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Post-transplant metabolic syndrome in children and adolescents after liver transplant: a systematic review

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Abstract

In long-term follow-up, 18-67% of pediatric liver transplant recipients are overweight or obese—with rates varying by age and pre-transplant weight status. Similar prevalence of post-transplant obesity is seen in adults. Adults also develop post-transplant metabolic syndrome, with consequent cardiovascular disease, at rates that exceed age and gender-matched populations. Post-transplant metabolic syndrome has never been studied in pediatric liver transplant recipients—a growing population as transplant outcomes continue to improve. This paper systematically reviews the literature on each component of metabolic syndrome—obesity, hypertension, dyslipidemia, and glucose intolerance—in pediatric liver transplant recipients. Rates of obesity are similar to that of the general U.S. population of children. But hypertension, dyslipidemia, and diabetes are more common than expected for age, gender, and obesity severity in transplant recipients. Immunosuppressive medications are major contributors. Limitations of prior studies—including heterogeneous methods of diagnosis, follow-up times, and immunosuppressive regimen—hinder the analysis of risk factors. Importantly, no studies report on graft or patient outcomes associated with metabolic syndrome components after pediatric liver transplant. However, if trends in children are similar to those seen in adults, these conditions may lead to significant long-term morbidity. Further research on the prevalence, causes, and consequences of post-transplant metabolic syndrome in pediatric liver transplant is needed and ultimately will help improve long-term outcomes.

Keywords

pediatric; liver transplant; metabolic syndrome; obesity; hypertension; dyslipidemia; diabetes mellitus; insulin resistance

Introduction

In pediatric liver transplant recipients, pre-transplant obesity has been associated with higher risk of death in long-term follow-up. (1) We recently found that 15-21% of children are overweight or obese prior to transplant. After transplant, 18-67% are overweight or obese—with rates varying by age and pre-transplant weight status. (2)

Factors linking pre-transplant obesity with morbidity and mortality in children have not been explored. In adult liver transplant recipients, post-transplant metabolic syndrome—including obesity, hypertension, dyslipidemia, and diabetes mellitus—is emerging as an important link

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between obesity and poor outcomes. Adults have a similar prevalence of post-transplant obesity compared to children: 21% - 58%. (3-5) In addition, 43-58% of adults develop metabolic syndrome.(6-9) Liver transplant recipients are at higher risk for metabolic syndrome than their non-transplanted peers—likely secondary to a combination of post-transplant weight gain and side effects of immunosuppressants. Post-transplant metabolic syndrome and diabetes increase the risk of major cardiovascular events, a leading cause of death after liver transplant. (6, 9, 10)

Post-transplant metabolic syndrome has never been studied in children after liver transplant. But if the prevalence echoes that in adults, it could be a key contributor to long-term morbidity and mortality. Studies of population-based pediatric cohorts show that childhood metabolic syndrome increases the risk of cardiovascular disease in adulthood (11-16). Childhood obesity, hypertension, and glucose intolerance are associated with early death. (17) Early detection and treatment of these disorders may prevent longer term complications. (18, 19)

This paper systematically reviews existing evidence on the components of metabolic syndrome in pediatric liver transplant recipients. We also review the literature on pediatric post-transplant non-alcoholic fatty liver disease (NAFLD), which some consider the hepatic manifestation of metabolic syndrome.

Methods

Literature search

A computer-aided, systematic search of literature published 1992-2012 on the prevalence of metabolic syndrome in pediatric liver transplant recipients was performed using MEDLINE/PubMed, Cochrane Library, Web of Science, and BIOSIS Previews. Because our initial search identified no eligible articles on metabolic syndrome in this population, we did a systematic search for each component of metabolic syndrome—obesity, hypertension, dyslipidemia, diabetes mellitus/insulin resistance—and for the related condition NAFLD using the same databases. Search terms are detailed in SUPPLEMENTARY TABLE 1. Reference lists of selected articles were searched manually to identify additional articles. Published abstracts from annual meetings of the American Association for the Study of Liver Diseases, the American Transplant Congress, and Digestive Disease Week between 1992 and 2012 were also reviewed using the search terms “pediatric” AND “liver transplant.”

Study inclusion/exclusion criteria

We included all studies published in English between 1992 and March 2012 that reported on children 0-18 years who had undergone liver transplant. We excluded studies that included only pre-transplant measurements, studies of multi-organ transplant, studies that did not separate children from adults or liver transplant from other transplant populations, and studies that provided measurements of interest but no prevalence of abnormal values (i.e. blood pressure data but no prevalence of hypertension).

Data extraction

One author (E.P.) searched the databases, reviewed reference lists, and identified studies for full-text review. Two reviewers (E.P. and A.L.) independently read and extracted data from all selected studies. Study design, number of participants, year of transplant, participant age at transplant and follow-up after transplant, diagnostic criteria, prevalence, and reported risk factors were pre-specified as data categories. Disagreements were discussed by the two

reviewers and adjudicated by the principal investigator (P.R.) if consensus could not be reached.

Data analysis

The inconsistent definitions of each condition, follow-up times, and immunosuppressive regimens prevented meta-analysis of prevalence estimates. Given the lack of validated scoring systems for observational studies (20, 21) and the heterogeneity of studies included in our review, we did not formally score studies for data quality. For comparison, we provide recent estimates of each condition's prevalence in population-based cohorts of U.S. children. We did not formally compare these estimates with estimates from reviewed studies, again because of the heterogeneity of cutoffs for abnormal values.

Results

Of 1212 articles and abstracts identified by our search terms, 106 required full-text review. Thirty-nine met our inclusion criteria, including one randomized controlled trial (22), nine prospective cohort studies, 14 retrospective cohort or case-control studies, and 6 cross-sectional studies. (FIGURE 1) Five of the nine prospective studies reported on the Studies in Pediatric Liver Transplantation (SPLIT) cohort. (23-27) All 9 studies on post-transplant NAFLD were case series or case reports.

Since no studies reported on outcomes associated with pediatric post-transplant obesity, hypertension, dyslipidemia, diabetes mellitus/insulin resistance, or NAFLD, our review focuses on the prevalence of each condition and associated risk factors. We emphasize recent studies, as they are most applicable to current post-transplant management—specifically tacrolimus-based regimens instead of cyclosporine.

Pre- and post-transplant obesity in pediatric liver transplant

Most of the literature on growth in pediatric liver transplant recipients has focused on growth failure and post-transplant catch-up growth. (28-31) We identified four studies that describe overweight and obesity in this population.

The four studies suggest that overweight and obesity are common post-transplant, particularly in those overweight prior to transplant. (TABLE 1) The prevalence of overweight/obesity (32%) and obesity (17%) reported in the general U.S. pediatric population is similar to the prevalence of these conditions in children after liver transplant. (32)

Pre-transplant obesity appears to be the strongest predictor of post-transplant obesity.(2, 26) Hispanic ethnicity was the other independent predictor of post-transplant obesity consistent across age groups and time periods.(2, 26) One study from the SPLIT group identified persistent steroid use as a risk factor for post-transplant obesity(26), although the two studies of long-term follow-up from this same cohort found no difference in the prevalence of obesity by steroid use at five and ten years post-transplant. (23, 25)

Hypertension

Of the 16 studies included in this review, 50% relied on use of anti-hypertensive medication as evidence of hypertension, and 13% provided no definition. Estimates of hypertension prevalence from these studies vary from 4-100%. (TABLE 2)

Six studies (37%) applied age and gender-specific blood pressure percentiles in addition to using medication regimens. In the four studies that used percentiles to report hypertension

prevalence at five to ten years post-transplant, three estimated prevalence at 20-28% (27, 33, 34); one reported lower prevalence. (35) The two studies that reported hypertension one year post-transplant estimated a prevalence of 58-64%, although the majority of these children were on cyclosporine. (36, 37) In contrast, the estimated prevalence of childhood hypertension in population-based pediatric cohorts is 3-5%. (38-40)

Hypertension was less common in patients on tacrolimus than on cyclosporine in all six studies that compared these groups. (22, 35, 41-44) However, these findings may have been confounded by steroid use. Indeed, in the SPLIT cohort persistent steroid use increased the risk of hypertension. (23, 27)Three studies note that children on tacrolimus were significantly more likely to be steroid-free or on lower steroid doses long-term than those on cyclosporine. (22, 43, 44)

Studies conflicted on the relationship between post-transplant hypertension and renal function. Four studies found an association between hypertension and low glomerular filtration rate (GFR) (27, 33, 41, 42), but two found no association. (34, 45) One linked hypertension at one year post-transplant to higher GFR (36); these authors posited that anti-hypertensive medications might protect against calcineurin inhibitor nephrotoxicity. (i.e. 46, 47)

Of note, only one study used ambulatory blood pressure monitoring to diagnose hypertension. They found that seven of the eight children classified as hypertensive were normotensive in the clinic but hypertensive on ambulatory monitoring. (34) None of the studies explored the relationship of hypertension to obesity or other features of metabolic syndrome.

Dyslipidemia

Eight studies that evaluated post-transplant dyslipidemia used varying definitions (n=5) or did not report their cutoffs (n=3). Only three studies reported on fasting levels. (48-50). Only one study reported on high-density lipoprotein (HDL) (50), and one examined low-density lipoprotein (LDL) (48). In five studies, the majority of children were on cyclosporine and prednisone, limiting the utility of their findings for current practice. (TABLE 3)

Elevated triglycerides were the most common dyslipidemia found in five studies, with most studies estimating prevalence between 16 and 50%. (TABLE 3) Elevated triglycerides were associated with higher body mass index (BMI) z-score in one study (51) but not with overweight in another (52), although both studies were small.

Observational studies and trials in other transplant populations suggests that tacrolimus is associated with less dyslipidemia than cyclosporine. (53-55) None of the studies that we reviewed reported prevalence by calcineurin inhibitor. The one study that examined the impact of immunosuppressive medications found that steroid dose correlated with dyslipidemia but type of calcineurin inhibitor had no effect; however, sample size was small. (52)

Among all U.S. children, approximately 10% have elevated triglycerides, 10% have elevated total cholesterol, and 8% have low HDL. (56, 57) However, heterogeneity in definitions of dyslipidemia between studies and the lack of fasting levels limit this comparison.

Diabetes mellitus, glucose intolerance, and insulin resistance

Ten studies addressed post-transplant diabetes mellitus, glucose intolerance, or insulin resistance in children after liver transplant. Five studies relied on report of diabetes diagnosis or use of insulin or hypoglycemic medications by the transplant center. (23-25, 58,

59) The other five incorporated blood glucose measurements (49, 60-63) The estimated prevalence of post-transplant diabetes, which ranged from 1-17%, did not vary systematically based on definition. (TABLE 4)

Three longitudinal studies showed that diabetes was most prevalent in the first months post-transplant, with decreasing prevalence over time. (24, 25, 61) Corticosteroid use was a risk factor in multivariate analysis of the largest study, in which 78% of diabetes occurred within one month post-transplant. Mean duration of diabetes was 74 days in those diagnosed <1 month post-transplant and 80 days in those diagnosed >1 month post-transplant. (24) One study reported increasing cumulative incidence over time; (58) however, their analysis did not account for possible resolution of diabetes.

The reviewed studies support the theory that tacrolimus is more “diabetogenic” than cyclosporine in children, but do not provide conclusive evidence. Four studies identified tacrolimus-based immunosuppression as a risk factor for post-transplant diabetes (23, 24, 60, 62), and another two studies included only patients on tacrolimus. (61, 63)However, all the studies were observational.

The two studies that addressed pre-transplant obesity found no association with post-transplant diabetes in children.(24, 58) Kuo et al. reported a higher prevalence of diabetes in those under or normal weight 6 months after transplant. (58) No studies assessed post-transplant obesity and timing or duration of diabetes. None correlated diabetes with dyslipidemia or hypertension.

Two small cross-sectional studies examined insulin resistance and glucose intolerance in children without diabetes after liver transplant. In one study, all children were on tacrolimus and steroid-free. (63) 18% had glucose intolerance, but none were obese, had a family history of diabetes, were taking steroids, or had had early diabetes following transplant. The four children that did have early post-transplant diabetes had normal glucose and insulin levels. (63)

Among all U.S. adolescents, 7% have impaired fasting glucose (100-125 mg/dL) (64) and 0.5% have diabetes mellitus. (65) Available estimates suggest a higher prevalence in children after liver transplant, but further longitudinal research is needed to define incidence and risk factors.

Non-alcoholic fatty liver disease

Post-transplant NAFLD has been documented only in case series and reports in pediatric liver transplant recipients. (TABLE 5) Of the 19 children reported in these studies, four were transplanted for cirrhosis associated with non-alcoholic steatohepatitis (NASH). All four were overweight and had other features of metabolic syndrome. Interestingly, all four had hepatopulmonary syndrome at transplant. (66-68)

Twelve children with post-transplant NAFLD had progressive intrahepatic familial cholestasis type 1 (PFIC 1). None were overweight. Rather, 11 had chronic diarrhea and malnutrition thought secondary to restored bile flow from the liver with persistently abnormal intestinal re-absorption and to pancreatic insufficiency. (69) One had resolution of NASH after external biliary diversion. (69)

One retrospective review identified three children who developed steatosis within 30 days after transplant. (70) NAFLD in these patients may have been related to overall liver dysfunction.

Discussion

There are no studies of post-transplant metabolic syndrome in children after liver transplant. We thus systematically reviewed the literature on the prevalence of metabolic syndrome components in this population. Post-transplant obesity occurs in 10-67%, with prevalence highest in those overweight before transplant and decreasing over time. The reported estimates are similar to those of overweight and obesity in the general U.S. pediatric population.

As with obesity, hypertension, dyslipidemia, and glucose intolerance appear to be most common in the early post-transplant period. But even five to ten years post-transplant, all remain much more common in children after liver transplant than in the general population. The most rigorous studies of post-transplant hypertension reported a prevalence of 20-28% in long-term follow-up. Hypertriglyceridemia was reported in 10-56% and hypercholesterolemia in 7-57%. Persistent corticosteroid use seems to increase hypertension and dyslipidemia, but the impact of specific calcineurin inhibitors is difficult to discern from existing literature.

Post-transplant diabetes in pediatric liver transplant seems to occur most commonly in the early post-transplant period and appears to be mostly short-term. Corticosteroid use appears to be a major risk factor. The impact of tacrolimus is difficult to assess from currently available evidence. Post-transplant obesity has not been identified as a risk factor.

The high prevalence of these conditions suggests that post-transplant metabolic syndrome may also be common in children after liver transplant—as it is in other post-transplant groups. In adults after liver transplant, metabolic syndrome develops in 43-58%. (6-9) In pediatric renal transplant patients, 25-38% develop metabolic syndrome in the 2 years post-transplant, with cumulative steroid exposure an important risk factor.(71, 72) Further research is needed to establish prevalence after pediatric liver transplant and its impact on cardiovascular disease, graft health, and other outcomes.

Post-transplant insulin resistance and NAFLD—which may be harbingers of later morbidity — have only been evaluated in small studies or case series. Insulin resistance and diabetes in adult liver transplant recipients are associated with advanced fibrosis, increased risk of late hepatic artery thrombosis, acute and chronic rejection, and mortality. (10) Importantly, post-transplant metabolic syndrome has been associated with de novo NAFLD in adults. (73) Thus, further investigation into these conditions in pediatric liver transplant recipients is warranted.

The limitations of this systematic review reflect the limited literature on this topic. All studies were observational except one. The heterogeneity of definitions and immunosuppressive regimens limited the generalizability of the prevalence estimates and risk factors to current pediatric liver transplant recipients. This heterogeneity prevented meta-analysis of extracted data.

We do not suspect that publication bias explains the paucity of published studies on this topic. It is possible that studies finding very low prevalence of, for example, post-transplant obesity or diabetes would be more difficult to publish. However, the abstracts included in this review did not systematically report lower prevalence of any condition—arguing against this bias.

An additional limitation is that most of the data reviewed was not collected specifically for the assessment of post-transplant metabolic syndrome or its components. Post-transplant obesity estimates relied on weight or BMI percentile. No studies in this population assessed

waist circumference, which is used in strict definitions of metabolic syndrome. (74) No studies measured body composition of children before after liver transplant, for example using anthropometrics or dual x-ray absorptiometry (DEXA) scans to assess fat mass and distribution. The inclusion of non-fasting lipids and blood sugars and non-resting blood pressure measurements also decreases the accuracy of available estimates. In summary, both the prospective and retrospective cohorts lacked significant amounts of important data.

Further research on post-transplant metabolic syndrome and its components may help explain the relationship between pre-transplant obesity and long-term mortality seen in children after liver transplant. (1) This is particularly important because metabolic syndrome is modifiable if detected early and managed appropriately.(19, 75) Systematic screening could improve early diagnosis. (TABLE 6) More intensive counseling on healthy lifestyles or modification of immunosuppressive regimens could be undertaken.(76) Though efforts are generally made to minimize steroid exposure in children and adolescents, this may be even more important in those with features of metabolic syndrome. A better understanding of metabolic complications in children after liver transplant would help in the design of screening protocols and the coordination of multidisciplinary teams to manage these conditions once they are diagnosed.

Investigating metabolic syndrome and its components in children after liver transplant also offers an opportunity to disentangle some of the correlates identified in adults. The effects of immunosuppression are difficult to isolate in adults because other risk factors are so common — including NAFLD, hepatitis C, and alcoholic liver disease as indications for liver transplant and older age. The interplay of immunosuppression and the systemic inflammation associated with obesity, NAFLD, and atherosclerosis is also less confounded in children. (77, 78)

This systematic review suggests a high prevalence of the components of post-transplant metabolic syndrome in children after liver transplant. However, it also highlights the limitations of existing evidence. Assessment of metabolic syndrome prevalence in cross-sectional studies and association with outcomes in longitudinal studies are needed. These studies would improve our understanding of how post-transplant metabolic syndrome impacts transplanted livers and children’s overall health. They would also aid physicians in appropriately treating this condition, reducing overall morbidity in a growing population of post-transplant children.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations (used in text and tables)

NAFLD	Non-alcoholic fatty liver disease
SPLIT	Studies in Pediatric Liver Transplantation
GFR	Glomerular filtration rate

HDL	High-density lipoprotein
LDL	Low-density lipoprotein
BMI	Body mass index
NASH	Non-alcoholic steatohepatitis
PFIC 1	Progressive intrahepatic familial cholestasis type 1
UNOS	United Network for Organ Sharing
IQR	Interquartile range
CSA	Cyclosporine
TAC	Tacrolimus
PRED	Prednisone
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
SD	Standard deviation
BP	blood pressure
GFR	Glomerular filtration rate
TC	Total cholesterol
TG	Triglycerides
HCC	Hepatocellular carcinoma
DM	Diabetes mellitus
ICU	Intensive care unit
OGTT	Oral glucose tolerance test
HOMA-IR	Homeostatic model assessment of insulin resistance
HPS	Hepatopulmonary syndrome

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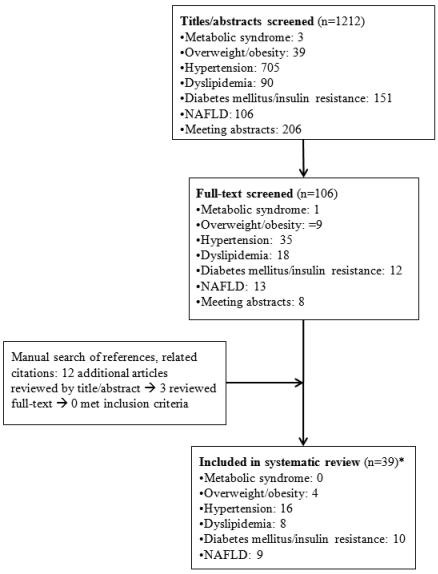

Figure 1.

Flow diagram of search strategy. *Four articles reviewed for more than one category, but counted once in total n. Total n includes 33 articles and 6 abstracts. Abstracts are noted in the summary tables.

Table 1

Overweight and obesity after liver transplant in children

Prevalence	Diagnostic criteria	n	Year of transplant	Study design	Post-transplant follow-up [median (range)*]	Age at transplant: [median (range)*]	Reported risk factors	Ref
• 1y: 18-67% • 2y: 21-61% • 5y: 21-57% • 10y: 20-50%	BMI or weight-forheight>85th percentile for age/gender	• 1y: 3059 • 2y: 2411 • 5y: 1308 • 10y: 442	1987-2010	Retrospective (UNOS)	5.6y (2-10.2y)	6m-20y	• Overweight/obese pre-transplant • Hispanic ethnicity • Biliary atresia, cholestatic liver disease (for children age <6y at transplant)	(2)
• 12%	Weight>95th percentile	461	1996-2001	Prospective (SPLIT)	6y (4.8-15y)	1.6y (IQR 0.7-6.5y)	• NOT associated with steroid use at 5y • **Meds**: 74% Tac, 24% CSA, 26% Pred†	(23)
• 10%	BMI>95th percentile	167	1995-1999	Prospective (SPLIT)	9.5-10.5y	1y (IQR 0.6-3.6y)	• NOT associated with steroid use or AST/ALT at 10y • **Meds**: 68% Tac, 23% CSA, 19%Pred	(25)
• 1y: 19% • 3y: 18% • 5y: 11%	BMI>95th percentile	1706	1995-2007	Prospective (SPLIT)	NA‡	Mean 4.6y	• Overweight/obese pre-transplant • Age <6y at transplant • Persistent steroid use • Hispanic ethnicity	(26) //

BMI Body mass index; UNOS United Network for Organ Sharing; SPLIT Studies in Pediatric Liver Transplantation; IQR Interquartile range; AST Aspartate aminotransferase; ALT Alanine aminotransferase

*Unless otherwise indicated.

†CSA Cyclosporine; Tac Tacrolimus; Pred Prednisone. Listed medications represent proportion of patients on each medication at time of study visit or last follow-up unless otherwise indicated. Other immunosuppressive medications with <10% prevalence in study population not listed.

‡Data not available in published study.

//Abstract

Table 2

Hypertension after liver transplant in children

Prevalence	Diagnostic criteria	n	Year of transplant	Study design	Post-transplant follow-up [median (range)*]	Age at transplant [median (range)*]	Reported risk factors	Ref
• 5y: ○ 20.7% elevated ○ 7.9% borderline • 10y: ○ 27.5% elevated ○ 7.3% borderline	• Elevated: SBP or DBP>95th percentile or on anti-hypertensive medication • Borderline: SBP or DBP 90-95th percentile	815	2005-2008	Prospective (SPLIT)	5-10y	Mean 3.5y (SD 4y)	• Age 5-7y at transplant (vs. <1y) • On steroid at last BP measurement • Low GFR at last BP measurement • 63% of those with 1 elevated BP had recurrent elevated BP • **Meds**: At transplant: 58% Tac, 28% CSA. At last follow-up: 70% Tac, 13% CSA. †	(27)
• 9%	On anti-hypertensive medication	461	1996-2001	Prospective (SPLIT)	6y (4.8-15y)	1.6y (IQR 0.7-6.5y)	• At 5y, 49% with hypertension on Pred vs. 23% without hypertension on Pred (p=0.0003) ‡ • **Meds**: 74% Tac , 24% CSA, 26% Pred	(23)
• 23%	SBP>95th percentile for age/height or treatment with anti-hypertensive medication after 1y	69	1987-2005	Retrospective	9.3y (IQR 6.3-11.9y)	3.2y (IQR 1.3-7.9y)	• Hypertension at 1y increased risk of renal insufficiency • **Meds**: 61% CSA, 39% Tac, Pred 100%	(33)
7.1% Tac 9.2% CSA	SBP>95th percentile for on anti-hypertensive medication	129	1991-2006	Retrospective	>5y post-transplant	NA §	• **Meds**: 67% CSA, 33% Tac, Pred 100%	(35)
• 1y: 58%	SBP or DBP>95th percentile for age and gender, or on anti-hypertensive medication at 1y	107	1986-1999	Retrospective	Mean 7.6y (range 3-14.6y)	Mean 4.9y (range 0.08-20.8y)	• Hypertension at 1y decreased risk of renal insufficiency	(36)

Prevalence	Diagnostic criteria	n	Year of transplant	Study design	Post-transplant follow-up [median (range)*]	Age at transplant [median (range)*]	Reported risk factors	Ref
							• **Meds**: 59% CSA, 41% Tac	
• 1y: 64%	Arterial hypertension, per "age-related guidelines," and treated with anti-hypertensive medications	101	1986-2003	Prospective	6y (1-17y)	2.9-4.8y (0.1-18.9y)	• Tyrosinemia • **Meds**: At transplant: 87% CSA, 100% Pred. At last follow-up: 47% CSA, 53% Tac, Pred unknown	(37)
• 1y: 34% • 2y: 24% • Any hypertension: ○ 19% Tac ○ 45% CSA	NA	50	1999-2002	Prospective	3y	Mean 9.9y (range 9m-18y)	• 64% of children with hypertension had GFR below normal • **Meds**: 100% Pred, CSA/Tac unknown	(41)
• 88%	On anti-hypertensive medication	24	1991-2003	Retrospective	Mean 2.1y (range 0.4–7.3y)	Mean 6.6y (range 0.8–13.3y)	• **Meds**: 79% Tac, 21% CSA, Pred unknown	(79)
• 50%	On anti-hypertensive medication	28	NA	Retrospective	Primary liver disease (n=23): Mean 29.3m (SD 1m) Metabolic (n=5): Mean 43.8m (SD 4.7m)	Mean 4y (range 7m-14y)	• Meds: 75% CSA, 25% Tac, Pred unknown	(80)
• 28%	• Mean SBP/DBP >95th percentile • If ≥18y: ≥135/85 (day), 120/75 (night)	29	NA	Cross-sectional	5.1 y (1.1–11.5y)	Age at follow-up:10.8 y (3.9–24.8y)	• No difference in medications, BMI, age, gender, GFR, cumulative CSA or Pred dose for hypertensive vs. normotensive. • **Meds**: 86% CSA, 14% Tac, 48% Pred	(34)
• 25%	On anti-hypertensive medication	32	1986-1992	Retrospective	12.8y (10-15.8y)	3.5y (0.5-17.3y)	• 25% of those with hypertension diagnosed > 5y post-transplant	(81)

Prevalence	Diagnostic criteria	n	Year of transplant	Study design	Post-transplant follow-up [median (range)*]	Age at transplant [median (range)*]	Reported risk factors	Ref
							• **Meds** at 10y: 75% CSA (53% monotherapy), 16% Tac, 28% Pred	

• 1-2y: 26%
  ○ 17% Tac
  ○ 32% CSA
• "Long-term": 22%
	On anti-hypertensive medication	46	NA	Prospective	5.4y (2–13y)	4.7y (0.7-23.2y)	• Lower GFR at 1y and last follow-up
							• **Meds**: 54% CSA, 46% Tac, 100% Pred
								(42)

• 93% Tac • 100% CSA	On anti-hypertensive medication	50	NA	Randomized controlled trial	1y	Mean 3.2-3.5y (SD 3.8y)	• **Meds**: 100% Pred (lower doses in Tac vs. CSA)	(22)
• "Early" post-transplant: 65% • >12m: 28%	NA	210	1984-1992	Retrospective	NA	Mean 4.1y (SD 5.0y)	• Hypertension not associated with GFR • **Meds**: 100% CSA, Pred unknown	(45) //

• 1m:
  ○ 17% Tac
  ○ 60% CSA
• 6y:
  ○ 4% Tac
  ○ 21% CSA
	On anti-hypertensive medication	353	1988-1994	Prospective	4.7-11.6y	Tac: Mean 5.1y (SD 5.3y) CSA: Mean 4.6y (SD 5.0y)	• CSA
							• 32% CSA, 80% Tac steroid-free at 6 years
								(43)

• 29% Tac • 47% CSA	On anti-hypertensive medication	73	1989-1996	Retrospective	8.1y (5.2-9.9y)	Mean 6.6y (range 0.4-17.5y)	• 100% converted from CSA to Tac • Steroid-free increased from 3.6% CSA to 78% Tac	(44)

SBP Systolic blood pressure; DBP Diastolic blood pressure; SPLIT Studies in Pediatric Liver Transplantation; SD Standard deviation; BP blood pressure; GFR Glomerular filtration rate; IQR Interquartile range; BMI Body mass index

* Unless otherwise indicated.

[†] CSA Cyclosporine; Tac Tacrolimus; Pred Prednisone. Listed medications represent proportion of patients on each medication at time of study visit or last follow-up unless otherwise indicated. Other immunosuppressive medications with <10% prevalence in study population not listed.

[‡] Calculated using two-sample test of proportions, based on data supplied in reference

[§] Data not available in published study.

[//] Only abstract available for review.

Table 3

Dyslipidemia after liver transplant in children

Prevalence	Diagnostic criteria	n	Year of transplant	Study design	Post-transplant follow-up [median (range)*]	Age at transplant [median (range)*]	Reported risk factors	Ref
• 20% elevated TC (n=93) • 26% elevated TG (n=97)	Above "normal" range	97	1995-1999	Prospective (SPLIT)	Range 9.5-10.5y	1.0y (IQR 0.6-3.6y)	• Hyperlipidemia not associated with AST/ALT. • **Meds**: 68% Tac, 23% CSA, 19% Pred†	(25)
• 7% elevated TC • 10% elevated TG	NA≠	173	1996-2001	Prospective (SPLIT)	6y (4.8-15y)	1.6y (IQR 0.7-6.5y)	• **Meds**: 74% Tac, 24% CSA, 26% Pred.	(23)
• Elevated TC ○ 6m: 18% ○ 1y: 25% ○ Long-term (n=18): 17% • Elevated TG: ○ 6m: 81% ○ 1y: 91% ○ Long-term (n=18): 50%	TC, TG >75th percentile for age and gender	24	1987-2008	Retrospective	Mean 6.6y (range 1.4-16y)	Mean 6.2y (range 0.6-14.6y)	• Triple immunosuppression • Steroid dose at 3m • Not associated with CSA vs. Tac, overweight, age. • **Meds**: In long-term follow-up: 46% Tac, 30% CSA, 45% Pred. At 6m, 1y: Unknown	(52)
• 26% elevated TC • 45% elevated TG	NA	32	1986-1992	Retrospective	12.8y (10-15.8y)	3.5y (0.5-17.3y)	• **Meds**: 75% CSA, 16% Tac, 28% Pred	(81)
• 16% elevated TC • 30% elevated TG	TC, TG > 95th percentile of control group	34	1987-1997	Cross-sectional	Up to 5y	3.6y (0.4-16.3y)	• **Elevated TG**: BMI z-score, age at transplant, growth hormone use • **Elevated TC**: No end-stage liver disease at transplant (hepatoblastoma, HCC) • **Meds**: 91% CSA, 9% Tac, 100% Pred, 100% AZA	(51)

Prevalence	Diagnostic criteria	n	Year of transplant	Study design	Post-transplant follow-up [median (range)*]	Age at transplant [median (range)*]	Reported risk factors	Ref
• 16% elevated TG • 17% low HDL	TG: >95th percentile of control group HDL: NA All levels fasting.	25	NA	Cross-sectional	Mean 6.4y (range 1-11y)	2.0y (0.4-16.3y)	• **Meds**: 88% CSA, 12% Tac, 100% Pred, 100% AZA	(49) //
• All ○ 50% elevated TC ○ 56% elevated TG • Fasting (n=40) ○ 57% elevated TC ○ 41% elevated TG ○ 19% elevated LDL	• TC>170mg/dL • TG>140mg/dL • LDL>"upper limit of normal for age" • Fasting levels done if nonfasting elevated	102	1984-1990	Cross-sectional	2.1y (0.5-6.1y)	6y (1-18y)	• Serum bilirubin > 2mg/dL • **Meds**: 100% CSA/Pred. Levels, doses not associated with dyslipidemia.	(48)

TC Total cholesterol; TG Triglycerides; SPLIT Studies in Pediatric Liver Transplantation; IQR Interquartile range; AST Aspartate aminotransferase; ALT Alanine aminotransferase; BMI Body mass index; HCC Hepatocellular carcinoma; HDL High-density lipoprotein; LDL Low-density lipoprotein

*Unless otherwise indicated.

†CSA Cyclosporine; Tac Tacrolimus; Pred Prednisone; AZA Azathioprine. Listed medications represent proportion of patients on each medication at time of study visit or last follow-up unless otherwise indicated. Other immunosuppressive medications with <10% prevalence in study population not listed.

≠Data not available in published study.

//Abstract

Table 4

Diabetes mellitus and insulin resistance after liver transplant in children

Prevalence	Diagnostic criteria	n	Year of transplant	Study design	Post-transplant follow-up [median (range)*]	Age at transplant [median (range)*]	Reported risk factors	Ref
• >30d: 9% • 10y: 1%	DM, glucose intolerant, or insulin use based on patient response	167	1995-1999	Prospective (SPLIT)	Range 9.5-10.5y	1.0y (IQR 0.6-3.6y)	• **Meds**: 68% Tac, 23% CSA, 19%Pred†	(25)
• 13% • 5% insulin or anti-hyperglycemic	"Evidence of DM"	461	1996-2001	Prospective (SPLIT)	6y (4.8-15y)	1.6y (IQR 0.7-6.5y)	• Tac • **Meds**: 74% Tac, 24% CSA , 26%Pred	(23)
• 13.3%	On insulin or oral hypoglycemic, or reported by transplant center as glucose intolerant or DM	1611	1995-2004	Prospective (SPLIT)	51% >5y 49% < 5y	1.93y	• 78% of DM occurred ≤1m post-transplant • DM ≤1m: ○ ICU/hospitalized at transplant ○ Age>5y at transplant ○ Steroid use at transplant Tac ○ Cholestatic disease • **Meds**: 58% Tac, 27% CSA, 90% Pred at transplant	(24)
• 8%	Persistent random blood glucose >200mg/dL and insulin use	300	NA‡ (DM diagnosis 1997-2009)	Retrospective case-control	DM: 4.9y (0.9-9.1y)	Mean 13.8y (SD 3.7y)	• Rejection (prior and concurrent) • Triple immunosuppression • Higher Tac level • Lower BMI z-score • Meds: 100% Pred at DM diagnosis	(60) //
• 10.1% ○ 1y: 5.9% ○ 2y: 8.3%	"New-onset DM" reported by transplant center	1161	2004-2008	Retrospective (UNOS)	2.1y (IQR 1-4y)	24% 2-5y 36% 5-13y 40% 13-20y	• Age>5y at transplant • African-American race • Cystic fibrosis	(58)

Prevalence	Diagnostic criteria	n	Year of transplant	Study design	Post-transplant follow-up [median (range)*]	Age at transplant [median (range)*]	Reported risk factors	Ref
○ 3y: 11.2%							• Acute liver failure or primary sclerosing cholangitis	
• ≤30d: 17% • 1y: 5%	Insulin use or fasting blood sugar>126 mg/dL	123	1996-2002	Retrospective	NA	NA	• DM ≤1m: ○ Older age ○ Autoimmune/ metabolic disease ○ UNOS status 1 at transplant ○ Re-transplantation • **Meds**: 99% Tac/Pred; 1 unknown	(61) //
• 17.2%	Glucose>200mg/dL, >2 weeks after steroid induction, persisting >2 weeks	81	1997-2000	Retrospective	NA	Age at follow-up: • DM: Mean 12.3y (SD 4.6y) • No DM: Mean 5.3y (SD 5.6y)	• Older age at transplant • Autoimmune hepatitis • Tac • **Meds**: 59% Tac, 23% CSA.	(62) //
• 10%	Insulin-dependence (n=2), unknown (n=1)	32	1986-1992	Retrospective	12.8y (10-15.8y)	3.5y (0.5-17.3y)	• All developed > 2y after transplant, 2 of 3 “steroid-related” DM. • **Meds**: 75% CSA, 16% Tac, 28%Pred	(81)
• 11% impaired glucose tolerance • 11% hyperinsulinemia	**Impaired glucose tolerance**: Fasting glucose 100-125 mg/dL **Hyperinsulinemia**: Elevated basal, peak, or total insulin on OGTT	28	2000-2007	Cross-sectional	2.5y (0.7-7.3y)	8y (2.3–18.0y)	• All insulin resistant were adolescents • Not associated with age, pubertal status, time since transplant, weight in multivariate analysis • **Meds**: 100% Tac, 0% Pred	(63)

Prevalence	Diagnostic criteria	n	Year of transplant	Study design	Post-transplant follow-up [median (range)*]	Age at transplant [median (range)*]	Reported risk factors	Ref
• 16% hyperinsulinemic • 40% insulin resistance	**Hyperinsulinemia**: Fasting or peak insulin >150 mU/L on OGTT **Insulin resistance**: HOMA-IR>95th percentile	25	NA	Cross-sectional	Mean 6.4y (range 1–11y)	2.0y (0.4-16.3y)	• **Meds**: 88% CSA, 12% Tac, 100% Pred, 96% AZA	(49)

DM Diabetes mellitus; SPLIT Studies in Pediatric Liver Transplantation; IQR Interquartile range; ICU Intensive care unit; SD Standard deviation; BMI Body mass index; UNOS United Network for Organ Sharing; OGTT Oral glucose tolerance test; HOMA-IR Homeostatic model assessment of insulin resistance

*Unless otherwise indicated.

†CSA Cyclosporine; Tac Tacrolimus; Pred Prednisone; AZA Azathioprine. Listed medications represent proportion of patients on each medication at time of study visit or last follow-up unless otherwise indicated. Other immunosuppressive medications with <10% prevalence in study population not listed.

‡Data not available in published study.

//Abstract

Table 5

Non-alcoholic fatty liver disease after liver transplant in children

Ref	Primary diagnosis	Pre-transplant NAFLD	Age at transplant (years)	Type of donor	Donor steatosis	Time post-transplant to NAFLD/NASH diagnosis	Metabolic Syndrome Components	Outcomes
(66)	NASH, HPS, panhypopituitarism	Diagnosed age 16	16	NA*	NA	NASH: 2 months	**Pre-transplant:** Overweight **Post-transplant:** Acanthosis nigricans, insulin-dependent diabetes. Normal lipids.	Alive, persistent NASH
(67)	NASH, HPS, panhypopituitarism	Diagnosed age 6	13	NA	NA	NASH: 6 months	**Pre-transplant:** Obese, elevated cholesterol **Post-transplant:** Obese, insulin resistant	Alive, persistent NASH
(68)	NASH, HPS NASH, HPS	Diagnosed age 11 Diagnosed age 19	20 25	NA	NA	NASH: 9 months NASH: 6 weeks	**Pre-transplant:** Obese, elevated cholesterol and triglycerides **Pre-transplant:** Obese, low HDL	Alive, stage 2 fibrosis Retransplanted after 2 years (recurrent NASH, HPS) but died (multi-organ system failure)
(82)	PFIC1 PFIC1	None	5.5 4	Deceased	NA	NAFLD: 7 days NAFLD: 21 days NASH: 1year	**Post-transplant:** Not obese	Alive, chronic diarrhea
(83)	PFIC‡	NA	2.5	Living	NA	NASH: 10 months	**Post-transplant**: Not obese, normal lipids	NA
(84, 85)§	PFIC 1	NA	n=8 Median 4.5 years (range 1-18 years)	Living	None	NAFLD (n=8): Median 60 days (range 21-191 days) NASH (n=7): Median 161 days (range 116-932 days)	**Post-transplant:** Not obese. Normal lipids, fasting glucose	7 with chronic diarrhea 2 cirrhosis, 4 bridging fibrosis at last follow-up (median 7.6 years, range 2.3-16.1 years)
(69)	PFIC1	None	3.6	Living	NA	NASH: 2 months	NA	Chronic diarrhea. NASH resolved with external biliary diversion.
(70)	Biliary atresia Tyrosinemia Crigler-Najjar	NA NA NA	6 7 1.5	Deceased Living Living	<5% None None	NAFLD: 10 days, 25% steatosis NAFLD: 19 days, 30% steatosis NAFLD: 7 days, 30% steatosis	**Pre/post-transplant:** Not obese, normal lipids and fasting glucose	Died 12 days post-transplant (graft failure) Portal vein thrombosis, liver abscess. Alive at last follow-up. Died 20 days post-transplant (sepsis/graft failure)

*NA information not available from published study

‡Type of PFIC not specified.

§Papers report on same cohort of patients. Miyagawa-Hiyashino et al. reports only on the 8 PFIC1 patients with steatosis. Hori et al. includes these 8 plus 3 PFIC1 patients without post-transplant steatosis and 3 PFIC 2 without post-transplant steatosis. NAFLD Non-alcoholic fatty liver disease; NASH Non-alcoholic steatohepatitis; HPS Hepatopulmonary syndrome; HDL high-density lipoprotein; PFIC Progressive familial intrahepatic cholestasis

Table 6

Screening tests for post-transplant metabolic syndrome components in children after liver transplant

Overweight/obesity	• Children ≥ 2 years: BMI percentile, waist circumference percentile[86] • Children < 2 years: Weight-for-length percentile
Hypertension	Blood pressure percentile
Dyslipidemia	Fasting lipid panel (triglycerides, HDL, LDL, total cholesterol)
Glucose intolerance/diabetes mellitus	• Fasting glucose and insulin levels • Hemoglobin A1C • Oral glucose tolerance test
Non-alcoholic fatty liver disease	• ALT/AST • Ultrasound or MR spectroscopy for hepatic steatosis • Liver biopsy for steatosis/inflammation/fibrosis