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Posttransplant Metabolic Syndrome in the Withdrawal of Immunosuppression in Pediatric Liver Transplant Recipients (WISP-R) Pilot Trial

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Abstract

Posttransplant metabolic syndrome (PTMS)—obesity, hypertension, elevated triglycerides, low HDL and glucose intolerance—is a major contributor to morbidity after adult liver transplant. This analysis of the Withdrawal of Immunosuppression in Pediatric Liver Transplant Recipients (WISP-R) pilot trial is the first prospective study of PTMS after pediatric liver transplant. Twenty children were enrolled in WISP-R, at median age 8.5 years (IQR 6.4–10.8), and weaned from calcineurin-inhibitor monotherapy. The 12 children who tolerated complete immunosuppression withdrawal were compared to matched historical controls. At baseline, 45% of WISP-R subjects and 58% of controls had at least one component of PTMS. Calcineurin-inhibitor withdrawal in the WISP-R subjects did not impact the prevalence of PTMS components compared to controls. At 5 years, despite weaning off of immunosuppression, 92% of the 12 tolerant WISP-R subjects had at least one PTMS component and 58% had at least two; 33% were overweight or obese, 50% had dyslipidemia, 33% glucose intolerance and 42% systolic hypertension. Overweight/obesity increased the risk of hypertension in all children. Compared to controls, WISP-R tolerant subjects had similar GFR at baseline but did have higher GFR at 2, 3 and 4 years. Further study of PTMS and immunosuppression withdrawal after pediatric liver transplant is warranted.

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The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

Introduction

Posttransplant metabolic syndrome (PTMS) is emerging as a major contributor to long-term morbidity after solid organ transplantation. In adult liver transplant recipients, PTMS is a leading cause of death (1), and a risk factor for both cardiovascular events and *de novo* nonalcoholic fatty liver disease (NAFLD), which can progress to cirrhosis (2). In pediatric liver transplant recipients, PTMS prevalence has not been prospectively studied. However, UNOS data suggests that 20–50% of these children are overweight or obese in long-term follow-up (3). Hypertension, dyslipidemia and diabetes appear to be more common than expected for age, gender and obesity severity (4).

Metabolic syndrome is diagnosed by the presence of three or more of five conditions: overweight/obesity, hypertension, elevated triglycerides, low HDL and glucose intolerance. Obesity and insulin resistance are generally thought to drive metabolic syndrome (5). In transplant recipients, calcineurin inhibitors (CNIs), the mainstay of long-term immunosuppression, are likely a potent contributing factor. They cause hypertension through renal vasoconstriction, sodium retention and nephrotoxicity. They contribute to dyslipidemia by altering lipid metabolism (6,7) and induce glucose intolerance by impairing pancreatic b-cell function (8).

Given the adverse effects of long-term CNI use—including PTMS, infection susceptibility, and *de novo* malignancy— there has been mounting interest in CNI withdrawal as a long-term management strategy after solid organ transplantation (9–12). Liver transplant recipients appear to be more permissive of CNI weaning than recipients of other organs. Moreover, children appear to be more permissive than adults (9,13). Previous studies suggest that CNI withdrawal can be done safely in 20–60% of pediatric liver transplant recipients who have been stable on CNI monotherapy (13,14). Two reports have suggested that CNI withdrawal can ameliorate hypertension, dyslipidemia and glucose intolerance among adult liver transplant recipients, although they are less likely to tolerate complete immunosuppression withdrawal (15,16).

We studied PTMS components among pediatric liver transplant recipients who were followed during a single-group pilot trial of CNI withdrawal, the Withdrawal of Immunosuppression in Pediatric Liver Transplant Recipients (WISP-R) study (NCT00320606) (13). This analysis is the first study of PTMS in pediatric liver transplant recipients based on prospectively collected data.

Methods

Study population and design

This was a retrospective analysis of data collected in a prospective, multi-center, open-label, single group pilot trial of immunosuppression withdrawal (WISP-R) (13). The 20 WISP-R subjects were pediatric recipients of parental living-donor liver transplants who were at least 4 years posttransplant. All were <18 years of age at enrollment, on CNI monotherapy for at least 1 year, with stable graft function and no significant fibrosis (Ishak stage ≤1) on screening biopsy.

WISP-R subjects underwent stepwise CNI withdrawal over a minimum of 36 weeks. Dose reductions were suspended for allograft dysfunction, based on ALT or GGT elevations. Subjects failed immunosuppression withdrawal with any episode of biopsy-proven rejection or if medication reduction was suspended for more than four weeks during the trial. Additional details about WISP-R inclusion/exclusion criteria, study protocols and endpoints have been previously published (13).

Informed consent from parents/legal guardians and age-appropriate written informed assent was obtained from all WISP-R participants in person. The trial was approved by institutional review boards at all participating centers. This retrospective analysis was approved by the institutional review boards at the University of California, San Francisco (IRB#13-11278) and at Northwestern University (IRB#2014-15869) as well as investigators from the three participating centers.

Using retrospective data collected as standard-of-care, a control group of pediatric liver transplant recipients not undergoing immunosuppression withdrawal was matched to the 12 WISP-R subjects that tolerated complete immunosuppression withdrawal. Because of limited long-term follow-up data available on WISP-R subjects that failed withdrawal (nontolerant), they were not compared to controls. Controls were matched to WISP-R participants by transplant center, year of transplant (±5 years), age at transplant (±1 year) and race. To mirror WISP-R inclusion criteria, all controls were transplanted for biliary atresia or other cholestatic or cirrhotic disease, were on CNI monotherapy for ≥1 year prior to start of matched follow-up, had ≤3 previous episodes of acute rejection, and had no history of chronic rejection, autoimmune liver disease, or viral hepatitis. Data on controls were included if it was ±2 months from target matched date in the first year of follow-up and ±3 months in subsequent years.

Definition of PTMS components

WISP-R subjects had body measurements and fasting laboratory tests done at baseline, prior to CNI withdrawal, and at protocol follow-up visits. Lipid levels were not checked during active CNI withdrawal. Missing values were excluded from analysis. All data on controls was collected retrospectively from standard-of-care clinical visits and laboratory testing. Corticosteroid exposure times are estimates based on first recorded date off of steroids for both groups.

BMI percentile for age and gender was calculated based on 2000 CDC growth chart data (17). Children were considered overweight/obese if their BMI percentile was ≥85th percentile for age and gender (18). Diastolic and systolic hypertension were defined as blood pressure (BP) ≥95th percentile for gender, age and height based on National High Blood Pressure Education Program Working Group on Children and Adolescents 2004 guidelines (19). Elevated fasting glucose was considered at least 100 mg/dL, following American Diabetes Association definitions (20). Borderline high/high lipids represented values at or above the 75th percentile for children and young adults, using categories recommended by the 2011 American Academy of Pediatrics Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents (21). The cutoffs for borderline high/high triglycerides was ≥75 mg/dL for children 9 or younger and ≥90 mg/dL

for those 10 or older. Low HDL was ≤40 mg/dL, which represents the 10th percentile (21). We defined PTMS as the presence of three or more of the following: overweight, hypertension, hyperglycemia, elevated triglycerides and low HDL (5,21).

GFR was calculated using the modified Schwartz equation (22). Baseline GFR was calculated at 3 months for WISP-R subjects, as this was the first visit with concurrent height and creatinine. For controls, baseline GFR was calculated at start of matched follow-up.

Statistical analysis

Because of small sample size, all descriptive statistics are reported as medians with interquartile ranges (IQR, 25th–75th percentile). Nonparametric methods were used for all significance testing. Chi-squared and Kruskal– Wallis one-way analysis of variance were used to evaluate baseline differences by age and CNI. Wilcoxon matched-pairs sign-rank test and McNemar's tests were used to compare matched data. Linear mixed models were used for multivariate repeated-measures analysis. p-Values <0.05 were considered statistically significant. All statistical analyses were done using Stata 12 (Statacorp, College Station, TX).

Results

PTMS at baseline

WISP-R included 20 children. At trial enrollment, all were on CNI monotherapy. Prior exposure to corticosteroids is detailed in Table 1. Among WISP-R subjects, nine had at least one episode of rejection requiring steroid pulse; but all rejection episodes were within 5 months posttransplant. Four of 12 controls had an episode of rejection requiring steroids.

At enrollment, 9 of 20 WISP-R subjects (45%) had at least one component of PTMS, and three had two components (15%) (Table 1). One 8-year-old girl met criteria for PTMS, with a combination of overweight/obesity, hypertension and elevated triglycerides. Among controls, 58% had at least one PTMS component at baseline (Table 1). One 13-year-old boy qualified as PTMS with elevated triglycerides, low HDL and hyperglycemia. At baseline, there was no difference in years off of corticosteroids in those with overweight/obesity (median, range for overweight/obese 7.0, 4.0–10.8 years; normal weight 7.4, 2.5–10.0 years, n = 23, p =0.85) or hypertension (median, range for hypertensive 5.6, 2.5–10.0 years; normotensive 7.4, 3.0–10.8, years, n=23, p=0.36).

None of the WISP-R participants or controls was on medications for hypertension, dyslipidemia, or glucose intolerance during follow-up. One WISP-R subject carried a pretrial diagnosis of hypertension but during the trial only had elevated blood pressure percentile at the 2-year visit. One WISP-R participant was on intranasal steroids for seasonal allergies at baseline visit, but none were on inhaled or oral steroids. Two WISP-R participants received steroids intermittently during follow-up for asthma. One, on inhaled steroids, had persistent overweight/obesity, hyper-tension and elevated triglycerides. The second, who had three 1-week courses of oral steroids, had persistent low HDL, elevated triglycerides at 3 and 5 years, and overweight/obesity at 3 years. Two control subjects

received inhaled steroids for asthma intermittently during follow-up. Both were hypertensive at baseline but this resolved, and they had no other persistent PTMS components.

At baseline, WISP-R tolerant subjects had higher median systolic BP percentiles than controls, although this difference was not statistically significant (Table 1). There were no other differences in PTMS component prevalence between WISP-R tolerant subjects and controls (Table 1). Neither age at enrollment nor CNI (tacrolimus [TAC] vs. cyclosporine [CSA]) predicted overweight/obesity, hyper-tension, dyslipidemia, hyperglycemia, BMI or blood pressure percentiles, lipid values or GFR among WISP-R subjects or controls at baseline (data not shown).

PTMS during CNI withdrawal

Of the 20 children enrolled in WISP-R, 15 completed CNI withdrawal over a median (IQR) 8.1 (8.1–9.0) months. For this group, median systolic and diastolic BP percentiles, BMI percentiles and fasting glucose levels did not change significantly during CNI withdrawal (data not shown). The prevalence of overweight/obesity did increase from 14% at baseline to 43% at the 9-month visit ($p=0.09$, $n=14$). The prevalence of elevated fasting glucose increased from 13% to 29%, but the change was not statistically significant ($p=0.28$, $n=15$). Lipid levels were not drawn during CNI withdrawal.

Twelve WISP-R subjects were operationally tolerant and remained off of immunosuppression, with continued follow-up for median (IQR) 6.6 (5.9–6.8) years. For the eight nontolerant children, follow-up continued for a median (IQR) of 1.4 (0.9–2.3) years following enrollment. Data collection was limited after failing CNI withdrawal.

Three children successfully weaned off of CNIs but were restarted 1.6, 1.9 and 2.4 months after the last CNI dose respectively. At baseline, each had one component of PTMS (one elevated triglycerides, one hypertension and one elevated glucose). None of these three developed persistent PTMS components during follow-up, based on limited available data. Five children failed CNI withdrawal at a median (IQR) of 3.5 (2.8–5.2) months. One had hypertension and low HDL at baseline, with persistent hypertension but no additional lipids sent. One developed elevated triglycerides and hyperglycemia at 2 years but had no additional follow-up in the trial. None of the nontolerant children were overweight/obese.

PTMS during long-term follow-up

In WISP-R tolerant subjects and matched controls, PTMS components were common at baseline and during 5-year follow-up (Table 2). There were no differences in prevalence of PTMS components at any time point examined between WISP-R and controls. In the combined group, the overall prevalence of hyperglycemia increased from 10% at baseline to 32% at 5-year follow-up ($p = 0.06$). None of the other changes in prevalence between baseline and 5-year follow-up were statistically significant for the combined group (Table 2).

The 12 WISP-R tolerant children did demonstrate a decrease in average BP percentile when mean blood pressure percentiles for each patient were calculated for all visits during versus after withdrawal. Mean systolic BP percentile (95% CI) decreased from 81 (69–88) on CNIs

to 75 (55–82) off CNIs (p = 0.04). Mean (95% CI) diastolic BP percentile decreased from 77 (55–85) on CNIs to 55 (43–73) off CNIs (p = 0.005). In spite of the drop in BP percentiles, the prevalence of hypertension increased among WISP-R tolerant children during 5-year follow-up, from 25% at baseline to 50% at 5 years. This was driven by an increased prevalence of systolic hypertension—from 25% to 42%. Only one WISP-R subject exhibited diastolic hypertension at 5 years. WISP-R subjects were significantly more likely to have systolic hypertension at any timepoint at which they were overweight/obese (35%) versus normal weight (11%, p < 0.005 using 171 concurrent measurements). There was no significant correlation between diastolic hypertension and overweight/obesity.

In repeated-measures analysis, overweight/obesity was associated with a small but significant annual increase (3.7, 95% CI 0.04–7.3, p=0.05) in systolic BP percentile and normal weight with an annual decrease (−2.7, −4.8 to −0.64, p=0.01) in both WISP-R tolerant subjects and controls. WISP-R tolerant subjects had persistently higher systolic BP percentiles than controls even after adjusting for overweight/obesity (systolic BP percentile difference 19 for WISP-R versus controls, 95%CI 7–31, p=0.001). There was no difference over time in diastolic BP percentile, triglycerides, HDL or glucose in WISP-R subjects versus controls or by weight status in models adjusting for both factors (data not shown).

GFR was higher in WISP-R tolerant subjects than in controls at 2, 3 and 4 years. This difference was not statistically significant at 5 years, but GFR data was only available for four controls at this time point (Figure 1).

PTMS prevalence at 5-year follow-up

Among the 12 WISP-R tolerant children, two subjects had PTMS at the 5-year visit (17%). Both were overweight/ obese. Eleven of the 12 had at least one PTMS component (92%) and seven had at least two components of PTMS (58%). Four of these 12 qualified as PTMS at least once during the study. Only one child with overweight/obesity had no other components of PTMS at 5 years after study entry. Data on controls was much less complete at 5-year follow-up, but three of seven with some available data had at least one PTMS component (43%). One control had PTMS at 5 years, with overweight/obesity, hypertension and hyperglycemia.

Discussion

Analysis of children enrolled in the WISP-R pilot study of immunosuppression withdrawal suggests that components of PTMS are very common in long-term survivors after pediatric liver transplantation, even those on CNI monotherapy at relatively low doses. Prevalence of PTMS in the WISP-R cohort and among matched controls appeared to be higher than in the general U.S. pediatric population—as has been hypothesized by previous studies (Table 3) (4).

In this small cohort, weaning and remaining off of CNIs did not consistently resolve PTMS components—possibly because participants were taking low doses when they entered the study and because overweight/obesity increased as the study progressed. Subjects who remained off immunosuppression did have an improvement in GFR compared to controls

and a decrease in mean BP percentile, but no improvement in hypertension. Increasing overweight/obesity, particularly as the children progressed into adolescence, likely contributed to the persistent hypertension. Prior corticosteroid exposure did not seem to drive overweight/obesity or PTMS during the trial, although small sample size prohibited quantitative analysis of the role of steroids.

Although this study offers interesting preliminary data about PTMS after pediatric liver transplant, there are important limitations. WISP-R was a small pilot trial in a highly selected and homogenous population. Subjects that failed the CNI taper were followed solely for safety, and thus less intensively for a much shorter time period (approximately 1 year), resulting in insufficient data to fully evaluate PTMS components. Data on controls was collected retrospectively from clinical records, and thus offered an incomplete comparison. Data on insulin levels, glucose tolerance, waist circumference, pubertal stage or parental obesity/metabolic status were not collected on any subjects. Due to small sample size, we could not assess the role of ethnicity in PTMS.

This analysis is the first to prospectively explore PTMS components after pediatric liver transplant, but was not sufficiently powered to establish prevalence or fully describe changes over time. Our analysis may underestimate the response of PTMS to immunosuppression withdrawal because all subjects started the trial late after transplantation and on low doses of CNI monotherapy. Additional longitudinal studies in pediatric liver transplant recipients are needed to define PTMS risk factors, to evaluate the impact of modifying immunosuppression regimens on PTMS and its evolution, and to evaluate PTMS impact on long-term morbidity. PTMS and its components are treatable—and potentially reversible—conditions, so proactive strategies for their management may help optimize long-term outcomes after pediatric liver transplantation.

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Abbreviations

ALT	alanine aminotransferase
BP	blood pressure
CNI	calcineurin-inhibitor
CSA	cyclosporine
GGT	gamma-glutamyl transpeptidase
IQR	interquartile range
NAFLD	nonalcoholic fatty liver disease

PTMS	posttransplant metabolic syndrome
TAC	tacrolimus
WISP-R	Withdrawal of Immunosuppression in Pediatric Liver Transplant Recipients trial

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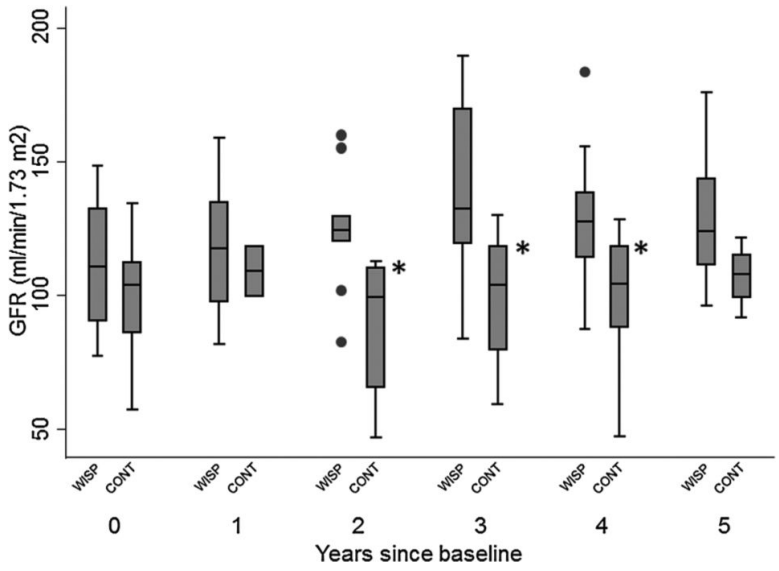

Figure 1. GFR, calculated using modified Schwartz formula, on WISP-R subjects that tolerated immunosuppression withdrawal during Year 0 (WISP) and historical matched controls (CONT)

Year 0 data on WISP-R subjects is from 3 months after baseline visit, during immunosuppression withdrawal. Year 0 data on controls is at start of matched follow-up. * $p < 0.05$ for difference in GFR using Wilcoxon signed-rank test for comparison of matched pairs. Only subjects with matched data included in calculation of p-values at each time point.

Table 1

Demographics and PTMS components at WISP-R enrollment and in matched controls *

Characteristic	All WISP-R subjects (n = 20)†	WISP-R tolerant subjects (n = 12)	Matched controls (n = 12)‡
Age (years)			
At transplant	0.6 (0.5–0.8)	0.6 (0.4–0.7)	0.4 (0.6–1.1)
At enrollment/baseline	8.5 (6.4–10.8)	8.9 (7.6–10.8)	8.5 (9.9–11.4)
Years posttransplant	7.1 (5.4–10.0)	8.4 (6.0–10.3)	9.3 (8.0–11.0)
Female	55%	33%	33%
Hispanic/Latino	20%	17%	25%
Biliary atresia, as indication for liver transplant	80%	75%	92%
Years on steroids posttransplant (median, range)	1.0 (0.5–6.0)	1.0 (0.5–4.0)	1.9 (0.2–5.7)
Years off steroids prior to baseline (median, range)	6.8 (2.0–10.0)	7.5 (2.5–10.0)	7.2 (4.0–10.8)
On tacrolimus (TAC vs. cyclosporine, CSA)	65%	42%	50%
CNI starting total daily dose (mg/kg/day)	TAC: 0.028 (0.024–0.058)	TAC: 0.026 (0.015–0.047)	TAC: 0.089 (0.054–0.171)
	CSA: 1.57 (0.84–3.75)	CSA: 1.45 (0.84–1.57)	CSA: 2.54 (1.36–3.88)
Off CNI at end of follow-up	60%	100%	0%
Total follow-up years	6.1 (5.3–6.7)	6.3 (5.7–6.5)	4.8 (4.4–5.0)
Number of follow-up visits	8 (4–12)	8 (4–12)	4 (2–7)
Obesity			
BMI percentile	75 (59–81)	78 (66–83)	68 (39–88)
Overweight/obese§	10%	17%	25%
Hypertension			
Systolic blood pressure	106 (102–117)	111 (104–121)	107 (98–115)
Systolic BP percentile for age/height	72 (47–89)	80 (66–93)	50 (34–90)
Systolic hypertension§	20% (n = 19)	25%	25%
Diastolic blood pressure	64 (57–74)	66 (58–77)	62 (60–68)
Diastolic BP percentile for age/height	67 (42–94)	78 (45–90)	61 (42–72)
Diastolic hypertension	5% (n = 19)	0%	0%
GFR¶		111 (90–132)	106 (86–112, n = 10)
Dyslipidemia			
Triglycerides	56 (34–89)	53 (32–89)	59 (43–82, n = 4)
Elevated triglycerides§	22%	18%	25% (n = 4)
HDL	53 (47–63)	52 (46–70)	53 (45–60, n = 5)
Low HDL§	17% (n = 18)	18% (n = 11)	20% (n = 5)
Hyperglycemia			
Glucose	90 (84–94)	91 (86–94)	94 (91–98, n = 11)
Elevated fasting glucose§	10%	8%	18% (n = 11)

[*] All values for continuous variables are medians, interquartile range (25th–75th percentile) unless otherwise noted.

[†] N = 19 for lipid and blood pressure measurements. One subject had missing baseline values.

[‡] No significant p-values (<0.05) for difference in baseline characteristics between tolerant WISP-R subjects and matched controls, using McNemar's test for categorical variables and Wilcoxon signed-rank test for continuous variables.

[§] Overweight/obese = BMI >85th percentile for age/gender. Hypertension = Systolic or diastolic blood pressure >95th percentile for age/gender/height. Elevated triglycerides = borderline high or high, representing >75th percentile with triglycerides cutoffs determined by age (0–9 years, 10–19 years). Low HDL represents < 10th percentile for HDL. Elevated fasting glucose ≥ 100 mg/dL. These categories are based on recommended cutoffs from the American Academy of Pediatrics Expert Panel on Integrated Guidelines for CV Health and Risk Reduction in Children and Adolescents (Pediatrics Vol 128, Suppl 5, Dec 2011).

[¶] GFR calculated using age, height, and creatinine by the modified Schwartz formula. GFR for WISP-R subjects calculated from 3-month visit because baseline visits did not have height and creatinine measurements on the same date.

Table 2

PTMS components in WISP-R tolerant subjects and controls over 5-year follow-up*

		Controls		
	WISP-R (n = 12) (%)	Prevalence in controls with available data (%)	N with available data	Overall prevalence (%)
Baseline				
Overweight/obesity	17	25	12	21
Hypertension	25	25	12	25
Elevated triglycerides	18	25	4	19
Low HDL	18 (n = 11)	20	5	12
Hyperglycemia	8	12.5	8	10
2 years				
Overweight/obesity	17	43†	7	26
Hypertension	33	14	7	26
Elevated triglycerides	25	33	3	27
Low HDL	25	67	3	33
Hyperglycemia	8	50	6	22
3 years				
Overweight/obesity	33	22	9	29
Hypertension	33	0†	9	19
Elevated triglycerides	17	50	2	21
Low HDL	25	67	3	33
Hyperglycemia	17	25	8	20
5 years				
Overweight/obesity	33	75	4	44
Hypertension	50	25	4	44
Elevated triglycerides	25	0	2	21
Low HDL	33	33	3	33
Hyperglycemia	33	29	7	32‡

*For all other comparisons except the two specified in the table, $p > 0.15$ using McNemar's test to account for matched pairs. Only subjects with matched data at each time point included in calculation of p-values.

†p-Value = 0.08 in comparison of WISP-R to controls.

‡p-Value = 0.06 for comparison of overall hyperglycemia prevalence at 5 years versus baseline.

Table 3

Metabolic syndrome components in children and adolescents

Condition	Prevalence in WISP-R pilot trial*	Prevalence in U.S. children‡	Systematic review prevalence estimates in children after liver transplant[4]
Obesity	Baseline: 10%	32%	20–57%
	5-years: 33%		
Hypertension	Baseline: 20%	3–5%	7.1–34.8%
	5-years: 58%		
Elevated triglycerides	Baseline: 22%	10%	10–56%
	5-years: 27%		
Low HDL	Baseline: 17%	8%	No available estimate
	5-years: 36%		
Diabetes/glucose intolerance	Baseline: 10%†	Diabetes: 0.5%	Diabetes: 1–13%
	5 years: 33%†	Glucose intolerance: 11%	
Metabolic syndrome	Baseline: 5%	2–9%	No available estimate
	5-years: 17%		

*At baseline: n = 20 for obesity, glucose intolerance; n = 19 for hypertension, dyslipidemia. At 5-year follow-up: n = 12 for obesity, hypertension, glucose intolerance, n = 11 for triglycerides and HDL.

†Prevalence of elevated fasting glucose, >100 mg/dL.

‡Prevalence estimates from references (23–29).