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Growth of Liver Allografts Over Time in Pediatric Transplant Recipients

S.G. Chaudhry, MD¹, S. Bentley-Hibbert, MD², J. Stern, MD³, S. Lobritto, MD⁵, M. Martinez, MD⁵, J. Vittorio, MD⁵, K.J. Halazun, MD⁴, H.T. Lee, MD, PhD⁶, J. Emond, MD¹, T. Kato, MD¹, B. Samstein, MD⁴, and A. Griesemer, MD.¹

¹Department of Surgery, Columbia University Medical Center, New York, NY

²Department of Radiology, Columbia University Medical Center, New York

³Columbia Center for Translational Immunology, Columbia University, College of Physicians and Surgeons, New York, NY

⁴Department of Surgery, Weill-Cornell Medical Center, New York, NY

⁵Department of Pediatrics, Columbia University Medical Center, New York, NY

⁶Department of Anesthesiology, Columbia University Medical Center, New York, NY

Abstract

The liver's capacity to grow in response to metabolic need is well known. However, long-term growth of liver allografts in pediatric recipients has not been characterized. A retrospective review of pediatric recipients at a single institution identified patients who had cross-sectional imaging at 1, 5, and 10-years post-transplant. Using volumetric calculations, liver allograft size was calculated and percent standard liver volumes (SLV) were compared across the different time points. 18 patients ranging from 0.3–17.7 years old were identified that had imaging at two or more time points. Measured liver volumes increased by 59% after 5 years and 170% after 10 years. The measured liver volumes compared to calculated %SLV for these patients were $123 \pm 37\%$, $97 \pm 19\%$, and $118 \pm 27\%$ at 1, 5, and 10 years after transplant, respectively. Our data

Corresponding author: Adam D. Griesemer, MD, Columbia University College of Physicians & Surgeons, 622 W 168th Street, PH 14 Center, New York, NY 10032-3784, Phone: 212-305-9691, Fax: 212-342-5600, adg2101@cumc.columbia.edu.
DR. ADAM GRIESEMER (Orcid ID : 0000-0003-4894-2024)

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We have no conflicts of interest to disclose.

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Sulemon Chaudhry: Wrote the institutional review board proposal, performed collection and data analysis and was the primary author for this manuscript.

Stuart Bentley-Hibbert: Performed volumetric analysis of livers, reviewed and edited the manuscript.

Jeffrey Stern: Assisted in data collection and reviewed and edited the manuscript.

Karim J. Halazun: Assisted in data collection and reviewed and edited the manuscript.

Steve Lobritto: Assisted in data collection and reviewed and edited the manuscript.

Mercedes Martinez: Assisted in data collection and reviewed and edited the manuscript.

Jennifer Vittorio: Assisted in data collection and reviewed and edited the manuscript.

Jean Emond: Assisted in data collection and reviewed and edited the manuscript.

Tomoaki Kato: Assisted in data collection and reviewed and edited the manuscript.

Benjamin Samstein: Participated in study design, data collection and reviewed and edited the manuscript.

Adam Griesemer: Conceived of study design, assisted in data collection and assisted in construction of the manuscript.

suggest that liver allografts in pediatric recipients increase along with overall growth, and reach levels standard liver volumes for height and weight by 5 years post-transplantation. Additionally, as pediatric recipients grow, the livers appear to maintain appropriate SLV.

Introduction

The liver's capacity to regenerate after damage and grow in response to metabolic demands is well established. Ancient Greeks first recognized this unique aspect of liver physiology in the myth of Prometheus, where the titan was punished for bringing fire to man by having his liver eaten by the Eagle of Zeus only for it to regrow and be eaten again. Liver regeneration was then first experimentally established in 1931, where after removal of two-thirds of the liver in rats, the remaining lobes enlarge to make up the lost mass within 5 to 7 days.(1) Further studies showed both large animal and human livers also have the capacity to regenerate lost mass. The regenerative response after partial hepatectomy is directly proportional to the amount of liver tissue removed.(2) In adult humans, up to 70% of healthy liver can be safely resected with recovery of normal liver function within 2–3 weeks.(3)

The liver's unique segmental anatomy has allowed for large resections for disease without loss of hepatic function, and also for the use of modified-partial grafts in transplantation(4, 5). Because of the disparity between the number of pediatric patients requiring a liver transplant and the availability of size-matched donors, partial grafts have led to an expansion of the donor pool for pediatric patients with end-stage liver disease. Reduced size grafts were the first type of modified liver graft used in pediatric patients, where whole liver grafts were reduced to the left lobe with similar clinical outcomes.(6) Surgical technique was further developed to allow for the transplantation of partial liver grafts from deceased donor split-livers(7) and living donors.(8) Younger prospective recipients are more likely to receive a partial allograft with one center reporting up to 74% of pediatric liver transplants performed with partial grafts.(9, 10) Despite the use of reduced size livers, small pediatric patients often receive a liver that has excess mass compared to the metabolic need. These large livers will atrophy in the early post-operative period and allow for the strategy of delayed abdominal closure. As the pediatric recipients age and grow, the transplanted liver increases in volume. However, little is known about the appropriateness of the long-term growth of the transplanted liver relative to overall patient growth in the pediatric population years after transplantation, when the size of the patients has drastically increased. Here, we present the long-term growth of transplanted livers and compare this growth to standard liver volumes for the pediatric recipients at a single-center.

Methods

Study Design and Patient Selection

The study was approved by the Institutional Review Board at Columbia University Medical Center (Protocol number AAAO4705). Between January 1, 1998 and December 31, 2010, 171 patients under the age of 18 were recipients of liver transplants at Columbia University Medical Center. Retrospective review of records identified patients who had cross-sectional imaging, either computed tomography (CT) or magnetic resonance imaging (MRI), at two or

more of the following time points: 1-year, 5-years, and 10-years after transplant. Height and weight measurements at the time of imaging were collected in addition to demographic and clinical data.

Volumetric Measurements—Cross-sectional imaging for selected patients at each time point post-transplant was reviewed by a single abdominal radiologist. Data sets from either the CT or MRI were transferred to a dedicated 3D server (VitreaAdvanced 6.5.3, Minnetoka, Minnesota) and post processed using a manual segmentation tool which isolated the organs and then volume calculations were applied to the isolated voxels (Figure 1).

Standard Liver Volume (SLV) Calculations—Using height and weight measured at the time of imaging, standard liver volumes were calculated using age appropriate formulas. The following formulae were used.

$$0 \text{ to } \leq 1 \text{ year of age: SLV (mL)} = -143.062973 + 4.274603051 \times \text{height (cm)} + 14.78817631 \times \text{weight (kg)}$$

(11)

$$>1 \text{ to } \leq 16 \text{ years of age: SLV (mL)} = -20.2472281 + 3.339056437 \times \text{height (cm)} + 13.11312561 \times \text{weight (kg)}$$

(11)

$$>16 \text{ years of age: SLV (mL)} = 1072.8 \times ([\text{weight (kg)}]^{0.425} \times [\text{height (cm)}]^{0.725} \times 0.007184) - 345.7$$

(12)

The %SLV was calculated as a ratio of the liver volume measured by volumetric analysis to the SLV calculated based on height and weight measured at the time of imaging.

Statistical Analysis

Measured and calculated values are expressed as mean $\pm$ standard deviation. Statistical significance, defined as $P < 0.05$, was determined with an unpaired Student *t* test. Analysis was performed with Prism 5.4 (GraphPad La Jolla, CA).

Results

Patient Characteristics

18 patients were identified that had cross-sectional imaging (CT or MRI) one year after liver transplantation (Table 1). 3 patients were <1 year old at the time of transplant, while 12 were between 1 and 16 years old and 3 >16 years old. 8 patients were male, while 10 were female. A total of 6 patients received transplants due to biliary atresia, 4 as primary treatment and 2

after an initial Kasai procedure. 3 patients each were transplanted to treat hepatoblastoma and progressive familial intrahepatic cholestasis (PFIC). 2 patients each had hepatitis C and cryptogenic cirrhosis. 1 patient each was transplanted for citrullinemia and primary sclerosing cholangitis (PSC). Patients received one of three graft types: 8 received a partial liver graft from a living donor, 3 a partial graft from a deceased donor, and 7 a whole graft from a deceased donor.

Our center does not perform cross sectional imaging as a standard part of post-transplant monitoring. Therefore, all imaging was performed due to a medical indication. The indications for imaging at the different time points and the imaging modality used were also recorded (Table 2). All MRIs that were performed were to evaluate the elevation of LFTs and rule out biliary obstruction occurring both early and late with similar frequency. CT scans, however, were most often performed for the evaluation of suspected intra-abdominal infection, accounting for 13/29 CT scans performed in our cohort. Of those 13 CT scans performed for infection 11 were performed with one-year post-transplant. The next most common indication for CT scan was for malignancy work-up, most often occurring at least 5 years post-transplant. Other reasons CT scans were performed included to evaluate abdominal distension, pain, and GI bleeding.

Liver Volumes at 1-, 5- and 10-years post-liver transplant

13 of the identified patients had imaging 5 years after transplant, 2 had imaging 10 years after transplant, and 3 had imaging both 5 and 10 years post-transplant allowing for volumetric measurements of liver graft (Table 3). Absolute changes in liver volume were also calculated as percent change in measured volume with 1-year post-transplant volume as baseline (Table 4). The volume of liver in these patients changed by $59 \pm 66\%$ at 5-years post-transplant and $170 \pm 86\%$ at 10-years post-transplant when compared to measured volumes 1-year post-transplant. Using height and weight corresponding to time of imaging, SLV was calculated and used to determine the actual liver volume as %SLV (Table 5). Percent standard liver volumes were $123 \pm 37\%$, $97 \pm 19\%$, and $118 \pm 27\%$ at 1-, 5-, and 10-years post-transplantation, respectively. The only time points where %SLV is statistically significantly different were between 1 and 5 years ($p=0.016$).

Children who were younger than 4 years old at the time of transplantation had $94 \pm 59\%$ overall increase in liver volume from 1-year to 5-years post-transplant while those older than 4 had $22 \pm 46\%$ change in liver volume, a statistically significant difference ($p=0.02$). However, the difference in %SLV between these two age groups did not reach statistical significance. Liver volumes for children <4 were $123 \pm 40\%$ of SLV 1-year after transplant and $91 \pm 16\%$ SLV after 5 years. Children >4 had a %SLV of 124 ± 32 1-year after transplant and 103 ± 20 5-years after transplant. There was no statistically significant difference of %SLV or percent liver growth when accounting for whole vs. partial graft, donor type, or sex between 1- and 5-years post-transplant (Table 6 & 7).

Discussion

Liver growth and regeneration is mediated by a number of different mitogens. Essential factors that increase the rate of hepatocyte DNA synthesis include hepatocyte growth factor

(HGF) and ligands of the epidermal growth factor receptor (EGFR), such as epidermal growth factor (EGF) and tumor growth factor- α (TGF α).⁽¹³⁾ Numerous other factors serve as auxiliary mitogens that are non-essential to liver growth and whose absence only slows the regenerative process. Examples include norepinephrine, tumor necrosis factor (TNF), interleukin (IL)-6, vascular endothelial growth factor (VEGF), insulin, and many others. ^(14–17) After partial hepatectomy, the entirety of portal circulation flows through a smaller organ. Portal blood is rich in insulin from the pancreas, EGF from Brunner's glands of the duodenum, and in factors that activate HGF.^(18, 19) Thus the remnant liver receives a relatively increased amount of growth factors and this may explain the requirement of portal flow on maintaining appropriate liver mass.⁽²⁰⁾ Cessation of liver regeneration is a complex and partially undefined process, but seems to depend on inhibitors of liver mitogenic activity such as TGF β .⁽²¹⁾

The short-term regeneration and growth of partial-liver allografts in adult recipients has been well-studied. Within 3 months post-transplant, recipients of living donor livers have rapid regeneration of their transplanted organ to normal size.⁽²²⁾ Recipients of a partial graft from a deceased donor also showed similar liver regeneration and growth.⁽²³⁾ Similarly, adults who undergo partial hepatectomy for living donation have rapid regeneration of their native liver, reaching volumes exceeding standard liver volumes within two months but gradually decrease to normal volume within one year.⁽²⁴⁾ However, to our knowledge, there are no studies of long-term growth of transplanted livers in pediatric patients. Since these grafts have to hypertrophy for years after transplantation when they may have been subjected to rejection, recurrent disease or technical issues, it is important to determine their ability to maintain appropriate volume relative to recipient size in the short, medium and long term.

Our retrospective analysis reveals that, overall, transplanted livers change in size to accommodate overall growth. Despite the use of modified partial grafts, liver grafts are often large for the recipient where 48% of recipients required delayed primary closure in one series.⁽²⁵⁾ Even one-year after transplant, recipients' livers in our cohort were larger than the standard volume for their respective size. However, by 5 years after transplantation, when the recipients have grown, the liver size approximates 100% standard liver volume. The percent change in liver volumes in small recipients was greater than in recipients that were larger at the time of transplant. In fact, some livers that were extremely large for a small recipient (patients 6 and 8) actually shrank from 1–5 years. At the 5-year imaging, these patient's livers were near 100% SLV and were thus a more appropriate volume for the patient size. Although older children had less percent change in liver volume than those younger than 4, the %SLV at later time points was no different. This suggests the livers are able to atrophy or hypertrophy in response to the metabolic demands of the patients for up to 10 years after transplant. The growth and regeneration of the livers were not affected by the type of graft the patient received (whole or partial liver, deceased or living donor) or the recipient's sex.

Our study has several limitations. One limitation is the small patient sample. Although there were many pediatric liver transplant recipients at our center, imaging at the interested post-transplant time-points was limited by the lack of obtaining cross sectional imaging as part of our post-transplant monitoring protocol. We do not routinely obtain this imaging since CT

scanning is associated with high levels of ionizing radiation and increased risk of malignancy, especially in children. MRI, on the other hand, requires patient cooperation to remain stationary and children often require light sedation or even anesthesia to obtain an appropriate scan. These considerations lead to a high threshold for performing cross-sectional imaging this is necessary for volumetric measurements. In our cohort, almost all scans were performed to evaluate for complications related to transplant including infections, biliary stricture, or tumor recurrence. Although this introduces a bias in our patient population, it would be unlikely to alter the conclusion of the study, as it is reasonable to assume that patients suffering such complications would be more likely to have impaired liver growth. The fact that these patients maintained appropriate SLV suggests that patients without complications would also maintain appropriate SLV. A second limitation is the relatively small number of time points we were able to analyze. We chose to analyze growth at 1, 5 and 10 years as markers for short-term growth, intermediate term growth, and long-term growth, respectively. In our living donor program, we consider the liver volumes at the 1-year time point to represent the final regeneration of the liver after resection. Therefore, in this study, the volumes at 1 year were selected to represent the volumetric change induced by the immediate demand of the recipient's size. Growth thereafter was felt to be attributable to changes in the size of the recipient as they aged. We did not analyze the growth of the liver beyond 10 years because we did not have a sufficient number of patients with cross sectional imaging early and > 10 years. However, it would be important to confirm the liver can maintain appropriate SLV beyond 10 years in future studies. Despite these limitations, we have shown that livers in pediatric recipients change in size to accommodate children's overall growth many years after transplant. Younger patients have a greater overall increase in liver size due to greater relative increase in body weight over time. However, all ages analyzed were able to maintain appropriate liver size relative to calculated standard liver volume.

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Abbreviations

CT	Computed Tomography
GI	Gastrointestinal
LFT	Liver Function Tests
PSC	Primary Sclerosing Cholangitis
SLV	Standard Liver Volume

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Figure 1.

Representative example of volumetric measurements. A segmentation algorithm was applied to semi-automatically delineate liver margins on each scan in multiple cuts (shown in blue). The computer-generated contours were visually inspected and modified, if needed, by a radiologist. Volumes of livers were then calculated based on the final contour results. The major vessels were not included in volume calculations.

Table 1

Patient Characteristics

Patient	Age at Transplant	Gender	Indication	Graft-Type	Donor Type
1	4 yr 1 mo	F	Failed Kasai	Partial	Living
2	17 yr 8 mo	M	PSC	Whole	Deceased
3	17 yr 2 mo	F	Failed Kasai	Partial	Living
4	1 yr 0 mo	F	Hepatoblastoma	Partial	Deceased
5	12 yr 6 mo	F	HCC	Partial	Living
6	9 yr 4 mo	M	PFIC	Whole	Deceased
7	0 yr 7 mo	M	Biliary Atresia	Whole	Deceased
8	16 yr 2 mo	M	Hepatitis C	Whole	Deceased
9	9 yr 3 mo	M	Cryptogenic	Whole	Deceased
10	0 yr 7 mo	F	Biliary Atresia	Partial	Living
11	1 yr 0 mo	M	Hepatoblastoma	Partial	Deceased
12	0 yr 4 mo	F	Biliary Atresia	Partial	Living
13	2 yr 7 mo	F	Hepatoblastoma	Whole	Deceased
14	1 yr 11 mo	M	Biliary Atresia	Partial	Living
15	1 yr 1 mo	M	cryptogenic	Whole	Deceased
16	1 yr 1 mo	F	PFIC	Partial	Living
17	0 yr 4 mo	F	Citrullinemia	Partial	Deceased
18	4 yr 7 mo	F	PFIC	Partial	Living

Table 2

Reason for Imaging and Modality

Patient	Liver Volume (mL)		
	1 year	5 years	10 years
1	CT infection	CT GI bleed	
2	MRI elevated LFTs	CT pain	
3	CT infection	MRI elevated LFT	
4	CT infection	CT cancer work-up	
5	CT cancer work-up	CT cancer work-up	
6	CT distension	MRI elevated LFTs	
7	CT infection	CT distension	
8	CT distension	CT cancer work-up	
9	CT infection	CT ascites	
10	CT infection	CT cancer work-up	
11	CT infection	CT cancer work-up	
12	MRI elevated LFTs	MRI elevated LFTs	
13	CT infection	MRI elevated LFTs	
14	MRI elevated LFTs		MRI elevated LFTs
15	CT infection		CT cancer work-up
16	CT infection	CT pain	MRI elevated LFTs
17	CT distension	CT renal artery stenosis	CT infection
18	CT infection	CT infection	MRI elevated LFTs

CT: Computed Tomography; MRI: Magnetic Resonance Imaging; LFT: Liver Function Tests

Table 3

Measured Liver Volumes Post-Transplant

Patient	Liver Volume (mL)		
	1 year	5 years	10 years
1	564.27	682.72	
2	1567.95	1827.40	
3	2144.23	2130.63	
4	346.74	530.88	
5	777.89	1097.57	
6	1088.97	804.19	
7	242.20	756.42	
8	1647.64	1257.32	
9	564.27	682.72	
10	545.24	497.97	
11	298.89	536.17	
12	239.96	506.67	
13	342.77	744.16	
14	427.81		902.61
15	434.38		739.75
16	274.26	583.47	1043.67
17	322.33	583.50	1064.88
18	470.98	1081.11	1224.16

Table 4

Percent Liver Growth

Patient	Change Liver Volume	
	1→5 years	1→10 years
1	20.99	
2	16.55	
3	-0.63	
4	53.11	
5	41.10	
6	-26.15	
7	212.31	
8	-23.69	
9	20.99	
10	-8.67	
11	79.39	
12	111.15	
13	117.10	
14		110.98
15		70.30
16	112.74	280.54
17	81.03	230.37
18	129.54	159.92

Table 5

%Standard Liver Volume

Patient	%Standard Liver Volume		
	1 year	5 years	10 years
1	105.31	94.14	
2	94.14	102.25	
3	135.73	125.03	
4	89.06	88.18	
5	89.42	81.69	
6	195.08	106.11	
7	115.24	119.47	
8	131.66	104.54	
9	107.87	73.95	
10	148.51	73.72	
11	91.68	83.95	
12	150.24	81.24	
13	89.49	72.62	
14	90.66		82.52
15	159.42		100.93
16	87.55	108.69	127.01
17	210.43	103.98	154.67
18	130.31	137.76	124.67

Table 6

Statistical Analysis of %SLV

	1-year %SLV	p-value	5-year %SLV	p-value
Age	<4	123 ± 40	91 ± 16	0.24
	>4	124 ± 32	103 ± 20	
Graft Type	Whole	128 ± 35	96 ± 17	0.90
	Partial	121 ± 37	98 ± 20	
Donor Type	Living	117 ± 25	100 ± 22	0.61
	Deceased	128 ± 43	95 ± 15	
Recipient Sex	Male	123 ± 35	98 ± 15	0.87
	Female	124 ± 38	97 ± 21	

Table 7

Statistical Analysis of Liver Growth

		Liver growth	p-value
Age	<4	95 ± 59	0.02
	>4	22 ± 46	
Graft Type	Whole	53 ± 86	0.80
	Partial	62 ± 46	
Donor Type	Living	58 ± 54	0.98
	Deceased	59 ± 71	
Recipient Sex	Male	47 ± 82	0.59
	Female	66 ± 49	