Cardiovascular risk in patients submitted to liver transplantation

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Summary

Objective: To determine the prevalence of cardiovascular risk in patients undergoing liver transplantation according to the Framingham score, and to evaluate possible associations with traditional and non-traditional risk factors. **Methods:** Cross-sectional study in which patients undergoing liver transplantation were stratified by cardiovascular risk according to the Framingham score. Demographic, socioeconomic, clinical, and anthropometric variables were collected to assess the association with cardiovascular risk factors using univariate and multivariate statistical analyses. **Results:** A total of 115 patients were evaluated, of which 46.1% showed medium or high risk for the occurrence of cardiovascular events over ten years. The mean percentage risk of evaluated patients was of 9.5 ± 7.8%. Male gender (OR: 4.97; CI: 1.92-12.85; $p < 0.01$), older age (OR: 1,09; CI: 1.04-1.13; $p < 0.01$), and higher BMI at the moment of assessment (1.09; CI: 0.99-1.20; $p = 0.03$) were factors associated with medium and high cardiovascular risk. A higher percentage of cardiovascular risk was also associated with cyclosporine use ($p = 0.01$). **Conclusion:** The probability of occurrence of cardiovascular events in the assessed patients undergoing liver transplantation was higher than that in the Brazilian population. Special attention should be paid to this population, especially in relation to potentially modifiable factors associated to higher BMI and cyclosporine use.

Keywords: Risk factors; cardiovascular diseases; liver transplant.

Study conducted at Instituto Alfa de Gastroenterologia – Hospital das Clínicas da Universidade Federal de Minas Gerais
Belo Horizonte, MG, Brazil

Submitted on: 10/24/2011
Approved on: 01/13/2012

Financial Support:
Coordenação de Aperfeiçoamento Pessoal do Ensino Superior - CAPES - HSR is a MSc fellow and LRA is a PhD degree fellow. Fundação de Amparo à Pesquisa do Estado de Minas Gerais - FAPEMIG - LGF is a PhD degree fellow. Conselho Nacional de Desenvolvimento Científico e Tecnológico - CNPq - MITDC is a research fellow.

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Conflict of interest: None.

Introduction

Liver transplantation is the treatment of choice for patients with irreversible acute or chronic liver failure. The combination of advances in surgical technique, patient selection, better perioperative care, and adequate availability of immunosuppressive agents has resulted in significant improvement in the overall survival aftertransplantation[1]. Currently, almost 90% of patients survive one year after the transplantation[2], and up to 75% survive after 5 years[3].

However, the increased survival of patients undergoing liver transplantation has been accompanied by increased prevalence of chronic diseases, usually higher than that found in the general population[4]. Obesity, diabetes mellitus, arterial hypertension, dyslipidemia and metabolic syndrome are widely diagnosed in these patients[5-6]; consequently, the incidence of cardiovascular disease has also been increasingly described in this population[7]. Cardiovascular disease has been identified as the third leading cause of death after liver transplantation[8]. Some authors demonstrated that the risk of ischemic cardiac events and cardiovascular death are respectively 3.07 and 2.56 times higher in recipients of liver graft compared to age-matched population not submitted to transplantation[9].

The immunosuppressive agents used in the post-transplantation (usually tacrolimus or cyclosporine, and prednisone – at least in the early stages), although broadly described as responsible for the increase in cardiovascular risk[10], have not always shown that association[9,11]. While much attention has been devoted to the study of immunosuppressive drugs associated with chronic diseases such as those present in these patients, few risk factors, except these, have been studied, and to date, the cardiovascular risk in the Brazilian population referred for liver transplantation is still unknown.

The present study aimed to determine the prevalence of cardiovascular risk in patients undergoing liver transplantation according to the Framingham score, and to evaluate possible associations with other variables not included in this score.

Methods

This is a cross-sectional study in which cardiovascular risk according to Framingham score was evaluated in patients undergoing liver transplantation followed at the outpatient clinic of transplantation of the Instituto Alfa de Gastroenterologia, Hospital das Clínicas, Universidade Federal of Minas Gerais (Belo Horizonte – MG). Data were collected from March to October 2008. Patients who underwent liver transplantation and were at least 18 years of age were included in the study. Pregnant women and patients with ascites were excluded from the sample, as these conditions would hinder the identification of patients with abdominal obesity. Likewise, patients with time of transplantation of less than one year were not included, as they often have new and transient metabolic disorders as a result of graft implantation and high doses of immunosuppressants. The study was approved by the Ethics Committee of the Universidade Federal de Minas Gerais under protocol No. ETIC 44/08.

The patients were approached and asked about their interest in participating in the study while waiting for medical consultation at the clinic. After signing the informed consent, a questionnaire was applied covering demographic, socioeconomic, lifestyle, clinical and anthropometric data.

Demographic and socioeconomic data included age, gender, marital status, paid professional activity, education, and income. Variables related to lifestyle consisted of usual hours of sleep per night, smoking and former smoking status, and physical activity level.

Patients were asked about daily physical activities and the corresponding responses were transformed into metabolic equivalent tasks (METs)[12]. The daily activities transformed in METs were multiplied by the respective time spent, expressed as fractions of the hour; the results were summed and then divided by 24 hours. This value was categorized according to the level of activity performed (< 1.3: sedentary, 1.3 to 1.5: little active, 1.5 to 1.8: active, > 1.9: very active)[13] .

Clinical data included indication for transplantation; time of use and cumulative dose of corticosteroids after transplantation; use of tacrolimus or cyclosporine; hypertension prior to transplantation and at the time of the interview; diabetes mellitus prior to transplantation and at the time of the interview; excess weight and obesity prior to liver disease (based on the weight reported by the patient during the interview); family history of hypertension, diabetes mellitus, overweight, and cardiovascular disease.

Anthropometric data consisted of weight, height, body mass index (BMI), waist circumference (WC), hip circumference (HC), and waist-to-hip ratio (WHR). BMI was calculated by dividing weight (kg) by height squared (m^2), and patients were classified as overweight (BMI ≥ 25 kg/m^2) or obese (BMI ≥ 30 kg/m^2)[14]. The WC measurement (two fingers above the umbilicus) was classified as indicative of abdominal obesity according to the definitions of the World Health Organization (≥ 88 cm for women and ≥ 102 cm for men)[14] and of the International Diabetes Federation (IDF) (≥ 80 cm and ≥ 90 cm, respectively)[15].

The Framingham risk score was calculated and stratified according to gender, age, total cholesterol (TC), high density lipoprotein (HDL), smoking, systolic blood pressure (SBP), and diastolic blood pressure (DBP).

Patients were classified into groups according to cardiovascular risk consistent with the obtained score (< 10%, low risk, 10% to 20%, medium risk, ≥ 20%, high risk), and

by clinical manifestations of atherosclerotic disease or equivalent, such as the presence of diabetes mellitus type 1 or type 2 (such individuals show risk > 20% of new cardiovascular events over 10 years)[16].

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) for Windows (version 17.0), adopting a statistical significance level of 5%. The variables are shown as mean and standard deviation, and variables with non-normal distribution are shown as median, minimum, and maximum values (Kolmogorov-Smirnov test).

Patients with medium (10%-20%) and high risk (≥ 20%) were grouped and compared to low risk patients (< 10%) in the statistical analysis, as the medium-risk group had a small numbers of patients. Factors associated with medium/high cardiovascular risk were tested by univariate and multivariate analyses. The statistical tests used in univariate analysis were the chi-square test, Fisher's exact test, Student's *t*-test, and the Mann-Whitney test. Variables with $p < 0.2$ in the univariate analysis were included in the multiple logistic regression model. The model was subsequently adjusted according to the stepwise backward method. The Hosmer and Lemeshow test was used to check the fit of the model ($p > 0.05$). Also, multiple linear regression was used to identify factors associated with a higher percentage of cardiovascular risk.

Results

The sample comprised 115 subjects, of which 58.2% were males (n = 67). The mean age at evaluation was 52.5 ± 13.1 years. The average time of transplantation was 56.8 ± 34.7 months. Regarding schooling, the plurality of the individuals had not graduated from college/university (39.1%, n = 45), high school (26.1%, n = 30), and elementary school (26.1%, n = 30). Furthermore, 11.3% (n = 13) of the evaluated individuals reported to be illiterate. The general characterization of the patients is described in Table 1.

The most frequent indications for transplantation were alcoholic cirrhosis (31.3%, n = 36), cirrhosis due to hepatitis C virus (27.8%, n = 32), cirrhosis due to autoimmune hepatitis (14.8%, n = 17), cryptogenic cirrhosis (n = 14 12.2%), and cirrhosis with hepatocellular carcinoma (7%, n = 8). Other indications were observed in 20.9% (n = 24) of cases.

Family history of hypertension, diabetes mellitus, obesity, and cardiovascular disease were reported by 74.3% (n = 84), 49.6% (n = 56), 64.6% (n = 73) and 61.1% (n = 59)

Table 1 – Demographic, socioeconomic, lifestyle, and clinical data of patients submitted to liver transplantation, Belo Horizonte, MG, Brazil, 2011

Categorical variables	%	n
Marital status – married	32.2	37
Unemployed/retired/on leave/homemaker	63.5	73
Physical activity level		
Active	7.0	8
Low active	27.8	32
Sedentary	65.2	75
Smoker	13.0	15
Former smoker	39.3	39
Use of tacrolimus	88.7	102
Use of cyclosporine	11.3	13
Arterial hypertension before transplantation	19.1	22
Current arterial hypertension	38.3	44
Diabetes mellitus before transplantation	5.3	6
Current diabetes mellitus	22.6	26
Numerical variables	**Mean/median**	**± Standard deviation/minimum-maximum**
Income per capita (R$)	415	83-6.000
Hours of sleep (per day)	7.6	± 1.3
Physical activity factor (MET/24)	1.35	± 0.16
Glucose (mg/dL)	97	68-346
Total cholesterol (mg/dL)	166.2	± 43.2
HDL (mg/dL)	44	21-99
Triglycerides (mg/dL)	124	28-659
Systolic arterial pressure (mmHg)	120	90-180

of patients, respectively. Personal history of overweight prior to liver disease was observed in 42.6% (n = 49) of patients and obesity, in 13.9% (n = 16). At the time of evaluation, the prevalence of overweight was 58.2% (n = 96) and of obesity, 20.9% (n = 24) of patients. Abdominal obesity was observed in 44.3% (n = 51) patients according to the WHO classification, and in 71.1% (n = 82) according to the IDF classification.

According to the Framingham risk score, 53.9% (n = 62) patients had low risk for cardiovascular events over ten years and 46.1% (n = 53) had medium to high risk, of which 16.5% (n = 19) of patients were classified as medium and 29.6% (n = 34) as high risk for cardiovascular events in ten years. The mean percentage risk was 9.5% ± 7.8%. Male gender, older age, indication for transplantation due to alcoholic cirrhosis, overweight, obesity, higher BMI prior to liver disease, higher BMI, WC, and WHR at the time of assessment were statistically associated, in the univariate analysis, to a probability higher than 10% of coronary events occurring within ten years for these patients (Tables 2 and 3).

Factors that are directly or indirectly associated with the calculation of the Framingham score were also associated with risk in the univariate analysis (glucose, total cholesterol, HDL, and triglycerides), but were not included in the multiple or linear logistic regression models.

The multiple logistic regression model created to identify factors independently associated with medium and high cardiovascular risk showed a good fit (Hosmer and Lemeshow test = 0.88) and resulted in the following variables: age (OR: 1.09 CI: 1.04-1.13, p < 0.01), male (OR: 4.97 CI: 1.92-12.85, p < 0.01), and BMI at the time of evaluation (OR: 1.09, CI: 0.99-1.20, p = 0.09). Variables independently associated with a higher percentage of cardiovascular risk through the multiple linear regression model were age (p < 0.01), male sex (p < 0.01), cyclosporine use (p = 0.01), and higher body mass index at evaluation (p = 0.03).

Discussion

The Framingham risk score was used in this study as it is recommended by the Brazilian Society of Cardiology[16] and is the standard most often used for stratification of coronary risk worldwide. The estimated risk of cardiovascular disease in asymptomatic individuals and the identification of associated factors may be useful to classify vulnerable groups and allow the development of strategies to prevent these problems. However, it is important to emphasize that this algorithm has limitations, as it only considers traditional risk factors: age, total cholesterol, systolic and diastolic blood pressure, diabetes mellitus and smoking status.

Other important risk factors in the epidemiology of cardiovascular disease are not considered, such as plasma levels of triglycerides and LDL, family history of early cardiovascular disease, family history of hypertension, BMI

Table 2 – Categorical variables associated with risk of cardiovascular disease > 10% in patients submitted to liver transplantation by univariate analysis, according to Framingham score, Belo Horizonte, MG, Brazil, 2011

Parameters	Risk of cardiovascular disease > 10%				
	% (n)		OR	95% CI	p-value
Gender (male x female)	58.2 (39)	29.2 (14)	3.38	1.54-7.45	< 0.01*
Marital status (single x married)	51.3 (40)	35.1 (13)	1.96	0.86-4.34	0.10
Unemployed/retired/homemaker x others	47.9 (35)	42.9 (18)	1.23	0.57-2.64	0.59
Smokers and nonsmokers x former smokers	38.7 (24)	48.7 (19)	1.50	0.67-3.38	0.32
Use of cyclosporine x tacrolimus	69.2 (9)	43.1 (44)	2.94	0.85-10.00	0.08
Transplantation indication due to alcoholic cirrhosis × other indications	66.7 (53)	36.7 (13)	3.45	1.50-7.91	< 0.01*
BMI					
BMI prior to liver disease > 25 kg/m² × < 25 kg/m²	59.2 (29)	36.4 (24)	2.54	1.19-5.42	0.01*
BMI prior to liver disease > 30 kg/m² × < 30 kg/m²	81.3 (13)	40.4 (40)	6.39	1.71-23.88	< 0.01*
BMI at evaluation > 25 kg/m² × < 25 kg/m²	53.7 (36)	35.4 (17)	2.12	0.99-4.54	0.05
BMI at evaluation > 30 kg/m² × < 30 kg/m²	58.3 (14)	42.9 (39)	1.87	0.75-4.65	0.18
WC					
WC > 80/90 cm × < 80/90 cm	50.6 (41)	33.3 (11)	2.05	0.88-4.77	0.09
WC > 88/102 cm × < 88/102 cm	52.9 (27)	39.7 (25)	1.71	0.81-3.60	0.16

BMI, body mass index; WC, waist circumference; *p < 0.05, chi-square test.

Table 3 – Numerical variables associated with the risk of cardiovascular disease > 10% in patients submitted to liver transplantation, by univariate analysis, according to Framingham score, Belo Horizonte, MG, Brazil, 2010

Parameter (mean ± standard deviation)	Patients with low risk	Patients with medium/high risk	p-value
Age (years)	47.9 ± 14.6	58 ± 8.5	< 0.01*
Time of transplantation (months)	60.0 ± 37.8	50.8 ± 30.4	0.16
Income per capita (R$)	758.32 ± 801.9	953.74 ± 1084.0	0.49
Hours of sleep (per day)	7.71 ± 1.3	7.57 ± 1.4	0.57
Physical activity factor (MET/24)	1.35 ± 0.2	1.3 ± 0.2	0.55
BMI before liver disease (kg/m²)	23.5 ± 3.5	26.9 ± 4.8	< 0.01*
BMI at evaluation (kg/m²)	25.4 ± 4.6	27.6 ± 4.8	< 0.02*
Glucose	89.4 ± 13.4	128.1 ± 56.2	< 0.01*
Total Cholesterol (mg/dL)	161.3 ± 45.1	171.9 ± 40.4	0.19
HDL (mg/dL)	51.2 ± 18.1	44.4 ± 20.6	< 0.01*
Triglycerides (mg/dL)	110.5 ± 49.4	174.7 ± 99.2	< 0.01*
Time of use of prednisone (months)	22.3 ± 30.3	12.4 ± 18.1	0.13
Accumulated dose of prednisone (grams)	6.37 ± 7.28	5.29 ± 6.89	0.77
Waist circumference (cm)	91.4 ± 13.7	99.6 ± 14.2	< 0.01*
Hip circumference (cm)	101.0 ± 10.4	103.8 ± 10.6	0.16
Waist-to-hip ratio (cm)	0.90 ± 0.1	0.96 ± 0.1	< 0.01*

*p < 0.05, Student's t test and Mann-Whitney test.

(overweight, obesity), abdominal obesity, eating habits, and level of physical activity. The cross-sectional design of the study is also a limiting factor, as the estimated risk of cardiovascular disease development over 10 years was assessed rather than the direct verification of events.

Another limiting factor was the combination of medium and high risk groups for statistical analysis, as the great advantage of scores is their discriminative power. In this study, on the one hand, patients in the medium risk group could have a similar evolution to that of the patients in the low risk group; on the other hand, associating them to the low risk group could underestimate their chance of developing cardiovascular disease.

The mean absolute risk of occurrence of a cardiovascular event over the next ten years in the studied sample was 9.5%, which is higher than the values reported in the literature for the Brazilian population. In a study of 329 executives in São Paulo, Rodrigues and Phillip[17] found a low probability of occurrence of cardiovascular events over ten years (average risk of 5.7%). Similar values were also found in a study conducted in the state of Amazonas (average risk of 5.4 to 5.7%, depending on location)[18].

Another study, involving 1,712 individuals aged between 30 and 59 years residing in Bambuí, state of Minas Gerais, also showed low cardiovascular risk (more than half of the population did not exceed the 5% risk)[19]. The data found in the present study population are in agreement with the mean values of cardiovascular risk described in populations submitted to liver transplantation – 7.9% in the study by Johnston et al.[9] and 11.5% in the study by Neal et al.[20], supporting the premise that these patients have higher risk of developing cardiovascular disease.

The mean risk found (9.5%) is very close to the value of 10% (considered intermediate risk); nearly half the studied population (46.1%) showed medium to high risk, and of these, approximately 30% were classified as high risk. Therefore, these results emphasize the need for intervention measures proposed in the last Brazilian guideline on dyslipidemia and atherosclerosis prevention[16].

The level of physical activity and categorization of patients as sedentary, low active, and active were not associated with cardiovascular risk in this study. Although low levels of physical activity and a sedentary lifestyle are classic risk factors for cardiovascular disease[16], it should be noted that the calculation of the daily physical activity level had limitations, as the time available for detailed descriptions of daily activities at the time of data collection was short. Furthermore, the calculation was made based on the activities performed by that patient at the time of the data collection, and thus, it may not reflect the entire period of time elapsed from transplantation (or since liver disease limited the daily activities and reduced the level of daily physical activities) to the date of evaluation.

In the present study, male gender, older age, and higher BMI at the time of evaluation were considered predictive factors for medium and high risk of cardiovascular events

in the population undergoing liver transplantation. It is known that cardiovascular disease mortality is higher in males, when compared to females, at all circumstances and all age ranges, and that the occurrence of events increases progressively with age[21]. The higher incidence of cardiovascular disease in males compared to females of similar ages has been attributed not only to gender differences related to sexual hormones, but also to differences in cell and vascular tissue that mediate specific sexual responses[22]. Moreover, a higher score in the Framingham risk score is attributed to both older age and male sex. However, the permanence of these variables in the model would help to eliminate confounding factors.

In the studied population, BMI was the anthropometric measure most often related to higher incidence of cardiovascular events. The results showed that a higher BMI at the time of assessment tended to show statistical significance ($p = 0.09$) in the multivariate analysis as an independent factor for cardiovascular risk.

On the other hand, the removal of this variable would negatively impact the fit of the model and thus, it was kept in the analyses. The association between the degree of obesity and the incidence of cardiovascular events has been well described in the literature[23-24].

It has been know for some time that weight gain after adulthood results in an increased risk of cardiovascular disease in both genders[25]. Overweight and obesity are also indicated in the population undergoing liver transplantation as related to cardiovascular risk[6,11]. The WC and WHR were associated with increased likelihood of developing cardiovascular events only in the univariate analysis. Although the BMI at the time of evaluation was the best predictor of cardiovascular risk, WC and WHR measure the amount of central adipose tissue, which is more metabolically active than peripheral fat tissue, thus implying in a higher risk factor for metabolic syndrome, insulin action resistance and cardiovascular disease in the general population[26,27]. A high BMI reflects a great mass of adipose tissue, which, especially when it is visceral, influences the regulation of adipokines.

Adiponectin is an anti-inflammatory adipokine (it antagonizes the development of atherosclerosis and vascular inflammation), which shows decreased serum concentrations in obese individuals. Serum concentrations of leptin, which controls food intake, are increased in these individuals influencing the energy balance and compromising the immune response.

The evidence suggests that leptin increases blood pressure and sympathetic nerve activity, stimulates the generation of reactive oxygen species, induces platelet aggregation, and promotes arterial thrombosis, being considered an independent risk factor for cardiovascular disease. In addition, resistin expression in adipocytes is reduced but it is high in macrophages and monocytes, suggesting an important role in inflammation. Resistin levels are elevated in obese individuals and, therefore, are linked with obesity-related insulin resistance. Resistin has a high atherogenic action by increasing the expression of intercellular adhesion molecules. Concomitantly, there is increased secretion of proinflammatory cytokines that collectively damage the endothelium, stimulating inflammatory/proliferative reaction in the vascular wall[28].

In addition to increased BMI, patients classified as having medium/high risk had significantly higher triglycerides and glucose levels and lower HDL levels. These findings suggest that these patients have a higher prevalence of metabolic syndrome than low risk patients. Metabolic syndrome is described in approximately half of patients undergoing liver transplantation[29], and has also been described as a risk factor for cardiovascular disease in this population[30], as well as in the general population[31]. These results were expected, as triglycerides, glucose, and HDL are part of the Framingham score, either directly or indirectly.

The multiple linear regression analysis demonstrated that the use of cyclosporine, at the expense of the use of tacrolimus, was associated with greater percentage of risk of cardiovascular events. Other studies also showed this association[32-33].

This fact can be explained by the influence of this drug on blood pressure, and cyclosporine is considered to be more hypertensive than tacrolimus[6,20,32]. Although these results are in agreement with literature data, it is important to note that, at the moment of the evaluation, few patients were taking cyclosporine (11.3%, $n = 13$), as the current immunosuppression protocol for transplants where the study was carried out is based on the use of tacrolimus.

Based on the results, it can be concluded that the risk of incidence of cardiovascular events over the next ten years in patients undergoing liver transplantation is higher than that of the general Brazilian population. These aspects indicate the need for greater attention of multidisciplinary teams involved in the care of these patients. These patients should be introduced early into lifestyle modification programs, especially male and older individuals.

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