, or with a cut-off value of 5.2 mmol/L (4) or in tertiles (17).

We also demonstrated a statistically significant relationship between serum triglycerides and mortality, as previously reported (3,4,17). Further, we did not observe a statistically significant association between body mass index and mortality. This finding may be related to the fact that few patients with cardiac cachexia were included in the present study.

We have previously addressed the contribution of left ventricle ejection fraction as evaluated by echocardiography to prognosis (19). In the present study sample, we were not able to demonstrate that ejection fraction, estimated by echocardiography, predicts a less favorable outcome. Serum sodium level in this study sample was a significant prognostic factor in the univariate analyses, but this significance was lost in multivariate analysis.

Our findings further support the concept of an increase in HDL cholesterol as an additional therapeutic target for patients with severe heart failure. Recently, drugs that were meant to increase HDL cholesterol because of their effects as inhibitors of cholesteryl ester transfer protein (torcetrapib) have shown an increased risk of cardiovascular events (HR = 1.25; 95%CI = 1.09-1.44; P = 0.001) and death from any cause (20,21).

Limitations of study

This study was performed at a large outpatient clinic of a tertiary care university hospital. Thus, our observations were not made under strict protocol conditions. We were not able to control for specific drugs of medical therapy and it is interesting to notice that our sample was a large one, and our study was undertaken before routine statin therapy became more widely used in this clinical setting.

Thus, observations in this series may not be applicable to other populations. Patients with heart failure of different etiologies are also a limitation of the study.

In conclusion, we demonstrated that higher serum HDL cholesterol and serum triglycerides were associated with lower mortality in patients with heart failure of different etiologies.

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