Long-Term Survivors After Pediatric Liver Transplantation Are at Increased Risk for Development of Cardiovascular Disease Events: Analysis of 30 Cases

S. de la Fuente[a,*], M.J. Citores[a], I. Baños[a], A. Duca[a], and V. Cuervas-Mons[a,b]

[a]Unidad de Trasplante Hepático, Servicio de Medicina Interna, Hospital Universitario Puerta de Hierro-Majadahonda, Majadahonda, Madrid, Spain; and [b]Departamento de Medicina, Universidad Autónoma de Madrid, Madrid, Spain

ABSTRACT

Background. Liver transplantation (LT) in adult patients is associated with a higher incidence of cardiovascular risk factors (CVRF), chronic kidney disease (CKD), and cardiovascular disease mortality than the general population. Available information about these problems in adult patients with LT from a pediatric age is limited. The aim of this study was to analyze the incidence of CVRF, risk of developing CKD, and risk of 10-year coronary event in adult patients who received LT in childhood.

Methods. Thirty adult patients (11 female, 19 male; mean age, 29.3 years) who underwent LT in childhood were analyzed, and CVRF, estimated glomerular filtration rate, and current immunosuppressive regimen were recordered. The risk of 10-year coronary event was calculated with the use of validated equations (Framingham and Regicor) and compared with the estimated risk in the general population.

Results. None of the patients had CVRF before LT, except 1 patient who received a transplant because of familial hypercholesterolemia. Median age of patients at the time of study was 28.6 years (range, 19.3–43.1 y), and mean follow-up after LT was 17.83 ± 5.21 years. Twenty-nine patients (96.7%) were receiving a calcineurin inhibitor (69% tacrolimus, 31% cyclosporine), along with steroids in 13 of them. The average CVRF per patient was 2, and 11 patients (43.33%) had ≥3. Thirteen patients (43.33%) had CKD. The estimated risk of developing a coronary event at 10 years according to the Framingham score was 3%, higher than expected in the general population of same age and sex. With the use of the Regicor equation, adapted to the Spanish population, the estimated cardiovascular risk was 1.6%, corresponding to Spanish men without CVRF aged 50–55 years. None of the patients had cardiovascular events during the follow-up.

Conclusions. Our data show a high incidence of CVRF and CKD in young adults who received LT in childhood, resulting in an increased risk of cardiovascular disease.

PEDIATRIC liver transplantation (LT) achieves excellent patient and graft survival in the short and medium terms, with patient survival rates of 94.2% and 89.2% at 5 and 10 years, respectively [1]. In adults with LT, atherosclerotic cardiovascular disease is the 3rd leading cause of late death [2], owing to increased prevalence of many cardiovascular risk factors (CVRF), most of them associated with prolonged immunosuppression. Long-term survivors after pediatric LT are exposed to immunosuppression from an early age and for a longer period of time. It is therefore likely that long-term survivors after pediatric LT have significantly increased cardiovascular risk compared with the general population in the same age range, but information in this regard is limited.

Funding: Cátedra de Patrocinio UAM–Fundación Lair (in part).

*Address correspondence to Sara de la Fuente, MD, Hospital Universitario Puerta de Hierro-Majadahonda, Servicio de Medicina Interna, C/Manuel de Falla, N° 1, CP 28222, Majadahonda, Madrid, Spain. E-mail: sarafm28@hotmail.com

0041-1345/14
http://dx.doi.org/10.1016/j.transproceed.2014.10.003

The aim of this study was to analyze the prevalence of established CVRF and chronic kidney disease (CKD) and to estimate the risk of developing cardiovascular disease at an early age in adult patients who received LT in childhood.

METHODS

The population studied were consecutive young adults who received pediatric LT at Universitary Children's Hospital La Paz (Madrid, Spain) during the period 1987–2008 and that were referred at adult age to our outpatient clinic during the period 2007–2012 for follow-up. General and demographic data, general biochemistry, maintenance immunosuppression, renal function, established risk factors for atherosclerotic cardiovascular disease, including smoking, diabetes, hypertension, and hyperlipidemia, and their treatment were assessed by information collected at the time of the 1st visit in our clinic. Major coronary heart disease risk factors were defined as total cholesterol ≥200 mg/dL (≥5.17 mmol/L), systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, smoking, and diabetes according to American Diabetes Association 2013 criteria. CKD was defined as estimated glomerular filtration rate, according to the Modification of Diet in Renal Disease 6-variable equation, of <60 mL/min/1.73 m^2. Estimation of CVRF was based on validated scores (Framingham and Regicor, the latter adapted for the Spanish population [3]) and compared with the estimated CVRF for the general population, determined with the use of data from the Monitoring Trends and Determinants in Cardiovascular Disease (MONICA-Catalunya) study [4].

RESULTS

Study population included 30 patients (11 female and 19 male) with a median age at the time of the study of 28.6 years (range, 19.3–42.1 y). Median age at transplantation was 11.4 years (range, 1.9–20.4 y). The indications for LT were biliary atresia ($n = 10$), cryptogenic cirrhosis ($n = 7$), Byler disease ($n = 3$), Alagille syndrome ($n = 3$), alpha1-antitrypsin deficiency ($n = 2$), familial hypercholesterolemia ($n = 2$), disorder in the metabolism of cholesterol esters, maple syrup disease, and neonatal hepatitis ($n = 1$ each). Eight patients received a retransplantation at a pediatric age, mostly because of hepatic artery thrombosis. Only 1 patient, whose underlying disease was familial hypercholesterolemia, had CVRF before LT.

Maintenance inmunosuppression at the time of study was based on calcineurin inhibitor (CNI) in 29 patients (97%): 20 patients (69%) tacrolimus and 9 (31%) cyclosporine. Eleven patients received CNI in monotherapy, and 18 patients in combination (9 patients with triple therapy with mycophenolate mofetil (MMF)/azathioprine and glucocorticoids (GC), 5 patients received double therapy with steroids (CNI + GC), and 4 patients were treated with 2 immunosuppressive drugs without steroids (CNI + MMF or inhibitor of mammalian target of rapamycin). The remaining patient was in monotherapy with steroids.

After a post-transplantation follow-up of 17.83 ± 5.21 years, none of the patients had atherosclerotic cardiovascular events (coronary heart disease, cerebrovascular disease, or peripheral artery disease).

Table 1. Prevalence of Cardiovascular Risk Factors (CVRF) and Chronic Kidney Disease (CKD)

	All ($n = 30$)	Male ($n = 19$)	Female ($n = 11$)
Median age, y (range)	28.6 (19.3–42.1)	28.4 (20.9–35.7)	29.3 (19.3–42.1)
HTN	17 (56.6%)	14 (73.7%)	3 (27.3%)
Dyslipidemia	10 (33.3%)	6 (31.5%)	4 (36.3%)
DM, preDM	4 (13.3%)	4 (21.1%)	0 (0%)
Smoking	5 (16.6%)	4 (21.1%)	1 (9.1%)
CKD	13 (43.3%)	9 (47.36%)	4 (36.3%)
Hyperuricemia	13 (43.3%)	11 (57.9%)	2 (18.1%)
Number of CVRF			
0	5 (16.6%)	1 (5.2%)	4 (36.3%)
1	10 (33.3%)	6 (31.5%)	4 (36.3%)
2	2 (6.6%)	2 (10.5%)	0 (0%)
3	8 (26.6%)	5 (26.31%)	3 (27.8%)
≥4	5 (16.6%)	5 (26.31%)	0 (0%)

Abbreviations: HTA, hypertension; DM, diabetes mellitus.

The most frequent CVRF found was hypertension ($n = 17$; 58.6%), followed by CKD and hyperuricemia ($n = 13$; 43.3% each), and dyslipidemia ($n = 10$; 33.3%), mostly hypercholesterolemia (Table 1). Only 1 patient (3.3%) had CKD in stage 4.

The average number of risk factors per patient was 2, and 13 patients (43.3%) had ≥3. The estimated major cardiovascular event at 10 years, calculated with the use of the Framingham prediction model, was 3%, which is higher than expected in the general population for the same age and sex. When using the risk calculator Regicor, the risk of cardiovascular event at 10 years was 1.6%, which represents a risk similar to that of nontransplanted Spanish 45-year-old male smokers, and for nonsmokers aged 50–55 years [4]. The excess of CVRF was even more evident in women. Although the estimated CVRF was higher for men (1.83% at 10 years), the CVR of young women with LT in childhood was higher compared with healthy women, showing an estimated 10-year risk of 1.23%, which is equivalent to healthy Spanish women at the age of 60 years.

DISCUSSION

Cardiovascular disease is the 3rd leading cause of late death after adult LT, accounting for 22% of mortality after the 1st year of transplantation [2]. The prevalence of CVRF is increased in adult patients with LT, with rates observed in different series of 40%–85% hypertension, 40%–65% hyperlipidemia, 25%–40% obesity, and 15%–60% diabetes [5]. The association of some of these risk factors markedly increases the prevalence of metabolic syndrome in liver transplant recipients, reaching 60% in some series [6]. Consequently, the estimated cardiovascular risk at 5 and 10 years is increased from 2.6 to 3 times that of the non-transplant population [7]. In fact, several studies have reported an incidence of major cardiovascular events in adult recipients undergoing LT of ~11% [8].

In adult patients receiving LT in childhood, the information available in this regard is scarce. Cardiovascular

morbidity and mortality in this scenario is especially relevant, because life expectancy is prolonged. Recently, Perito et al [9] described in a systematic review increased hypertension rates (~30%), dyslipidemia (50%–60%), and metabolic syndrome (45%–60%) among LT recipients in childhood, compared with those expected for the healthy population of same age and sex. The data obtained in our study are thus consistent with the literature, although it is necessary to draw attention to the hyperuricemia, a known marker of cardiovascular risk and highly prevalent in patients undergoing LT, which is not mentioned in most series.

Chronic kidney disease is one of the most common complications among adult recipients of LT, with a prevalence of ~50%. The association of CKD and increased cardiovascular events is well known. In patients undergoing pediatric LT, CKD prevalence is ~30%, according to data from a study from the Cincinnati Children's Hospital [10], which offers the largest series ($n = 117$), with a mean age of 7.6 years and range of 3–14.6 years. In young adults who received LT in childhood, CKD rates will probably be higher, reaching advanced stages at younger ages, although there are no data available in the literature. We found a prevalence of CKD of 44.33%.

The estimated CVRF for our study population, with a mean age of <30 years, is very high. The estimated risk of cardiovascular event at 10 years according to the Regicor scale is equivalent to that of Spanish men aged 55 years without CVRF and even higher for women.

Most CVRF observed after transplantation are modifiable. Several risk-reduction strategies have been suggested, including the identification and early treatment of CVRF, absolute CVRF estimation, conventional treatment of hypertension, diabetes, hyperlipidemia, and obesity, as well as the modification of immunosuppressive therapy with steroid-free regimens and CNI-saving strategies that may improve the risk profile of these patients.

Our study has some methodologic limitations. First, the review of some data was performed retrospectively. Second, the mean age of the study subjects is too low to study cardiovascular events and it is possible only to estimate the risk. Also, the use of predictive scores validated for the general population underestimate the absolute risk of the transplant population, by not taking into account specific risk factors for this group, such as the presence of CKD. Finally, although the sample is small, owing to the special characteristics of the study group, our series is one of the longest available upon review of the literature.

In conclusion, our data highlight the high prevalence of CVRF in long-term survivors after pediatric LT, resulting in an increased risk of cardiovascular disease at an early age. Therefore, strategies are needed for prevention, identification, and risk stratification to allow an aggressive management of CVRF, guided by the individual absolute risk in this population.

REFERENCES

[1] Soltys KA, Mazariegos GV, Squires RH, et al. Late graft loss or death in pediatric liver transplantation: an analysis of the SPLIT database. Am J Transplant 2007;7:2165–71.

[2] Watt KD, Pedersen RA, Kremers WK, et al. Evolution of causes and risk factors for mortality post-liver transplant: results of the NIDDK long-term follow-up study. Am J Transplant 2010;10:1420–7.

[3] Marrugat J, Solanas P, d'Agostino R, et al. Estimación del riesgo coronario en España mediante la ecuación de Framingham calibrada. Rev Esp Cardiol 2003;56:253–61.

[4] Sans S, Fitzgerald AP, Royo D, et al. Calibración de la tabla SCORE de riesgo cardiovascular para España. Rev Esp Cardiol 2007;60:476–85.

[5] Parekh J, Corley DA, Fenga S. Diabetes, hypertension and hyperlipidemia: prevalence over time and impact on long-term survival after liver transplantation. Am J Transplant 2012;12:2181–7.

[6] Laryea M, Watt KD, Molinari M, et al. Metabolic syndrome in liver transplant recipients: prevalence and association with major vascular events. Liver Transpl 2007;13:1109–14.

[7] Madhwal S, Atreja A, Albeldawdi A, et al. Is liver transplantation a risk factor for cardiovascular disease? A meta-analysis of observational studies. Liver Transpl 2012;18:1140–6.

[8] Albeldawi M, Aggarwal A, Madhwal S, et al. Cumulative risk of cardiovascular events after orthotopic liver transplantation. Liver Transpl 2012;18:370–5.

[9] Perito ER, Lau A, Rhee S, et al. Posttransplant metabolic syndrome in children and adolescents after liver transplantation: a systematic review. Liver Transpl 2012;18:1009–28.

[10] Campbell KM, Yazigi N, Ryckman FC, et al. High prevalence of renal dysfunction in long-term survivors after pediatric liver transplantation. J Pediatr 2006;148:475–80.