Subclinical Atherosclerosis in Pediatric Liver Transplant Recipients: Carotid and Aorta Intima-Media Thickness and Their Predictors

Emily R. Perito, MD, MAS[1,2], Andrew Phelps, MD[3], Tabitha Vase, BA[4], Vickie A. Feldstein, MD[3], Robert H. Lustig, MD[1], and Philip Rosenthal, MD[1,5]

Objective To investigate prevalence and predictors of cardiovascular risk in pediatric liver transplant recipients using noninvasive markers of subclinical atherosclerosis: carotid intima-media thickness (cIMT) and aorta intima-media thickness (aIMT).

Study design Cross-sectional study of 88 pediatric liver transplant recipients. The cIMT and aIMT were measured by ultrasound imaging using standardized protocol.

Results Participants were 15.4 ± 4.8 years of age, and 11.2 ± 5.6 years post-transplantation. The cIMT and aIMT were both higher in males than females. In analyses adjusted for sex, age, and height, the cIMT was higher in subjects transplanted for chronic/cirrhotic liver disease and lower in subjects on cyclosporine (n = 9) than tacrolimus (n = 71). The cIMT was not associated with rejection history or current corticosteroid use. The cIMT increased with increasing diastolic blood pressure and triglycerides. The aIMT (n = 83) also increased with age, and its rate of increase post-transplant varied by age at transplantation. In adjusted analyses, aIMT was higher in subjects with glucose intolerance. In analysis of patients ≤20 years of age for whom blood pressure percentiles could be calculated (n = 66), aIMT increased with increasing diastolic blood pressure percentile (0.010 mm per 5-percentile; 95% CI, 0.000-0.021; $P = 0.05$). Neither the cIMT nor the aIMT was associated with obesity, systolic hypertension, or other dyslipidemia at study visit.

Conclusion Measures of long-term cardiovascular risk were associated with conditions that are more common in pediatric liver transplant recipients than nontransplanted peers, namely, diastolic hypertension and glucose intolerance. Larger, longitudinal studies are warranted to investigate whether cIMT could be useful for stratifying these patients' cardiovascular risk—and potential need for proactive intervention—during long-term follow-up. *(J Pediatr 2017;■■:■■-■■).*

In adult liver transplant recipients, cardiovascular disease is the third leading cause of death.[1] A key risk factor for cardiovascular events in adults, ie, myocardial infarction or stroke, is the post-transplant metabolic syndrome (PTMS)—a clustering of obesity, hypertension, dyslipidemia, and glucose intolerance.[2,3] In pediatric liver transplant recipients, we have recently shown that PTMS and its components are common: 28% of children and young adults are overweight or obese, almost 35% have hypertension or prehypertension, 44% have prediabetes, and 37% have low high-density lipoprotein (HDL) cholesterol.[4]

Survival well into adulthood is now the norm for these children. However, the impact of PTMS components on long-term cardiovascular health in these children is not known. Thus, elucidation of cardiovascular disease precursors and risk factors—particularly those that could be treated to prevent later morbidity—is a priority.[5]

In nontransplanted children, carotid intima-media thickness (cIMT) has proven useful as a noninvasive method for predicting later cardiovascular risk. The cIMT is measured by ultrasound examination in the common carotid arteries, and standard measurement protocols have been endorsed by the American Heart Association for assessing subclinical atherosclerosis in pediatric clinical research.[6] The cIMT is a direct measure of arterial thickening, so it is appealingly applicable across populations that may have different risk factors for cardiovascular disease. Norms by age, height, and sex have

aIMT	Aortic intima-media thickness
BMI	Body mass index
cIMT	Carotid intima-media thickness
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
LMS	Least mean squares
PFIC	Progressive familial intrahepatic cholestasis
PTMS	Post-transplant metabolic syndrome
UCSF	University of California San Francisco

From the [1]Department of Pediatrics; [2]Department of Epidemiology and Biostatistics; [3]Department of Radiology and Biomedical Imaging; [4]School of Medicine; and [5]Department of Surgery, UCSF Benioff Children's Hospital, University of California, San Francisco, San Francisco, CA

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been established. It changes reliably enough with treatment, for example, of hypertension or dyslipidemia, that it is used an endpoint in clinical trials.[6,7] Most important, it predicts future cardiovascular events in adults.[6,7]

In this study, we measured the cIMT in pediatric liver transplant recipients with the aim of investigating whether the high prevalence of PTMS components is accompanied by end-organ evidence of early atherosclerosis.[6] We also assessed aortic intimal-medial thickness (aIMT), which may detect earlier subclinical atherosclerosis than cIMT.[8-10] There are no previous reports of aIMT in this population.

Methods

We performed a cross-sectional study of pediatric liver transplant recipients, aged 8-30 years at study visit, who were less than 18 years of age at first liver transplantation. At the study visit, all were at least 1 year from transplantation and on stable immunosuppressive regimens for at least 3 months. This study was approved by the University of California San Francisco's (UCSF) Committee on Human Research (UCSF CHR, IRB# 12-10290, 14-13939). After age-appropriate consent and assent were obtained, subjects were evaluated in UCSF's Pediatric Clinical Research Center or during elective inpatient admission for a surveillance liver biopsy, which were done only during clinically stable periods. Ultrasounds were done in UCSF's Pediatric Radiology suite. Visits were completed from September 2013 through March 2017. In addition to demographic factors like age and sex, we evaluated disease for which the participants were transplanted as a predictor; we classified patients by major disease categories (**Table I**) and by acute/noncirrhotic disease (eg, acute liver failure, hepatoblastoma, urea cycle disorders) versus chronic/cirrhotic liver disease (eg, biliary atresia, progressive familial intrahepatic cholestasis [PFIC], Alagille syndrome, and alpha 1 antitrypsin deficiency).

For subjects younger than 18 years of age at the study visit, body mass index (BMI) percentile for age and sex was calculated based on 2000 Centers for Disease Control and Prevention growth chart data.[11] Subjects were classified as overweight for BMI percentile 85th-94th percentile and obese for BMI percentile of the 95th percentile or greater.[12] Increased waist circumference was considered at the 90th percentile or greater for age and sex.[13,14] Systolic and diastolic hypertension were defined as use of antihypertensive agents or blood pressure at the 95th percentile or greater for sex, age, and height; prehypertension included those with blood pressure percentiles in the 90the-94th percentile.[13,15]

Subjects 18 years or older were classified according to adult guidelines. Overweight was considered as a BMI of 25-29.9 kg/m^2 and obese at 30 kg/m^2 or greater. Increased waist circumference was 88 cm or greater for females and 102 cm or greater for males.[14] Hypertension was defined as use of antihypertensives or systolic blood pressure of 140 mm Hg or greater and a diastolic blood pressure of 90 mm Hg or greater. Prehypertension included those with a systolic blood pressure of 120 mm Hg or greater and a diastolic blood pressure of 80 mm Hg or greater.[13]

Table I. Demographics, transplant, and post-transplant characteristics of pediatric liver transplant recipients

	All (n = 88)*
Age at visit (y)	15.4 ± 4.8
Female	48%
Hispanic	41%
Race	
White	36%
Black	6%
Asian	14%
Other†	26%
Multiracial	18%
Indication for transplant‡	
Biliary atresia	33%
Metabolic disease	17%
Cholestatic disease	7%
Acute liver failure, tumor, other	43%
Transplanted for chronic liver disease/cirrhosis	65%
Years since first liver transplant	11.2 ± 5.6
Retransplant	7%
Biopsy-proven acute rejection episodes	
0	40%
1-2	47%
≥3	13%
Chronic rejection	6%
Calcineurin inhibitor	
Tacrolimus	80%
Cyclosporine	10%
None	10%
Tacrolimus trough at visit (μg/L; n = 71)	4.2 (2.7-6.2)
Mean recent tacrolimus trough (μg/L; n = 71)§	4.7 (3.3-6.1)
Cyclosporine trough at visit (μg/L; n = 9)	53 (41-70)
Mean recent cyclosporine trough (μg/L; n = 9)§	89 (43-157)
Aspartate aminotransferase (IU/L)	33 (24-45)
Alanine aminotransferase (IU/L)	29 (21-46)
Gamma-glutamyl transferase	22 (13-51)
Total bilirubin	0.8 (0.6-1.2)
Creatinine (mg/dL)	0.57 (0.47-0.78)
Overweight/obese by BMI percentile/BMI	26%
Systolic hypertension/prehypertension	33%
Diastolic hypertension/prehypertension	10%
Elevated fasting glucose	20%
Glucose intolerance (n = 81)	27%
Hypertriglyceridemia	17%
Low HDL	39%
Hypercholesterolemia	7%
Elevated LDL	3%
PTMS	16%
Family history of stroke/myocardial infarction	51%
Family history of obesity	59%
Family history of diabetes (1st or 2nd degree)	68%

*Data represent proportion or median (IQR) except for age and years since transplantation, which are listed as mean ± standard deviation.
†Race and ethnicity self-reported. Other ethnicity includes Native American, Alaskan, Pacific Islander, Hawaiian, and unknown.
‡Metabolic liver disease includes alpha-1-antitrypsin deficiency, Crigler-Najjar syndrome, cystic fibrosis, glycogen storage disease, inborn errors in bile acid metabolism, neonatal hemochromatosis, primary hyperoxaluria, tyrosinemia, urea cycle defects, and Wilson disease. Cholestatic conditions include Alagille syndrome, Byler disease, progressive intrahepatic cholestatic syndromes, total parenteral nutrition cholestasis, sclerosing cholangitis, and idiopathic cholestasis. Other liver disease includes congenital hepatic fibrosis, Budd-Chiari syndrome, autoimmune hepatitis cirrhosis, drug toxicity, hepatitis C cirrhosis, and unknown cirrhosis.
§Mean of 3 most recent trough levels before the study visit.

Increased lipids for all subjects represented values at or above the 75th percentile for children and young adults.[13] Cutoffs were: triglycerides, 75 mg/dL or greater for children 9 year of age or younger and 90 mg/dL or greater for those 10 years of age or older; low-density lipoprotein (LDL) cholesterol of greater than 110 mg/dL, and total cholesterol of 170 mg/dL or greater.

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