Pediatr Transplantation 2008: 12: 289–299

Copyright © 2008 Blackwell Munksgaard

Pediatric Transplantation
DOI: 10.1111/j.1399-3046.2008.00901.x

Adherence and health-related quality of life in adolescent liver transplant recipients

Fredericks EM, Magee JC, Opipari-Arrigan L, Shieck V, Well A, Lopez MJ. Adherence and health-related quality of life in adolescent liver transplant recipients.
Pediatr Transplantation 2008: 12: 289–299. © 2008 Blackwell Munksgaard

Abstract: Adolescence is a particularly high-risk period for non-adherence with post-transplant medical regimens. There remains a lack of research investigating factors related to non-adherence in adolescent LT recipients. The present study empirically assessed the relationship between adherence and HRQOL in adolescent LT recipients. Participants included 25 adolescents (mean = 15.1 yr, range 12–17.9) and their parent/guardian(s). Adherence was assessed using multiple indices including clinician-conducted interviews, rate of clinic attendance, and s.d. of consecutive tacrolimus blood levels. HRQOL was examined using self-report and parent-proxy report on well-validated assessment measures. Results indicated that 76% of participants were non-adherent on at least one measure of adherence, and HRQOL was significantly lower than normative data for healthy children. Tacrolimus s.d. were significant related to poor HRQOL across domains of physical, school, and social functioning. Non-adherent adolescents reported poorer health perceptions, self-esteem, mental health, family cohesion, and more limitations in social and school activities related to physical, emotional, and behavioral problems. These results suggest that empirically based assessment of HRQOL may help identify those at highest risk for behavior, emotional and school difficulties, as well as non-adherence. The examination of tacrolimus s.d. may also help identify patients who may benefit from intervention to promote adherence and HRQOL. Prospective investigations are necessary to further identify the impact of HRQOL on adherence and long-term health outcomes to further guide clinical intervention.

Emily M. Fredericks[1], John C. Magee[2], Lisa Opipari-Arrigan[3], Victoria Shieck[4], Andrew Well[1] and M. James Lopez[1]

[1]Department of Pediatrics, University of Michigan Medical School, Ann Arbor, MI, USA, [2]Department of Surgery, University of Michigan Medical School, Ann Arbor, MI, USA, [3]Behavioral Medicine & Clinical Psychology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA, [4]Transplant Center, University of Michigan Medical School, Ann Arbor, MI, USA

Key words: adherence – quality of life – liver transplantation

Emily M. Fredericks, PhD, 1924 Taubman Center, SPC 5318, 1500 E. Medical Center Drive, Ann Arbor, MI 48109-5318, USA
Tel.: 734 615 3866
Fax: 734 936 6897
E-mail: emfred@med.umich.edu

Accepted for publication 19 December 2007

Non-adherence to post-transplant medical regimens is estimated to be as high as 50–65% among pediatric LT recipients (1, 2). The clinical and economic consequences of transplant-related non-adherence have the potential to be quite substantial. It has been estimated that non-adherence is related increased medical complications, graft rejection, post-transplant mortality, and increased health care utilization rates (3–5).

Abbreviations: CHQ, Child Health Questionnaire; CHQ-CF, Child Health Questionnaire, Child Form; CHQ-PF, Child Health Questionnaire, Parent Form; HRQOL, health-related quality of life; LT, liver transplant; MAM, Medication Adherence Measure; MEMS, Medication Event Monitoring System; OTIS, Organ Transplant Information System; PedsQL, Pediatric Quality of Life Inventory; s.d., standard deviation.

Adolescence is a particularly high-risk period for non-adherence with medical regimens (6, 7). The developmental tasks associated with adolescence, including developing autonomy from family, assimilating with peers and separating from parents, poorly developed abstract thinking and understanding long-term consequences of present actions, are often difficult to balance with the behaviors required for optimal regimen adherence (8). Indeed, among adolescent transplant populations, medication non-adherence has been reported to be more than four times greater than in adults (9). A recent review of the prevalence of non-adherence among adolescent LT recipients revealed that non-adherence ranged from 17% to 53% (mean = 36.3%) (10). These non-adherence rates are striking given that unlike other post-transplant complications,

adherence behavior has the potential to be directly modifiable.

Despite a growing recognition of the severity of adherence problems during adolescence, the assessment and treatment of non-adherence in this population remains challenging. Existing studies of adherence in pediatric transplantation are limited by a lack of an accepted ''gold standard'' method for assessing adherence. Patient/caregiver self-reports of adherence may be the most cost-effective and easiest way to monitor adherence (11, 12); however, self-reported medication adherence is often less accurate (13), and the concordance with objective measures and health outcomes varies widely (14). Electronic medication monitoring technology, such as the MEMS® (Aprex Corporation, Union City, CA, USA), is the recommended assessment measure in adherence research given its ability to provide continuous and long-term measurement of medication adherence in real-time, and can reveal patterns of underdosing, overdosing, delayed dosing, drug ''holidays,'' and ''white coat adherence'' (i.e., taking medications consistently before medical appointments) (15). The MEMS® have demonstrated relationships between measured adherence and health outcomes such as viral load in children with HIV/AIDS (16). Yet, there are barriers associated with the MEMS® technology including cost and the possibility that these devices may interfere with established adherence routines (17). Recent studies have attempted to measure adherence objectively using a measure of the fluctuation (i.e., s.d.) of medication blood levels of tacrolimus in pediatric LT recipients (9, 18, 19). Higher s.d. were predictive of clinical outcome, such as biopsy-proven rejection (9) and hospitalization rates (19) in children who had undergone liver transplantation. However, there are limitations to relying on blood serum levels as a measure of adherence given that they are subject to pharmacokinetic variations. Until there is an accepted gold standard for measuring adherence in transplantation, it may be useful to employ a multi-method assessment strategy (12, 20).

In addition to developing valid strategies to measure adherence, it is also necessary to identify variables that promote regimen adherence among pediatric LT recipients. Research with other pediatric chronic illness populations has identified poor HRQOL as a key construct related to non-adherence (7, 21). To date, there remains a lack of research examining the relationship between HRQOL and non-adherence among adolescent LT recipients. Moreover, further exploration of HRQOL in adolescent transplant recipients is warranted given the challenges associated with this developmental period.

Results from previous studies examining HRQOL in pediatric LT recipients have yielded equivocal results. Some studies report that pediatric LT recipients have poorer quality of life in areas of physical, psychological, social, and family functioning when compared with healthy peers, but equal to or better HRQOL than children with other chronic illnesses (22–25). However, a recent study of adolescent HRQOL following liver or kidney transplantation revealed that the level of overall physical and psychological functioning among adolescent transplant recipients was high, and most aspects of HRQOL were similar to a healthy school-based population (26). These studies have not examined the relationship between HRQOL and adherence to post-transplant regimens.

A recent study by our group examined the association between HRQOL and non-adherence in pediatric LT recipients. Non-adherence, as measured by tacrolimus s.d. and rate of clinic attendance, was related to lower physical HRQOL, more limitations in social and school activities, and decreased family cohesion (19). However, the average age of the study sample was 8.6 yr, thus little is known about the relationship between HRQOL and non-adherence in adolescents. Adolescence is a high-risk period for non-adherence, thus it is critical to focus on this population in studies of adherence (6). The aims of this study are to examine rates of adherence to post-transplant regimens using multiple assessment methods, empirically assess HRQOL using parent-proxy and adolescent self-report, and clarify the relationship between adherence and HRQOL in adolescent LT recipients. It is hypothesized that adolescents with poorer adherence will have poorer HRQOL.

Materials and method

Study population

Participants were recruited from the Pediatric Liver Transplant Clinic at the University of Michigan, (Ann Arbor, MI, USA). Adolescent LT recipients between the ages of 12 and 17 yr were eligible for participation if they were fluent in English, and if they had at least one parent/guardian willing to participate as well. Participants were excluded if they were actively being treated for post-transplant lymphoproliferative disorder or other malignancy, had undergone a solid organ transplantation other than liver transplantation (i.e., kidney), or if they had significant developmental delay (i.e., documented

IQ < 70). Patients who had undergone retransplantation were eligible for participation in this pilot study.

Procedures

This study was a cross-sectional assessment of LT recipients between the ages of 12 and 17 yr. All aspects of the study were approved by the Institutional Review Board of the University of Michigan Medical School, and study enrollment began in November 2006. Informed consent and adolescent assent were obtained for all participants. Parent/guardian(s) and adolescents completed standardized assessment measures of HRQOL during a Pediatric Liver Transplant Clinic visit. Demographic, medical, and adherence data were obtained from a demographic survey, the adolescent's hospital medical record, the University of Michigan's OTIS, and an adherence questionnaire. Parents and adolescents were each compensated for their time and effort devoted to study-related activities at a rate of $25 (USD) each. Parents and adolescents also received meal tickets and parking vouchers.

Measures

HRQOL

Two measures of HRQOL were used in the present study as there is considerable variability in the literature regarding HRQOL, and no measure has been demonstrated to have more clinical utility or predictive validity. Thus, two measures were used to determine which was most associated with measures of adherence and health outcomes. At this time, there are no validated transplant-specific measures to assess HRQOL in pediatric populations.

PedsQL 4.0-generic core scales: The PedsQL4.0 Core Scales (27) is a well-validated, 23-item modular instrument for measuring HRQOL in children and adolescents ages 2–18 yr, and allows for a comparison of HRQOL across acute and chronic health conditions, and with healthy children (27). The healthy child normative comparison group included healthy children who were assessed either in physicians' offices during well-child checks or by telephone and whose parents did not report the presence of a chronic health condition. Administration time is approximately five min. Parent-proxy report and adolescent self-report were measured for all participants. The PedsQL assesses HRQOL across 4 domains: Physical, Emotional, Social, and School functioning. Total, Physical, and Psychosocial Summary scores are also calculated. Scores are transformed to a 0–100 scale, with higher scores indicating more positive HRQOL.

CHQ: Parents completed the CHQ-PF50 and adolescents completed the CHQ-CF87 (28). The CHQ-PF50 is a 50-item scale, and the CHQ-CF87 is an 87-item scale. Both forms assess a broad spectrum of child- and family-focused health areas including: Physical Functioning, Role/Social Limitations – Physical, General Health Perceptions, Bodily Pain/Discomfort, Role/Social Limitations-Emotional/Behavioral, Parent Impact-Time, Parent Impact-Emotion, Self-Esteem, Mental Health, Behavior, Family Activities, Family Cohesion, and Change in Health. Administration time is approximately 15–20 min. Items are responded on a 4- or 5-point Likert scale depending on the subscale. Scores are transformed to a 0–100 scale, with higher scores indicating better health. The CHQ-PF50 has been normed using a representative sample of U.S. children (28), while the normative sample used for the CHQ-CF87 is a school-based population (n = 278) comprised predominately (92%) of African American children aged 10–15 yr (29). Representative U.S. population normative data for the CHQ-CF87 are unavailable.

Adherence behavior

A multi-method assessment of adherence was employed to measure adherence to immunosuppressive medication and clinic visits. Definitions of adherence were determined using stringent cut-offs based on previous research showing that minimal deviations from dosing schedules of the immunosuppressive regimens were associated with an increase risk of poor clinical outcomes (30, 31).

Clinician-conducted interview: Adolescents completed the MAM (Zelikovsky, unpublished data), as a self-report measure of adherence to immunosuppressive medication. The MAM is a semi-structured interview assessing knowledge of medical regimen, self-reported adherence, perceived obstacles to adherence, and the system used to organize medications. This measure has been used with pediatric solid organ transplant recipients (32–34). Adherence was defined as adolescent report of missing/taking late < 10% of any medication in the previous seven days, and/or adolescent report of not missing a dose within the previous two wk.

Clinic attendance: Adherence to clinic visits was assessed retrospectively by comparing clinic attendance to the number and interval

frequency recommended by the transplant team. The rate of clinic attendance for the year prior to study participation was obtained from the adolescent's medical record. Adherence was defined as a clinic attendance rate of ≥90%. This definition is consistent with the pediatric adherence literature (35). In our previous study of pediatric LT recipients, the rate of clinic attendance was significantly related to hospital admissions, liver biopsies, and rejection episodes (19).

Immunosuppressant levels: To measure adherence to post-transplant immunosuppressant medications, data from routine monitoring of tacrolimus blood levels were obtained from the adolescent's medical record and OTIS for the year prior to study participation. Tacrolimus levels obtained during inpatient hospitalization stays were not included in the analyses. S.d. of consecutive trough tacrolimus blood levels were calculated. Shemesh and colleagues have demonstrated the predictive and concurrent validity of the use of s.d. of tacrolimus blood levels as a measure of adherence to immunosuppressive medications (9). Specifically, higher fluctuations have been used as an indicator of variable medication administration, and tacrolimus s.d. significantly related to clinician ratings of non-adherence, as well as health outcome including episodes of rejection (9). In this study, adherence was defined as s.d. < 2 (36).

Health status

Measures of adolescent health status including frequency of hospital admissions, liver biopsies, and episodes of rejection for the year prior to study participation were collected via patient electronic medical records and the University of Michigan University's OTIS.

Statistical method

Sample mean subscale and summary scores obtained on the HRQOL measures were compared with published normative data for healthy children using two-tailed t-tests. Pearson correlation coefficients were used to assess the relationships between scores on the HRQOL measures and measures of adherence. Participants were categorized as ''adherent'' or ''non-adherent'' based on their self-reported medication taking behavior, rate of clinic attendance and tacrolimus s.d. Two-sample t-tests were used to assess differences between ''adherent'' and ''non-adherent'' participants with respect to measures of HRQOL and health outcomes. All analyses were conducted using Statistical Package for the Social Sciences (SPSS, Chicago, IL, USA) version 13.0.

Results

Participants

To date, 42 eligible participants have been identified and recruited by mail and/or face-to-face contact during their clinic visit. Of these eligible participants contacted, 28 (66.7%) agreed to participate. Fourteen families declined participation due to time constraints, transportation limitations, lack of interest, and/or the presence of other children at the clinic visit. Three of the adolescents enrolled in the study were not receiving tacrolimus immunosuppressive therapy. S.d. were not calculated for cyclosporine as this method assumes that medication blood levels are related to intake, which has been shown to be the case for tacrolimus but not for cyclosporine (37). Thus, only the 25 adolescents who were receiving tacrolimus immunosuppressive therapy are included in these analyses.

Table 1 describes the demographic characteristics of the study group. The mean age of adolescent LT recipients was 15.1 ± 1.9 yr (range 12.0–17.9 yr), and the mean age at the time of transplantation was 7.6 ± 5.6 yr (range 8 months–15.2 yr). The mean time elapsed since transplantation was 7.5 ± 5.7 yr (range 1 month–17.2 yr). Primary indication for transplantation was biliary atresia (48%) followed by autoimmune hepatitis (20%), hepatitis (12%), alpha-1 antitrypsin (8%), and other (12%). Three patients had undergone retransplantation

Table 1. Participant demographics

Factor	Mean ± s.d.
Participant age (yr)	15.1 ± 1.9
Time since transplantation (yr)	7.5 ± 5.7
Age at transplantation (yr)	7.6 ± 5.6
Maternal age (yr)	37.0 ± 7.8
Paternal age (yr)	40.3 ± 6.8
Parent-proxy respondent	Mothers = 19 (76%)
	Fathers = 5 (20%)
	Other = 1 (4%)
Participant gender	Female = 17 (68%)
	Male = 8 (32%)
Participant race (parent-reported)	White = 18 (72%)
	African American = 7 (28%)
Diagnosis	Biliary atresia = 12 (48%)
	Fulminant hepatic failure = 1 (4%)
	Autoimmune hepatitis = 5 (20%)
	Hepatitis = 3 (12%)
	Alpha-1 antitrypsin = 2 (8%)
	Sclerosing cholangitis = 1 (4%)
	Other = 1 (4%)

within an average of 40 days (3–96 days) of their initial transplantation for reasons including primary non-function, chronic rejection, and acute liver failure. The date of their second liver transplantation was used for all study analyses.

Adolescents were predominately female (68%). A majority of the parent/guardian respondents were mothers (76%), half of whom were married (52%), and most did not have more than a high school education (44%).

There were no significant relationships between time since transplantation, age at transplantation, race or other demographic variables and measures of psychosocial functioning, adherence, or health status.

HRQOL

PedsQL

Mean HRQOL scores for the adolescent self-report and parent-proxy are presented in Figs. 1 and 2 for both adolescent LT recipients and the healthy normative sample (27). Both self-reported and parent-proxy HRQOL scores were impaired and significantly lower than published normative data for healthy children. Parent-proxy reports indicate marked impairment with respect to Total Functioning ($p = 0.0001$), Physical ($p = 0.006$) and Psychosocial Health ($p = 0.0001$), Emotional ($p = 0.013$), Social ($p = 0.02$), and School Functioning ($p = 0.0001$). Adolescent self-reports are indicative of impairment in Total Functioning ($p = 0.007$), Psychosocial Health ($p = 0.01$), Emotional ($p = 0.04$), and School Functioning ($p = 0.001$).

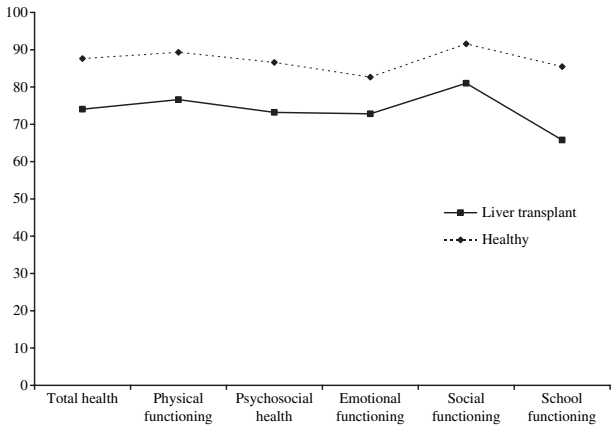

Fig. 1. PedsQL 4.0 parent proxy-report scores for adolescent LT population and healthy children. Normative data for healthy children were retrieved from published references (42). The full range of the PedsQL 4.0 is 0–100, with higher scores reflecting better health.

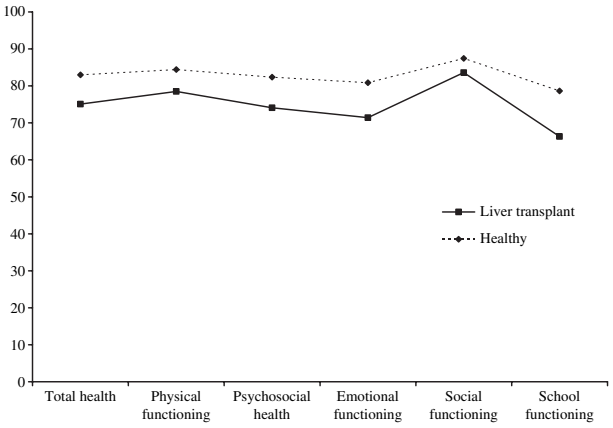

Fig. 2. PedsQL 4.0 adolescent self-report scores for LT population and healthy children. Normative data for healthy children were retrieved from published references (42). The full range of the PedsQL 4.0 is 0–100, with higher scores reflecting better health.

CHQ

Tables 2 and 3 present means and s.d. for the subscales of the CHQ-PF50 and CHQ-CF87 for LT recipients compared with published scores for healthy children (28, 29). Results from the CHQ-PF50 indicate that the Physical summary score was significantly lower for LT recipients than for the healthy comparison group ($p = 0.012$). Compared with the healthy sample, parents reported that their adolescent LT recipients had significantly lower scores on the Self-Esteem ($p = 0.017$) and General Health Perceptions ($p = 0.0001$) subscales, and endorsed significantly lower scores on the Parental Impact-Emotional scale ($p = 0.027$), and the Family Activities scale ($p = 0.007$). There were no significant differences across remaining subscales.

In contrast, on the CHQ-CF87, self-reports from the adolescent LT recipients were significantly lower than the healthy sample on the General Health Perceptions scale ($p = 0.031$), but there were no significant differences across remaining subscales.

Adherence behavior

Sixteen participants (76%) were non-adherent on at least one measure of adherence. However, there were no significant relationships between measures of adherence behaviors, suggesting that these assessment methods evaluate different aspects of regimen adherence. With non-significant correlations obtained between methods of measurement (self-report vs. immunosuppressant drug level), a composite adherence score was not used. As such, participants were classified categorically as ''adherent'' and ''non-adherent'' separately for different measures.

Table 2. CHQ-PF50 summary scores for liver transplant recipients compared with normative data for healthy children

Scales*	Liver transplant (mean ± s.d.)	Healthy† (mean ± s.d.)	t-value	Significance
Physical functioning	87.1 ± 22.4	96.1 ± 13.9	−2.003	p = 0.057
Role/Social – Emotional, behavioral	81.3 ± 32.8	92.5 ± 18.6	−1.701	n.s.
Role/Social – Physical	85.3 ± 27.8	93.6 ± 18.6	−1.488	n.s.
Bodily pain	73.6 ± 24.1	81.7 ± 19.0	−1.678	n.s.
Behavior	77.7 ± 15.5	75.6 ± 16.7	0.677	n.s.
Mental health	77.6 ± 12.4	78.5 ± 13.2	−0.362	n.s.
Self-esteem	68.5 ± 21.9	79.8 ± 17.5	−2.574	p = 0.017
General health perceptions	55.6 ± 16.6	73.0 ± 17.3	−5.234	p = 0.000
Parental Impact – Time	80.1 ± 26.2	87.8 ± 19.9	−1.441	p = 0.0001
Parental Impact – Emotional	72.3 ± 17.0	80.3 ± 17.3	−2.348	p = 0.027
Family activities	81.0 ± 14.8	89.7 ± 18.6	−2.933	p = 0.007
Family cohesion	70.6 ± 20.4	72.3 ± 8.8	−0.417	n.s.
Physical functioning summary‡	45.3 ± 13.8	53.0 ± 8.8	−2.730	p = 0.012
Psychosocial functioning summary‡	49.0 ± 9.3	51.2 ± 9.1	−1.133	n.s.

*Individual scores range from 0 to 100, with higher scores reflecting better HRQOL.
†Data for healthy population were retrieved from published references (28).
‡Physical and psychosocial summary scales are standardized (mean = 50, s.d. = 10).
CHQ-PF, Child Health Questionnaire, Parent Form; HRQOL, health-related quality of life.

Table 3. CHQ-CF87 summary scores for liver transplant recipients compared with normative data for healthy children

Scales*	Liver transplant (mean ± s.d.)	Healthy† (mean ± s.d.)	t-value	Significance
Physical functioning	90.2 ± 14.1	88.8 ± 14.0	0.504	n.s.
Role/Social-Emotional	87.6 ± 20.9	85.9 ± 21.0	0.397	n.s.
Role/Social – Behavioral	87.6 ± 21.6	86.5 ± 21.5	0.235	n.s.
Role/Social – Physical	88.4 ± 21.9	88.3 ± 21.0	0.033	n.s.
Bodily pain	72.4 ± 23.7	74.4 ± 23.1	−0.422	n.s.
Behavior	81.0 ± 15.1	76.6 ± 14.6	1.453	n.s.
Mental health	77.2 ± 18.7	72.7 ± 16.0	1.214	n.s.
Self-esteem	81.8 ± 12.1	81.8 ± 15.8	0.004	n.s.
General health perceptions	60.3 ± 13.3	66.4 ± 14.6	−2.297	p = 0.031
Family activities‡	79.7 ± 16.6	–		
Family cohesion‡	68.6 ± 22.8	–		

*Individual scores range from 0 to 100, with higher scores reflecting better HRQOL.
†Data for healthy population were retrieved from published references (29).
‡The Family Activities and Family Cohesion subscales were unavailable for the healthy sample.
CHQ-CF, Child Health Questionnaire, Child Form; HRQOL, health-related quality of life.

Clinician-conducted interview

Adherence was defined as adolescent report of missing/taking late $< 10\%$ of any medication in the previous seven days, and/or adolescent report of not missing a dose within the previous two wk. Ten adolescents (40%) were classified as non-adherent based on reports of missed and/or late doses of their immunosuppressive medication. Five participants (20%) stated they never missed a dose of tacrolimus, while 10 participants (40%) reported missing a dose within the past two wk. Eight participants (32%) reported it had been at least a month since they had missed a dose. When asked about their medication taking behavior in the week prior to study participation, overall, patients missed an average of 3% of weekly immunosuppressant doses (range 0–21.4%) and took an average of 11.1% (range 0–100%) of the doses more than two h late. Eighteen participants (72%) reported never missing a dose of tacrolimus, five participants (20%) reported missing at least one dose in the previous week, one adolescent (4%) reported missing at least two doses, and one adolescent (4%) reported missing three doses. Ten participants (40%) reported never taking their tacrolimus late, while five participants (20%) reported taking one dose late, seven participants (28%) reported taking two doses late, two participants (8%) reported taking three doses late, and one participant (4%) reported taking 14 doses late (i.e., being late with both doses every day). Adolescents who did endorse missed or late doses cited forgetting, not being home, interfered with activities, and ran out of medication as reasons.

Immunosuppressant levels

Participants had an average of 10.5 ± 6.7 blood levels of tacrolimus in the year prior to study participation (range 4–29 blood values). The mean tacrolimus s.d. was 1.9 ± 1.5 ng/mL (range 0.21–7.32 ng/mL). Eight participants

(32%) were classified as non-adherent based on tacrolimus s.d. > 2.

Clinic attendance

Participants attended an average of 85.8 ± 17.5% of scheduled clinic visits (range 50–100%). Twelve participants (48%) were classified as non-adherent based on a rate of clinic attendance of <90%.

Health status

Within the 12 months prior to participation, nine (36%) participants had been hospitalized at least once, five (20%) underwent at least one liver biopsy, and one (4%) had a documented biopsy-proven episode of rejection. Overall, there were 16 hospital admissions, 40 inpatient days, eight liver biopsies, and one biopsy-proven episode of rejection.

Relationship between HRQOL and adherence behavior

Correlations with HRQOL

Tacrolimus s.d. was significantly related to measures of parent-proxy and adolescent self-reported measures of HRQOL. Specifically, tacrolimus s.d. was significantly related to parent-proxy reports of adolescent school functioning on the PedsQL ($r = -0.415$, $p = 0.039$), and several subscales of the CHQ-PF50 including: Role/Social Limitations-Emotional-Behavioral ($r = -0.435$, $p = 0.030$), Role/Social Limitations-Physical ($r = -0.672$, $p = 0.0001$), Bodily Pain/Discomfort ($r = -0.619$, $p = 0.001$), Mental Health ($r = -0.438$, $p = 0.029$), General Health Perceptions ($r = -0.581$, $p = 0.002$), Physical Summary Score ($r = -0.728$, $p = 0.001$), and Parent Impact-Time ($r = -0.547$, $p = 0.006$).

Tacrolimus s.d. was significantly related to adolescent-self reports on numerous scales on the PedsQL including Physical Functioning ($r = -0.550$, $p = 0.004$), Social Functioning ($r = -0.397$, $p = 0.049$), School Functioning ($r = -0.666$, $p = 0.001$), and Total Functioning ($r = -0.471$, $p = 0.017$). There were also significant relationships between tacrolimus s.d. and several scales on the CHQ-CF87 including Physical Function ($r = -0.798$, $p = 0.0001$), Role/Social Limitations-Physical ($r = -0.453$, $p = 0.023$), General Health Perceptions ($r = -0.608$, $p = 0.001$), Bodily Pain/Discomfort ($r = -0.572$, $p = 0.003$), and Family Cohesion ($r = -0.421$, $p = 0.036$).

The MAM and rate of clinic attendance were not significantly related to parent-proxy or adolescent self-reports of HRQOL.

Differences between ``adherent'' and ``non-adherent'' participants

Based on the clinician-conducted interview and the rate of clinic attendance, there were no significant differences between the adherent and non-adherent groups with respect to HRQOL. However, based on tacrolimus s.d. classifications, there were significant between-group differences with respect to HRQOL (see Table 4). Specifically, parents in the non-adherent group reported that their adolescent's health had a greater impact on their time (CHQ-PF50, $p = 0.048$) than parents in the adherent group. Compared with parents in the adherent group, parents in the non-adherent group reported that their adolescents had significantly lower scores on CHQ-PF50 subscales measuring Role/Social Limitations-Physical Functioning ($p = 0.018$), Bodily Pain/Discomfort ($p = 0.010$), General Health Perceptions ($p = 0.007$), and on the Physical Summary Scale ($p = 0.007$).

In contrast, adolescents in the non-adherent group reported significantly lower scores on all domains of the PedsQL including Physical Functioning ($p = 0.001$), Emotional Functioning ($p = 0.001$), Social Functioning ($p = 0.01$), School Functioning ($p = 0.002$), and Total Functioning ($p = 0.000$). Adolescents in the non-adherent group also reported significantly lower scores than those in the adherent group on several subscales of the CHQ-CF87 including Physical Functioning ($p = 0.004$), Role/Social Limitations-Physical ($p = 0.008$), General Health Perceptions ($p = 0.003$), Bodily Pain ($p = 0.002$), Role/Social Limitations-Emotional ($p = 0.018$), Self-Esteem ($p = 0.001$), Mental Health ($p = 0.001$), and Family Cohesion ($p = 0.038$).

With respect to health outcomes, adolescents classified as non-adherent based on tacrolimus s.d. had significantly more hospital admissions than the adherent group ($p = 0.032$) and more inpatient days ($p = 0.037$). Participants in the non-adherent group as defined by clinic attendance also had significantly more hospital admissions ($p = 0.029$) than the adherent group.

Discussion

The current study objectives were to describe HRQOL and adherence to post-transplant regimens using multiple assessment methods, and to explore the links between adolescent HRQOL and adherence to post-transplant regimens. Results of the present study are consistent with our previous research (19) and indicate that

Table 4. Differences between adherent and non-adherent participants on measures of HRQOL

Factor	Tacrolimus s.d.		t-value	p-value
	Non-adherent (mean ± s.d.)	Adherent (mean ± s.d.)		
Parent-proxy report				
CHQ-PF50 Parent Impact-Time	65.3 ± 34.8	87.5 ± 17.6	−2.098	0.048
CHQ-PF50 Role/Social – Physical	66.7 ± 36.7	94.1 ± 17.6	−2.558	0.018
CHQ-PF50 Bodily Discomfort	56.2 ± 25.6	81.8 ± 19.1	−2.794	0.010
CHQ-PF50 General Health Perceptions	43.1 ± 13.9	61.4 ± 14.7	−2.953	0.007
CHQ-PF50 Physical Summary	35.1 ± 50.9	50.4 ± 9.9	−2.957	0.007
Adolescent self-report				
PedsQL Physical Functioning	64.8 ± 13.7	84.9 ± 11.3	−3.865	0.001
PedsQL Emotional Functioning	51.9 ± 20.0	80.6 ± 16.3	−3.828	0.001
PedsQL Social Functioning	72.5 ± 19.3	88.8 ± 10.1	−2.809	0.01
PedsQL School Functioning	50.8 ± 11.6	71.8 ± 12.6	−3.561	0.002
PedsQL Total Functioning	61.3 ± 12.2	81.5 ± 8.3	−4.864	0.000
CHQ-CF87 Physical Functioning	79.2 ± 19.8	95.4 ± 6.1	−2.915	0.004
CHQ-CF87 Role/Social – Physical	72.2 ± 32.0	96.1 ± 8.7	−2.915	0.008
CHQ-CF87 General Health Perceptions	49.4 ± 12.8	65.4 ± 10.4	−3.336	0.003
CHQ-CF87 Role/Social – Emotional	73.6 ± 31.4	94.1 ± 8.9	−2.539	0.018
CHQ-CF87 Bodily Pain	52.5 ± 19.1	81.8 ± 19.8	−3.490	0.002
CHQ-CF87 Self-Esteem	71.1 ± 9.9	86.9 ± 9.6	−3.807	0.001
CHQ-CF87 Mental Health	60.7 ± 21.9	85.0 ± 10.8	−3.756	0.001
CHQ-CF87 Family Cohesion	55.0 ± 23.1	75.0 ± 20.3	−2.199	0.038

CHQ-CF, Child Health Questionnaire, Child Form; CHQ-PF, Child Health Questionnaire, Parent Form; PedsQL, Pediatric Quality of Life Inventory; HRQOL, health-related quality of life.

adolescent LT recipients and their parents reported decreased HRQOL compared with normative data for healthy children across various domains of functioning.

Based on parent-proxy reports, adolescent LT recipients were perceived to have poorer physical, social, school, and emotional functioning compared with a healthy comparison group. Moreover, parents reported more impairment in family activities and in their own emotional functioning related to their adolescent's transplant than parents of the healthy comparison group.

Adolescent self-reported HRQOL varied by assessment measure. Based on the CHQ-CF87, self-reports from the adolescent LT recipients were significantly lower than the healthy comparison group on the General Health Perceptions scale, but were comparable with the healthy sample on remaining scales. Based on the PedsQL, with the exception of social functioning, adolescents reported poorer HRQOL across physical, emotional, and school functioning domains compared with the healthy comparison group. The findings using the CHQ are consistent with previous research (26). The discrepancies in HRQOL as measured by the PedsQL and the CHQ may be related to variability in content across domains, as well as the nature of normative comparison groups used. Both of these instruments have psychometric support (27, 38, 39), but there is limited research using these measures in pediatric transplantation. There is a need for continued research examining HRQOL of pediatric transplant recipients using validated measures and age-matched controls. Moreover, to date, there are no transplant-specific measures of HRQOL validated for use in pediatric populations.

Despite the variability with respect to the assessment of HRQOL, adolescent, and parent-proxy reports of HRQOL were related to adherence as measured by s.d. of tacrolimus blood levels. Poorer HRQOL was significantly associated with greater variability in tacrolimus blood levels, which is suggestive of medication non-adherence. Tacrolimus s.d. were related to poorer HRQOL across domains of physical, school, and social functioning, and general health perceptions. Tacrolimus s.d. were also related to parents' reports of their adolescents' mental health, and parental perceptions of limitations their adolescents have in school-related and social activities due to problems with physical, emotional, and behavioral functioning. Adolescent self-reports of limitations in family cohesiveness were also related to tacrolimus s.d.

There were significant differences in HRQOL between adherent and non-adherent adolescents. Parents in the non-adherent group only perceived their adolescents to be more limited in their school-related activities and activities with

friends caused by problems in physical health. In contrast, based on adolescent self-report, adolescents in the non-adherent group were more impaired across all domains of HRQOL including physical, emotional, social, and school functioning. Non-adherent adolescents reported poorer health perceptions, self-esteem, mental health, and family cohesion, and endorsed more school and social limitations due to physical, emotional, and/or behavioral problems.

The results of this study should be considered in light of study limitations. First, this study was conducted within a single pediatric LT program which limited the sample size and the ability to generalize these findings to other pediatric LT centers. To strengthen these findings, this research should be replicated in pediatric transplant centers across geographical locations. Moreover, the sample may not be representative due to a potential selection bias wherein patients and families who are non-adherent did not elect to participate. This selection bias is present in many studies investigating regimen adherence (21). Nevertheless, despite this potential selection bias, the majority of adolescent participants were non-adherent on at least one measure of adherence behavior.

Another limitation relates to the retrospective, cross-sectional study design. The current study reports an association between HRQOL and adherence, but the direction of these relationships remains unclear as the retrospective, cross-sectional nature of this study limits any conclusions regarding causality. It is commonly assumed that impaired HRQOL and psychosocial adjustment contributes to poor regimen adherence, however there is a lack of research investigating these relationships longitudinally. Overall, positive HRQOL and psychological adjustment is associated with better treatment adherence (7). However, research has also shown that non-adherence is associated with more frequent hospital admissions, longer hospital stays, over-utilization of health care services, and lower quality of life (40, 41). Indeed, non-adherent adolescents in the present study had more frequent and longer inpatient hospitalizations than the adherent adolescents. Thus, the diminished HRQOL reported by adolescents in the present study may be secondary to their suboptimal adherence and subsequent poorer health. Further work is needed to clarify the relationship between HRQOL, adherence, and medical variables as this has important implications for the development of interventions to promote adherence and improve health outcomes.

Lastly, these preliminary results are limited by the lack of agreement between measures of adherence. The current study implemented a multi-method approach to assessing adherence behavior; however, only tacrolimus s.d. were significantly related to HRQOL. Previous research has identified a relationship between tacrolimus s.d. and clinical health outcomes (9, 19) and psychosocial functioning (18, 19). Yet, there is limited research investigating the validity of clinic attendance and patient self-report as measures of adherence in adolescent transplant recipients. Further study of the relationship between measures of adherence and clinical outcomes, including episodes of rejection, graft function as well as psychosocial functioning, is warranted.

Despite limitations, the present study is strengthened by its significant clinical implications. Although this was a single center study with a reasonably small sample size, significant relationships were found between measures of adherence and HRQOL. Non-adherence as measured by tacrolimus s.d. was related to aspects of HRQOL, including social, emotional, and physical functioning. Empirically based assessment of modifiable factors will help identify patients at risk for non-adherence, and may allow for the appropriate delivery of interventions to ameliorate this risk. Given that adolescent self-reported HRQOL was associated with adherence in the present study, routine assessment of self-reported measures of HRQOL from adolescent LT recipients may help identify those at highest risk for behavior, emotional, and school difficulties, as well as non-adherence. Similarly, the routine examination of tacrolimus s.d. may also help identify patients who are not only at-risk for non-adherence, but who may benefit from intervention targeting HRQOL. To further elucidate the relationship between adherence and HRQOL among adolescent LT recipients, prospective longitudinal studies to identify impact of HRQOL on adherence and health outcomes are warranted.

Acknowledgments

This work was funded by a Grant from the CS Mott Children's Hospital & Division of Child Behavioral Health, University of Michigan Medical School to Emily M. Fredericks, PhD.

References

1. Wainwright SP, Gould D. Non-adherence with medications in organ transplant patients: A literature review. J Adv Nurs 1997: 26: 968–977.

2. Swanson MA, Palmeri D, Vossler ED, Bartus SA, Hull D, Schweizer RT. Noncompliance in organ transplant recipients. Pharmacotherapy 1991: 11: 173S–174S.
3. Denhaerynck K, Dobbels F, Cleemput I, et al. Prevalence, consequences, and determinants of nonadherence in adult renal transplant patients: A literature review. Transpl Int 2005: 18: 1121–1133.
4. Lurie S, Shemesh E, Sheiner PA, et al. Non-adherence in pediatric liver transplant recipients – An assessment of risk factors and natural history. Pediatr Transplant 2000: 4: 200–206.
5. Falkenstein K, Flynn L, Kirkpatrick B, Casa-Melley A, Dunn S. Non-compliance in children post-liver transplant. Who are the culprits? Pediatr Transplant 2004: 8: 233–236.
6. Shaw RJ. Treatment adherence in adolescents: Development and psychopathology. Clin Child Psychol Psychiatry 2001: 6: 137–150.
7. La Greca AM, Bearman KJ. Adherence to pediatric treatment regimens. In: Roberts MC, ed. Handbook of Pediatric Psychology. New York: The Guilford Press, 2003: pp. 119–140.
8. Suris JC, Michaud PA, Viner R. The adolescent with a chronic condition. Part I: Developmental issues. Arch Dis Child 2004: 89: 938–942.
9. Shemesh E, Shneider BL, Savitzky JK, et al. Medication adherence in pediatric and adolescent liver transplant recipients. Pediatrics 2004: 113: 825–832.
10. Dobbels F, Van Damme-Lombaert R, Vanhaecke J, De Geest S. Growing pains: Non-adherence with the immunosuppressive regimen in adolescent transplant recipients. Pediatr Transplant 2005: 9: 381–390.
11. De Geest S, Vanhaecke J. Methodological issues in transplant compliance research. Transplant Proc 1999: 31: 81S–83S.
12. Quittner AL, Modi AC, Lemanek KL, Ievers-Landis CE, Rapoff MA. Evidence-based assessment of adherence to medical treatments in pediatric psychology. J Pediatr Psychol 2007: [Epub ahead of print].
13. Farmer KC. Methods for measuring and monitoring medication regimen adherence in clinical trials and clinical practice. Clin Ther 1999: 21: 1074–1090; Discussion 1073.
14. Garber MC, Nau DP, Erickson SR, Aikens JE, Lawrence JB. The concordance of self-report with other measures of medication adherence: A summary of the literature. Med Care 2004: 42: 649–652.
15. Butler JA, Peveler RC, Roderick P, Horne R, Mason JC. Measuring compliance with drug regimens after renal transplantation: Comparison of self-report and clinician rating with electronic monitoring. Transplantation 2004: 77: 786–789.
16. Farley J, Hines S, Musk A, Ferrus S, Tepper V. Assessment of adherence to antiviral therapy in HIV-infected children using the Medication Event Monitoring System, pharmacy refill, provider assessment, caregiver self-report, and appointment keeping. J Acquir Immune Defic Syndr 2003: 33: 211–218.
17. Shellmer DA, Zelikovsky N. The challenges of using medication event monitoring technology with pediatric transplant patients. Pediatr Transplant 2007: 11: 422–428.
18. Shemesh E, Lurie S, Stuber ML, et al. A pilot study of posttraumatic stress and nonadherence in pediatric liver transplant recipients. Pediatrics 2000: 105: E29.
19. Fredericks EM, Lopez MJ, Magee JC, Shieck V, Opipari-Arrigan L. Psychological functioning, nonadherence and health outcomes after pediatric liver transplantation. Am J Transplant 2007: 7: 1974–1983.
20. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med 2005: 353: 487–497.
21. Lagreca AM, Schuman WB. Adherence to prescribed medical regimens. In: Roberts M, ed. Handbook of Pediatric Psychology, 2nd edn. New York, NY: The Guilford Press, 1995: pp. 55–83.
22. Taylor R, Franck LS, Gibson F, Dhawan A. A critical review of the health-related quality of life of children and adolescents after liver transplantation. Liver Transpl 2005: 11: 51–60; Discussion 57–59.
23. Bucuvalas JC, Britto M, Krug S, et al. Health-related quality of life in pediatric liver transplant recipients: A single-center study. Liver Transpl 2003: 9: 62–71.
24. Alonso EM, Neighbors K, Mattson C, et al. Functional outcomes of pediatric liver transplantation. J Pediatr Gastroenterol Nutr 2003: 37: 155–160.
25. Midgley DE, Bradlee TA, Donohoe C, Kent KP, Alonso EM. Health-related quality of life in long-term survivors of pediatric liver transplantation. Liver Transpl 2000: 6: 333–339.
26. Sundaram SS, Landgraf JM, Neighbors K, Cohn RA, Alonso EM. Adolescent health-related quality of life following liver and kidney transplantation. Am J Transplant 2007: 7: 982–989.
27. Varni JW, Seid M, Kurtin PS. PedsQL 4.0: Reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. Med Care 2001: 39: 800–812.
28. Landgraf JM, Abetz L, Ware JE. The CHQ User's Manual, Second Printing. Boston, MA: HealthAct, 1999.
29. Landgraf JL, Abetz LN. Functional status and well-being of children representing three cultural groups: Initial self-reports using the CHQ-CF87. Psychol Health 1997: 12: 839–854.
30. De Geest S, Abraham I, Moons P, et al. Late acute rejection and subclinical noncompliance with cyclosporine therapy in heart transplant recipients. J Heart Lung Transplant 1998: 17: 854–863.
31. Nevins TE, Kruse L, Skeans MA, Thomas W. The natural history of azathioprine compliance after renal transplantation. Kidney Int 2001: 60: 1565–1570.
32. Simons LE, Blount RL. Identifying barriers to medication adherence in adolescent transplant recipients. J Pediatr Psychol 2007: 32: 831–844.
33. Zelikovsky N, Walsh AP, Meyers K. Understanding barriers to adherence among adolescents with renal disease. National Conference on Child Health Psychology. Charleston, SC: 2004.
34. Zelikovsky N, Schast A, Hills T, Meyers K. Perceived barriers to optimal adherence among adolescent patients with kidney disease. National Conference on Child Health Psychology. Gainesville, FL: 2006.
35. Rapoff MA. Adherence to Pediatric Medical Regimens. New York: Kluwer Academic/Plenum Press, 1999.
36. Bucuvalas JC, Ryckman FC, Arya G, et al. A novel approach to managing variation: Outpatient therapeutic monitoring of calcineurin inhibitor blood levels in liver transplant recipients. J Pediatr 2005: 146: 744.
37. Cakaloglu Y, Tredger JM, Devlin J, Williams R. Importance of cytochrome P-450IIIA activity in determining dosage and blood levels of FK 506 and cyclosporine in liver transplant recipients. Hepatology 1994: 20: 309–316.
38. Varni JW, Seid M, Rode CA. The PedsQL: Measurement model for the pediatric quality of life inventory. Med Care 1999: 37: 126–139.
39. Varni JW, Limbers CA, Burwinkle TM. Parent proxy-report of their children's health-related quality of life: An analysis of 13,878 parents' reliability and validity across age subgroups using the PedsQLTM 4.0 Generic Core Scales. Health Qual Life Outcomes 2007: 5: 2.

40. Bunzel B, Laederach-Hofmann K. Solid organ transplantation: Are there predictors for posttransplant noncompliance? A literature overview. Transplantation 2000: 70: 711–716.
41. Griffin KJ, Elkin TD. Non-adherence in pediatric transplantation: A review of the existing literature. Pediatr Transplant 2001: 5: 246–249.
42. Varni JW, Burwinkle TM, Seid M. The PedsQLTM as a pediatric patient-reported outcome: Reliability and validity of the PedsQLTM Measurement Model in 25,000 children. Exp Rev Pharmacoeconomics Outcomes Res 2005: 5: 705–719.