Obstructive Coronary Disease in Patients with Chronic Liver Disease Awaiting Liver Transplantation

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Abstract

Background: Advanced liver failure (ALF) usually presents hypocholesterolemia. Nevertheless, some patients with ALF develops major coronary obstructive diseases with consequent increased risk or contraindication to liver transplantation.

Objective: To analyze the contribution of classical risk factors for coronary artery disease (CAD) in patients with ALF with and without obstructive coronary disease.

Methods: Evaluation of risk factors for CAD in 119 patients in a referral center for liver transplantation, with the following characteristics: patients older than 40 years of age with ALV who underwent coronary angiography.

Results: Obstructive coronary disease was detected in 21 (17.6%) of the cases. These patients had really low cholesterol levels, of which 129.0 ± 53.5 mg/dl averaging 117.0 mg/dl in liver disease patients with normal coronary arteries and 135.4 ± 51.7 mg/dl averaging 122.0 mg/dl in liver disease patients with obstructive coronary artery disease (P = 0.8215). In multivariate logistic regression, age, sex, body mass index and the presence of diabetes, smoking and alcohol consumption were not statistically significant in distinguishing groups. Nor was there an association with the etiology of the ALF. In turn, hypertension was proven to be relevant in association with CAD (P = 0.0474).

Conclusion: Only hypertension was a risk factor with statistical significance for the development of CAD in patients with ALF awaiting liver transplantation. Because it is a modifiable risk factor, this finding guides the practice of therapeutic attitudes in an attempt to prevent or delay the development of CAD in these patients. (Arq Bras Cardiol 2011; 96(1): 26-30)

Keywords: Coronary artery disease; liver transplantation; risk factors.

Introduction

Coronary artery disease (CAD) is the most common cause of myocardial ischemia, which may culminate in myocardial infarction, and it is the leading cause of death in western civilization. CAD is characterized by the formation of fatty deposits (atheroma) on the arteries wall, gradually blocking their light, especially in medium-sized arteries, among which are the coronary arteries[1].

Risk factors for CAD include hypercholesterolemia, increased levels of low-density lipoproteins (LDL) in the plasma, smoking, hypertension, diabetes, obesity, sedentary lifestyle, increased serum triglycerides levels, genetic predisposition, age and male sex, among which hypercholesterolemia stands out[1].

High levels of LDL are also capable of increasing the adhesion capacity of circulating monocytes, which adhere to damaged endothelial cells, are attracted by chemotaxis into the subendothelial region, accumulate and become macrophages, which phagocytize LDL until they become foam cells. These macrophages are also responsible for the release of several growth factors that act on smooth muscle cells and fibroblasts, forming more connective tissue and leading to fibrous plaques.

A third action of high levels of LDL occurs on platelets. After endothelial injury, due to the retraction of endothelial cells, platelets may come into contact with the foam cells, which culminates with the adhesion, aggregation, and finally the formation of a mural thrombus, which occludes the artery lumen. That whole cycle that leads to formation of atheromatous plaques can be repeated continuously, providing progressive occlusion of the vessel[1].

Liver failure, however, is a disease characterized by severe loss of liver function due to some type of disturbance such as viral hepatitis, cirrhosis and liver disease due to drug or alcohol[2].

The liver is the most active cholesterol metabolism place, and in cases of advanced liver failure, loss of function of this organ leads to reduced plasma cholesterol.

Mortality from liver failure ranges from 40 to 80%, and liver transplantation is the only therapeutic option capable of providing the patient with this disease a significant improvement in survival[3]. Transplantation is the established treatment for advanced liver disease and liver failure. Therefore, in the United States 4000 liver transplants are performed annually[4].

Liver cirrhosis can be of alcoholic origin. It is known that a moderate intake of alcohol has beneficial effects on atherosclerosis, by raising levels of high-density lipoprotein (HDL) in the plasma, which would be a contradiction to the occurrence of coronary artery disease in patients with liver failure. The role of HDL is to do the reverse cholesterol transport, leading it from the tissue to the liver, where it is metabolized and excreted[1]. This explains why an appropriate level of HDL reduces the risk for atherosclerosis.

Based on these data, it would not be expected to find atherosclerosis in patients with liver failure awaiting liver transplantation. However, we found an overall prevalence of 16.2% of severe coronary artery disease (obstruction greater than 70% obstruction of the coronary arteries) in patients older than 50 years in the preoperative evaluation for liver transplantation, diagnosed by catheterization[5]. Plotkin et al[6] found, based on cardiac catheterization and dobutamine stress echocardiography, 5% of significant coronary artery disease (with obstruction of 70% or more of the coronary arteries) in patients older than 40[6].

It is known that the surgical mortality of patients with chronic liver disease undergoing liver transplantation is higher in the presence of obstructive coronary disease, and that mortality from cardiovascular disease continues to express itself in the post-operative period of patients who underwent transplantation[7].

Although coronary artery disease in patients diagnosed in the preoperative evaluation for liver transplantation is often considered an absolute contraindication, it does need not necessarily to be seen as such, but we know that the risks of morbidity and mortality in liver transplants in patients with coronary artery disease increase significantly, and they are also high in cases where transplant is performed after drug or surgical treatment of coronary artery disease[8]. However, there is no definition as to which risk factor best predicts the presence of obstructive coronary artery disease in patients with advanced liver failure[9].

The purpose of this study was to analyze patients with advanced liver failure with and without a diagnosis of coronary artery disease associated, to seek risk factors that could justify the development of obstructions.

Materials and methods

We reviewed medical records of 119 patients older than 40 suffering from advanced liver failure (ALF), who awaited in line for a liver transplant and who had undergone cardiac catheterization as part of preoperative clinical assessment procedures. The protocol of clinical assessment pre-liver transplantation at our institution included cardiac catheterization in all patients older than 40, since the stress test is often not feasible in this group. Moreover, they are often using vasodilators and beta-blockers.

This review was performed to seek the presence or absence of risk factors for coronary heart disease factors. The factors considered were: age, sex, hypertension, diabetes, body mass index (BMI), smoking, alcohol consumption, total serum cholesterol, HDL, LDL and triglycerides, as well as the cause of liver failure.

To calculate the frequency with which coronary artery may occur, we considered only patients with coronary artery with 50% light occlusion or more of at least one main branch compromised.

In the statistical analysis, the continuous quantitative variables with Gaussian distribution were studied with the aid of Student's t test, while the nominal (or ordinal) qualitative or quantitative variables without Gaussian distribution were studied with the aid of Fisher's exact test or Mann-Whitney's test. The evaluation was complemented with a multiple logistic regression test.

Cohort levels were: total cholesterol above 200 mg/dl, HDL below 40 mg/dl, LDL above 130 mg/dl and triglycerides above 150 mg/dl. Hypertensive patients were considered those with systolic blood pressure of 140 mmHg or greater; or diastolic blood pressure of 90 mmHg or greater; or those using antihypertensive medication. Diabetic patients were defined as those with glucose levels above 126 mg/dl or using oral hypoglycemic agents or insulin. Current smokers were those who smoked any amount of cigarettes or those who had quitted less than one year prior to coronary angiography. Alcohol drinkers were those who consumed more than two servings of alcohol a day. For use in logistic regression, age was considered by 55 (0) and more than 55 years (1); BMI was considered up to 29.9 kg/m^2 (0) and 30 or more kg/m^2 (1). The lipid values were not included in the logistic regression, because as a rule, they were often well below the maximum limits of normality.

To analyze the causes of advanced liver failure, patients were divided into four groups: carriers of viruses (including hepatitis B virus, hepatitis C virus, or both), and alcoholics, patients with a combination of virus and alcohol, and patients with idiopathic or cryptogenic liver failure. An alpha error of 5% was assumed. $P \leq 0.05$ was considered significant. The study was approved by the Ethics Committee of the Institution.

Results

The occurrence of coronary disease in 119 patients aged 40 and patients with advanced liver failure was 17.6% (21 of the cases).

Sex and serum levels of cholesterol and its fractions were not a significant risk factor for the emergence of obstructive coronary disease. It was shown that patients with advanced liver failure had really low levels of cholesterol. On the one hand, the group of normal patients, the mean and standard deviation for total cholesterol was 129.0 ± 53.5 mg/dl with

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a median of 117.0 mg/dl. On the other hand, in the group of coronary patients, these values were respectively 135.4 ± 51.7 mg/dl with a median of 122.0 mg/dl (P = 0.8215; Mann-Whitney's test). The other results are shown in Table 1. In the multivariate logistic regression, we included age, sex, BMI and the presence of hypertension, diabetes, smoking and alcohol consumption. Through this first analysis, we obtained P values below 0.20 only for age, sex, hypertension and diabetes. A new formulation with only these four variables showed that age, gender and diabetes were less relevant to the occurrence of CAD in severe liver disease patients. In turn, with P values of 0.0474, hypertension seemed to be relevant for the presence of CAD.

The final equation was presented as follows: logit Y = -3.727304 + 0.966403 [age] + 1.102597 [sex] + 1.032956 [hypertension] + 0.990118 [diabetes].

Finally, there was some relationship between the established causes of advanced liver failure and development of coronary artery disease. This means that none of the etiologies of advanced liver failure in particular predisposes to the development of coronary artery disease.

Discussion

The occurrence of coronary disease found in this study (17.6%) was equivalent to the rate of 16.2% found by Carey WD et al, who considered only patients older than 50 with severe obstruction of coronary arteries[5]. The prevalence of 5%, a finding from the studies by Plotkin et al[6] on patients older than 40 with significant coronary obstruction was much lower than that obtained in this study. This prevalence of 17.6% is alarming because the risks of morbidity and mortality in patients with coronary artery disease, once undergoing liver transplantation, are significantly increased, even when coronary artery disease is treated with drugs or surgery before liver transplantation[8].

Age is a known immutable risk factor for the development of CAD[1], so that its prevalence increases with age. In the patients studied, age did not appear as a risk factor for CAD development.

Likewise, being male is also an immutable risk factor for CAD. However, in this study, there was no significant difference in the prevalence of coronary disease in males or females with advanced liver failure. This fact may be attributable to higher estrogen levels found in cirrhotic patients[4].

BMI is a measure of obesity that is a risk factor for CAD, and it is also associated with increased mortality after a possible liver transplant[10]. However, among the patients in this study, there was no significant difference between obesity in patients with or without coronary artery disease. Likewise, smoking, a known risk factor for CAD, was not very different in groups of patients with advanced liver failure with CAD and without CAD.

Table 1 - Clinical characteristics of 119 patients with advanced liver failure who underwent coronary angiography as preoperative assessment for liver transplant

	Total group	Patients with coronary artery disease	No obstructions	P value	Test
No. of cases	119	21	98		
Age	59,9(6,6)	62,2(5,9)	59,4(6,6)	0,0838	Mann-Whitney
Male sex	90[75,6%]	18[85,7%]	72[73,5%]	0,2782	Fisher Exact test
BMI	26,2(4,7)	26,3(4,3)	26,2(4,8)	0,9917	Mann-Whitney
Hypertension	36[30,3%]	10[47,6%]	26[26,5%]	0,0995	Fisher Exact test
Diabetes	19[16,0%]	6[28,6%]	13[13,3%]	0,1587	Fisher Exact test
Smoking	56[47,1%]	10[47,6%]	46[46,9%]	0,9548	Fisher Exact test
Alcohol consumption	82[68,9%]	16[76,2%]	66[67,3%]	0,5928	Fisher Exact test
Etiology					
Alcohol	30	6	24	0,7827	Fisher Exact test
B virus	5	1	4	1,000	Fisher Exact test
C virus	23	4	19	1,000	Fisher Exact test
Alcohol + virus	44	8	36	1,000	Fisher Exact test
Miscelaneous	17	2	15	0,7338	Fisher Exact test
Total cholesterol	130,1(53,0)	135,4(51,7)	129,0(53,5)	0,8215	Mann-Whitney
HDL cholesterol	42,1(31,8)	38,6(7,7)	42,6(34,0)	0,4378	Mann-Whitney
LDL cholesterol	71,8(34,6)	69,6(30,7)	72,2(35,3)	0,9999	Mann-Whitney
Triglycerides	74,5(38,4)	85,2(40,6)	72,4(37,7)	0,2178	Mann-Whitney

Age (mean and standard deviation in years); BMI (mean and standard deviation in kg/m², hypertension, diabetes, smoking and alcohol consumption in the total amount and percentage of cases; total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides in mg/dl.

Diabetes, in turn, also did not appear as a risk factor for CAD in patients with advanced liver failure. This is an unexpected result, once diabetes tends to be associated with other comorbidities such as obesity, hypertension and CAD itself. Knowing that diabetes usually develops in micro and macrovascular changes and with increased risk of atherosclerosis[11], it would be expected that diabetes be confirmed as a risk factor for CAD, even in patients with advanced liver failure.

With regard to alcoholism, it is known that a moderate intake of alcohol reduces the risk of atherosclerosis by increasing HDL levels. However, in excessive amounts, alcohol leads to hypertension and an increased risk of arterial occlusion[12]. Despite this, alcohol consumption was not confirmed as a risk factor for CAD in the patients analyzed.

Hypertension is a powerful cardiovascular risk factor, which may prompt the development of atherosclerosis[13]. Furthermore, it is exacerbated by alcohol abuse[12] and it is often associated with diabetes[11]. As a general rule, lower blood pressure levels are found in cirrhotic patients[13,14].

With respect to serum levels of total cholesterol, HDL, LDL and triglycerides, no significant difference was found between the groups of liver disease patients with or without coronary artery disease. Due to chronic liver disease, these patients have reduced serum cholesterol levels, resulting from loss of liver function, but hypocholesterolemia would be a protective factor in relation to CAD.

Finally, the different etiologies of liver disease, also showed no relation with the predisposition to CAD. It would be expected that at least the alcoholic etiology stand out somehow, either by its beneficial effects by increasing HDL and reducing cardiovascular risk, either because its harmful effects, raising blood pressure and increasing the risk of arterial occlusion[12]. However, alcohol consumption was not significantly different between the groups with or without coronary artery disease.

Coronary angiography was used as the gold standard for diagnosis of obstructive coronary disease. In 2006, Tiukinhoy-Laing et al[15], also used coronary angiography as the gold standard in 161 patients aged 45 or older in the preoperative evaluation for liver transplantation. They found a high prevalence of risk factors for atherosclerosis, in which half of the patients had hypertension or diabetes and two or more risk factors besides age were found in a number greater than half. The prevalence of 26% of moderate or severe atherosclerotic disease was found. In this group, most were men, elderly, and often suffering from hypertension or diabetes, a similar result as that found in this study.

Other authors have sought alternative and non-invasive techniques such as, for example, Cardiac Computed Tomography. In 2008, McAvoy et al[16] evaluated 147 consecutive patients in pre-operative examinations for orthotopic liver transplantation with the aid of cardiac computed tomography, seeking coronary artery calcification. Out of that group, 46 were excluded from analysis for not informing the calcium score. They made a comparison with multiple risk factors through multivariate analysis concluding that age, systolic blood pressure, fasting glucose, amount of components of metabolic syndrome and number of vessels involved remained moderately associated with coronary artery calcification. Note that, basically, the same factors were found in this study.

Conclusion

Based on this study, we can conclude that the prevalence of obstructive coronary disease is high in patients with advanced liver failure in pre-operative examinations for liver transplantation and in the multivariate analysis, only hypertension was an independent risk factor with statistical significance for the development of CAD. Because hypertension is a modifiable risk factor, this finding guides the practice of therapeutic attitudes in an attempt to prevent or delay the development of CAD in patients with advanced chronic liver disease.

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