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LIPID PROFILE OF CIRRHOTIC PATIENTS AND ITS ASSOCIATION WITH PROGNOSTIC SCORES: a cross-sectional study

Lílian **BASSANI**[1], Sabrina Alves **FERNANDES**[1], Fabiana Viegas **RAIMUNDO**[1], Daniele Lazzarotto **HARTER**[1], Maria Cristina **GONZALEZ**[2] and Cláudio Augusto **MARRONI**[1]

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ABSTRACT - ***Background*** **-** In cirrhosis the production of cholesterol and lipoproteins is altered. ***Objective*** **-** Evaluate the lipid profile by measuring total cholesterol, very low-density lipoprotein, low-density lipoprotein, high-density lipoprotein and triglyceride levels in patients with cirrhosis caused by alcoholism and/or hepatitis C virus infection and determine its association with Child-Pugh and MELD scores. ***Methods*** - Cross-sectional retrospective study of patients treated at the outpatient clinic in Porto Alegre, Brazil, from 2006 to 2010. ***Results*** **-** In total, 314 records were reviewed, and 153 (48.7%) met the inclusion criteria, of which 82 (53.6%) had cirrhosis that was due to hepatitis C virus infection, 50 (32.7%) were due to alcoholism, and 21 (13.7%) were due to alcoholism and hepatitis C virus infection. The total cholesterol levels diminished with a Child-Pugh progression (P<0.001). Child-Pugh C was significantly associated with lover levels of low-density lipoprotein (<70 mg/dL; P<0.001), high-density lipoprotein (<40 mg/dL; P<0.001) and triglyceride (<70 mg/dL; P=0.003). MELD≥20 was associated with lower total cholesterol levels (<100mg/dL; P<0.001), very low-density lipoprotein (<16 mg/dL; P=0.006), and low-density lipoprotein (<70 mg/dL; P=0.003). Inverse and statistically significant correlations were observed between Child-Pugh and all the lipid fractions analyzed (P<0.001). The increase in MELD was inversely correlated with reduced levels in total cholesterol (P<0.001), high-density lipoprotein (P<0.001), low-density lipoprotein (P<0.001), very low-density lipoprotein (P=0.030) and triglyceride (P=0.003). ***Conclusion*** - A reduction in the lipid profile in patients with cirrhosis due to hepatitis C virus infection and/or alcoholism was significantly associated with the Child-Pugh and MELD prognostic markers. These results suggest that the lipid profile may be used as a tool to assist in evaluating liver disease.

HEADINGS - Liver cirrhosis. Lipid metabolism disorders. Lipids. Prognosis.

INTRODUCTION

Hepatocytes play a critical role in regulating lipid metabolism. The liver is considered the primary site for cholesterol and lipoprotein synthesis. In healthy organisms, a complex balance is maintained between the biosynthesis, utilization and transport of lipid fractions. However, in cirrhosis, the lipid metabolism is altered such that glycogen reserves are substantially reduced, inducing lipolysis and malnutrition[2].

Previous studies have shown that patients with cirrhosis have an altered lipid metabolism, in particular hypocholesterolemia and hypobetalipoproteinemia[6, 15]. Such modifications evolve along with liver disease progression and can be used as a prognostic indicator for decompensated disease[9, 18, 19]. The mechanisms involved in the reduction of lipid fractions in cirrhotic patients are complex and will still require many studies to be fully understood. Enzymatic (acylCoA: cholesterol acyltransferase - ACAT), protein (microsomal triglyceride transfer protein - MTP) and apoprotein (Apo AI) reductions are thought to be related to such changes[12, 16, 20].

METHODS

A cross-sectional, retrospective study was conducted in which medical records were reviewed for 314 patients from the Gastroenterology outpatient clinic, at Santa Casa Hospital Complex of Porto Alegre, Porto Alegre, RS, Brazil, from January 2006 to June 2010.

Study participants were adult patients (≥18 years old) with cirrhosis due to either excessive alcohol consumption, hepatitis C virus (HCV) infection or both. Their diagnosis was made by way of clinical, histological or imaging exams. Excluded from the study were patients with hepatic steatosis, hepatocellular carcinoma, Wilson's disease, auto-immune

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[1] Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA), Porto Alegre, RS; [2] Universidade Católica de Pelotas (UCPEL), Pelotas, RS, Brasil.
Correspondence: Lílian Bassani. Alameda Jaú, 796, 400. São Paulo, SP, Brasil. E-mail: lilian@nutrililian.com.br

diseases, antibodies against human immunodeficiency virus (HIV), and other diseases that could interfere with the lipid metabolism (primary dyslipidemia, hypothyroidism, cystic fibrosis, chronic renal failure).

The following relevant data were extracted from the medical records: age, gender, etiology of cirrhosis, comorbidities, biochemical parameters [total cholesterol (TC), very-low density lipoprotein (VLDL), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglyceride (TG) levels] and Child-Pugh (A,B,C) and MELD (Model for End-Stage Liver Disease) prognosis scores.

The biochemical evaluations were collected and analyzed at the same location (Central Laboratory of the Santa Casa Hospital Complex of Porto Alegre, RS, Brazil) and on the same day. Only the results obtained after a 12-hour overnight fast were considered. The Child-Pugh and MELD prognostic scores were calculated during the same examination period.

The lipid profile was classified as follows: hypocholesterolemia was diagnosed based on TC <100mg/dL, VLDL <16 mg/dL LDL <70 mg/dL, or HDL <40 mg/dL, and hypotriglyceridemia was diagnosed based on TG <70 mg/dL. In respect to MELD, the patients were divided into the following groups: <15; 15-19; ≥20.

The study was approved by the Ethics Committee of the Federal University of Health Sciences of Porto Alegre [Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA)] under the protocol number 564/09 - 01/21/2010 and was performed according to the Declaration of Helsinki.

Data analysis was performed using the software SPSS (Statistical Package for the Social Sciences) version 17.0. Quantitative variables were described using their means and standard deviations. Categorical variables were described using their absolute and relative frequencies. Kolmogorov-Smirnov (distribution-type) and Levene (homogeneity of variances) tests were used to verify assumptions for use in parametric tests.

To compare means, one-way analysis of variance (ANOVA) with Tukey's post-hoc test was used. To evaluate the association between categorical variables, Pearson's chi-squared test was used in combination with testing for adjusted residuals. The test for adjusted residuals was performed after the chi-squared test when there was a significant association. The test for adjusted residuals was performed after the chi-squared test when it presented significant association in tables with more than two lines or columns (polytomous variables) to locate the association. This test has a standard normal distribution, and for a confidence level of 95%, values equal to or above 1.96 indicated a statistically significant association.

To evaluate the association between quantitative or qualitative ordinal variables, Pearson's (symmetric distribution) or Spearman's (asymmetric distribution) correlation coefficient was applied. The level of statistical significance was set at 5% ($P \leq 0.05$).

RESULTS

Medical records for 314 patients were reviewed, of which 153 (48.7%) met the inclusion criteria. Of the remaining 161 patients, 69 (22%) were excluded as they presented hepatic dysfunction due to other etiologies and 92 (29.3%) due to insufficient data.

The characterization of the patient sample is shown in Table 1. HCV (53.6%) was the most prevalent etiology. Most patients were male (62.1%), and the mean age was 59.3±9.4 years. Regarding the Child-Pugh score, approximately half of the patients (46.4%) had a score of A. For the MELD, only 17 patients (11.1%) had a score ≥20.

TABLE 1. Sample characteristics and clinical and demographic data

Characteristics	All	Alcohol	HCV	Alcohol/HCV	*P*-value
	153 (%)	50 (32.7%)	82 (53.6%)	21 (13.7%)	
Male - n (%)	95 (62.1)	44 (88.0)	31 (37.8)	20 (95.2)	<0.001[a]
Age - Mean ±SD	59.3 ± 9.4	58.8 ± 9.2	60.6 ± 9.0	55.6 ± 10.7	0.09[b]
Age group - n (%)					
<50	22 (14.4)	8 (16.0)	8 (9.8)	6 (28.6)	0.245[a]
50 - 59	57 (37.3)	19 (38.0)	29 (35.4)	9 (42.9)	
60 - 69	50 (32.7)	17 (34.0)	30 (36.6)	3 (14.3)	
≥70	24 (15.7)	6 (12.0)	15 (18.3)	3 (14.3)	
Child-Pugh - n (%)					
A	71 (46.4)	27 (54.0)	38 (46.3)	6 (28.6)	0.268[a]
B	48 (31.4)	14 (28.0)	27 (32.9)	7 (33.3)	
C	34 (22.2)	9 (18.0)	17 (20.7)	8 (38.1)	
MELD - Mean ± SD	13.5 ± 5.6	13.4 ± 5.2	13.1 ± 6.0	15.1 ± 4.7	0.342
<15	99 (64.7)	35 (70.0)	55 (67.1)	9 (42.9)	0.1[a]
15 - 19	37 (24.2)	8 (16.0)	20 (24.4)	9 (42.9)	
≥20	17 (11.1)	7 (14.0)	7 (8.5)	3 (14.3)	

[a] Pearson's chi-squared test; [b] Analysis of variance (ANOVA). MELD: Model for End-stage Liver Disease.

The associations between the Child-Pugh classification and lipid profile are described in Table 2 .The TC serum levels decreased significantly with disease progression as defined by the Child-Pugh score. Patients with Child-Pugh A scores had significantly higher VLDL serum levels (VLDL ≥16 mg/dL), whereas patients with Child-Pugh B and C scores had lower values (VLDL<16 mg/dL). Patients with Child-Pugh C scores had lower LDL and TG serum levels (<70 mg/dL), whereas the Child-Pugh A group had higher serum levels (≥100 mg/dL). Lower HDL levels (<40 mg/dL) were observed in patients with Child-Pugh C scores, whereas intermediate values (40-59 mg/dL) were observed in patients with Child-Pugh A scores.

Table 3 shows the associations between the MELD score and lipid profile. There was a significant association between MELD scores ≥20 and lower TC (<100 mg/dL), VLDL (<16

TABLE 2. Association between Child-Pugh score and lipid profile

Characteristics	All 153	Child-Pugh A 71 (46.4%)	Child-Pugh B 48 (31.4%)	Child-Pugh C 34 (22.2%)	*P*-value[a]
Cholesterol (mg/dL)					
Total					<0.001
<100	23 (15.0)	2 (2.8)	5 (10.4)	16 (47.1)[b]	
100 - 149	68 (44.5)	24 (33.8)	30 (62.5)[b]	14 (41.2)	
≥150	62 (40.5)	45 (63.4)[b]	13 (27.1)	4 (11.8)	
VLDL					<0.001
<16	83 (54.2)	25 (35.2)	32 (66.7)[b]	26 (76.5)[b]	
≥16	70 (45.8)	46 (64.8)[b]	16 (33.3)	8 (23.5)	
LDL					<0.001
<70	66 (43.1)	18 (25.4)	24 (50.0)	24 (70.6)[b]	
70 - 99	49 (32.0)	25 (35.2)	18 (37.4)	6 (17.6)	
≥100	38 (24.9)	28 (39.4)[b]	6 (12.6)	4 (11.8)	
HDL					<0.001
<40	47 (30.7)	10 (14.1)	13 (27.1)	24 (70.6)[b]	
40 - 59	81 (53.0)	48 (67.6)[b]	24 (50.0)	9 (26.5)	
≥60	25 (16.3)	13 (18.3)	11 (22.9)	1 (2.9)	
TG					0.003
<70	60 (39.2)	18 (25.4)	23 (47.9)	19 (55.9)[b]	
70 - 99	56 (36.6)	27 (38.0)	19 (39.6)	10 (25.4)	
≥100	37 (24.2)	26 (36.6)[b]	6 (12.5)	5 (14.7)	

[a] Pearson's chi-squared test; [b] Statistically significant association based on adjusted residuals testing ($P<0.05$). VLDL: very low density lipoprotein; LDL: low density lipoprotein; HDL: high density lipoprotein; TG: triglycerides.

TABLE 3. Associations between MELD score and lipid profile

Characteristics	All 153 (%)	MELD <15 99 (64.7%)	MELD 15-19 37 (24.2%)	MELD ≥20 17 (11.1%)	*P*-value[a]
Cholesterol (mg/dL)					
Total					<0.001
<100	23 (15.0)	5 (5.1)	9 (24.3)	9 (52.9)[b]	
100 - 149	68 (44.4)	41 (41.4)	20 (54.1)	7 (41.2)	
≥150	62 (40.5)	53 (53.5)[b]	8 (21.6)	1 (5.9)	
VLDL					0.006
<16	83 (54.2)	45 (45.5)	24 (64.9)	14 (82.4)[b]	
≥16	70 (45.8)	54 (54.5)[b]	13 (35.1)	3 (17.6)	
LDL					0.003
<70	66 (43.1)	32 (32.3)	21 (56.8)	13 (76.5)[b]	
70 - 99	49 (32.0)	36 (36.4)	11 (29.7)	2 (11.8)	
≥100	38 (24.8)	31 (31.3)[b]	5 (13.5)	2 (11.8)	
HDL					<0.001
<40	47 (30.7)	15 (15.2)	18 (48.6)[b]	14 (82.4)[b]	
40 - 59	81 (52.9)	64 (64.6)[b]	15 (40.5)	2 (11.8)	
≥60	25 (16.3)	20 (20.2)	4 (10.8)	1 (5.9)	
TG					0.061
<70	60 (39.2)	34 (34.3)	15 (40.5)	11 (64.7)	
70 - 99	56 (36.6)	35 (35.4)	16 (43.2)	5 (29.4)	
≥100	37 (24.2)	30 (30.3)	6 (16.2)	1 (5.9)	

[a] Pearson's chi-squared test; [b] statistically significant association based on adjusted residuals testing ($P<0.05$). VLDL: very low-density lipoprotein; LDL: low-density lipoprotein; HDL: high-density lipoprotein; TG: triglycerides.

mg/dL) and LDL (<70 mg/dL) values, whereas higher values were associated with MELD scores <15. The groups with higher MELD scores (15-19 and ≥20) were associated with HDL <40 mg/dL, whereas MELD scores <15 were associated with intermediate HDL levels (40-59 mg/dL).

The correlations between lipid profiles and prognostic scores are shown in Table 4. Statistically significant and inverse correlations were observed between the Child-Pugh and all lipid fractions analyzed (P<0.001). The increase in MELD was inversely correlated with reduced levels of TC (P<0.001), HDL (P<0.001), LDL (P<0.001), VLDL (P=0.030) and TG (P=0.003).

DISCUSSION

This study showed that low TC, VLDL, LDL, HDL and TG serum levels are associated with increased hepatic impairment. Hypocholesterolemia and hypotriglyceridemia are both significantly associated and correlated with the Child-Pugh and MELD prognostic criteria. These findings were consistent with previous studies that showed changes in lipid metabolism in advanced stages of cirrhosis[1, 13, 21].

The liver plays a central role in regulating the synthesis, degradation and storage of cholesterol and lipoproteins. TC and lipoproteins have been shown to decrease with the progression of fibrosis and, further, with the onset of cirrhosis. This change in lipid levels can be used to estimate prognosis in cirrhotic patients[9, 12, 18].

A reduction in TC serum levels is believed to be a consequence of decreased synthesis or partial blockage of the same esterification processes, likely due to a decline in the production of the enzyme ACAT (acylCoA:cholesterol acyltransferase)[12, 16]. Decreased VLDL levels are associated with deficiencies in the microsomal triglyceride transfer protein (MTP) and a partial inhibition of cholesterol synthesis[14]. The formation of LDL is directly related to the production of VLDL and, when the metabolism of this lipoprotein is impaired, the other downstream lipid fractions also undergo changes[18]. The drop in HDL levels suggests that there is a strong correlation between prognosis and decreased synthesis of Apoprotein AI (Apo AI), the major HDL lipoprotein[10].

The prognosis of cirrhosis depends on the etiology, severity of illness, and presence of associated diseases and complications. Various laboratory and clinical evaluation systems have been developed over the years to assist in staging liver disease. The Child-Pugh classification and MELD score are among the most widely used systems[11]. The MELD score has been used as a prioritization measure for patients on liver transplantation waiting lists[3, 7] and is considered an independent predictor of morbidity[17] and mortality for cirrhotic patients[4, 5].

By analyzing the associations between the Child-Pugh classification and lipid profile, we found that the Child-Pugh score was significantly associated with a reduced lipid profile. Patients with Child-Pugh C scores had lower TC, VLDL, LDL, HDL (P<0.001) and TG (P<0.003) levels. These results were consistent with the findings reported by Cicognani[6] who evaluated TC, VLDL, LDL and HDL levels in patients with chronic hepatitis and cirrhosis and correlated them with disease severity (Child-Pugh score). The results showed that significant reductions in TC, LDL and HDL levels were observed in patients with cirrhosis compared with other groups (chronic hepatitis and control). This reduction was related to disease progression (Child-Pugh C classification). D'Arienzo[8] assessed the prognostic role of hypocholesterolemia in patients with advanced cirrhosis and observed a gradual decrease in plasma cholesterol in 34 patients with viral cirrhosis, Child-Pugh C classification. All patients with TC levels <100 mg/dL died within 17 months, whereas 75% of patients with TC levels >100 mg/dL survived at least 2 years.

The association between reductions in lipid profile and progression of MELD score was significant for all the lipid fractions except TG, which was reduced in patients with MELD scores >20. The inverse correlations between the prognostic criteria (Child-Pugh and MELD scores) and lipid markers were significant. A study conducted with patients with decompensated cirrhosis found that TG, TC, HDL and LDL levels decreased as the MELD score increased. A MELD score ≥21 and a TC level ≤108 mg/dL were considered independent prognostic factors of a survival time of less than 1 year in patients with cirrhosis[12]. Attempting to confirm and quantify the predictive value of TC and TG levels in cirrhotic patients, Janicko[3] conducted a study with 191 patients. The results suggested that the TC level was a significant marker of mortality, independent of other predictive measures (INR, bilirubin, creatinine, MELD). Habib[10] analyzed 413 patients with cirrhosis of different etiologies and reported that the need for liver transplantation within 1 year was higher in patients with HDL levels <30 mg/dL. In addition, the author reported a significant correlation between HDL level, biochemical markers (albumin, bilirubin and INR) and MELD score.

The present study had several limitations. The results were based on information from a single center, with a small

TABLE 4. Correlations between lipid profile and Child-Pugh and MELD prognostic scores

Variables	Pearson correlation	TC	VLDL	LDL	HDL	TG
Child-Pugh	r_s	-0.553	-0.333	-0.448	-0.442	-0.333
	P-value	<0.001	<0.001	<0.001	<0.001	<0.001
MELD	r	-0.574[a]	-0.236	-0.422[a]	-0.599[a]	-0.236
	P-value	<0.001	0.030	<0.001	<0.001	0.030

r: Pearson correlation coefficient; r_s: Spearman correlation coefficient; [a]regular association (0.3 to 0.6); TC: total cholesterol; VLDL: very low-density lipoprotein; LDL: low-density lipoprotein; HDL: high-density lipoprotein; TG: triglycerides.

sample size, and focused mainly on patients with Child-Pugh C classification and MELD scores ≥20. Although the absence of a control group prevented us from comparing these findings to other populations, the lack of a control group did not affect the proposed results when analyzed from the viewpoint of cirrhotic patients. The study design made it impossible to evaluate the results using a prognostic approach, given that the patients were evaluated in cross-section. However, the data highlighted the importance of long-term lipid profile evaluation in patients with cirrhosis.

The reduced lipid profiles in patients with cirrhosis due to HCV infection and/or alcoholism were significantly associated with the Child-Pugh and MELD prognostic markers. These results suggested that the lipid profile could be used as an auxiliary tool in evaluating liver disease, given that there were statistically significant differences in these levels using instruments validated for this purpose. There is a need to perform additional larger scale studies to verify its applicability in cirrhosis due to other etiologies.

Authors' contributions

Bassani L participated in the planning and coordination of the study, analysis, interpretation of results and writing the article. Fernandes SA, Raimundo FV, Harter DL, and Gonzalez MC collaborated with planning the study, data collection and data entry, discussion and writing. Marroni CA contributed to the conception of the study, discussion and critical editing of content and approval of its final version.

Bassani L, Fernandes SA, Raimundo FV, Harter DL, Gonzalez MC, Marroni CA. Perfil lipídico de pacientes cirróticos e sua associação com escores prognósticos: um estudo transversal. Arq Gastroenterol. 2015,52(3):210-5.

RESUMO - ***Contexto*** **-** Na cirrose a produção de colesterol e de lipoproteínas está alterada. ***Objetivo*** - Avaliar o perfil lipídico - através da dosagem do colesterol total, lipoproteína de muito baixa densidade, lipoproteína de baixa densidade, lipoproteína de alta densidade e triglicerídeos - de pacientes com cirrose, por álcool e/ou vírus da hepatite C, e verificar sua associação com os escores Child-Pugh e MELD. ***Métodos*** - Estudo transversal, retrospectivo de pacientes em acompanhamento ambulatorial no Complexo Hospitalar Santa Casa de Porto Alegre, Brasil, no período de 2006 a 2010. ***Resultados*** - Foram revisados 314 prontuários, destes 153 (48,7%) preencheram os critérios de inclusão, sendo que 82 (53,6%) tinham cirrose por vírus da hepatite C, 50 (32,7%) por álcool e 21 (13,7%) por álcool e vírus da hepatite C. Os níveis de colesterol total reduziram com a progressão do Child-Pugh (P<0,001). Child-Pugh C associou-se significativamente aos níveis mais baixos de lipoproteína de baixa densidade (<70 mg/dL; P<0,001), lipoproteína de alta densidade (<40 mg/dL; P<0,001) e triglicerídeos (<70 mg/dL; P=0,003). MELD≥20 esteve associado aos menores valores de colesterol total (<100 mg/dL; P<0,001), lipoproteína de muito baixa densidade (<16 mg/dL; P=0,006), lipoproteína de baixa densidade (<70 mg/dL; P=0,003). Correlações inversas e estatisticamente significativas foram observadas entre Child-Pugh e todas as frações lipídicas analisadas (P<0,001). O aumento do MELD esteve correlacionado inversamente com a redução do colesterol total (P<0,001), lipoproteína de alta densidade (P<0,001), lipoproteína de baixa densidade (P<0,001), lipoproteína de muito baixa densidade (P=0,030) e triglicerídeos (P=0,003). ***Conclusão*** **-** A redução do perfil lipídico, nos pacientes com cirrose por vírus da hepatite C e ou álcool, associou-se significativamente com os marcadores de prognóstico Child-Pugh e MELD. Tais resultados sugerem que o perfil lipídico poderá ser utilizado como uma ferramenta para auxiliar na avaliação da hepatopatia.

DESCRITORES - Cirrose hepática. Transtornos do metabolismo dos lipídeos. Lipídeos. Prognóstico.

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