Comparison of Lipid Profiles Between Pediatric Living- and Deceased-Donor Liver Recipients

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Abstract

Background: Hyperlipidemia is very common after liver transplantation and can be observed in up to 71% of patients. The etiology of lipid disorders in these patients is multifactorial, with different lipid profiles observed depending on the immunosuppressive agents administered and the presence of additional risk factors, such as obesity, diabetes mellitus and nutrition. The aim of the present study is to compare the lipid profile in liver transplant recipients from living-related and deceased donors.

Methods: This is a retrospective cross-sectional study performed in Shiraz University of Medical Science between 2005 till 2018. Patients under 18 years old who received liver transplant were included in the study and divided in 2 groups who received from living-related and deceased donors and lipid profiles were compared between two groups.

Results: 397 patients were included in the study, in the first group 234 received liver from deceased donor and in second group 161 from living-related donor. The mean TG and HDL level were 133 mg/dL and 46 mg/dL in the first group and 118 mg/dL and 54 mg/dL in the second group while the differences were statistically significant.

Conclusion: Patients who received liver from a living-related donor have a significantly lower TG and higher HDL and a lower cardiovascular risk.

Introduction

Following great success in solid organ transplant over the past 50 years, excellent short-term survival of transplant tissue and its long-term adequate function without the development of significant associated comorbidities is typically expected. (1) Immunosuppressive regimens have improved, meaning that acute graft rejection has been significantly reduced, and even chronic forms of graft rejection have been delayed and their prevalence has decreased. As a result, the main physicians' attention is focused on the general health of recipients, and apart from allograft health in particular, cardiovascular health is an important component. In turn, each of the risk factors of cardiovascular disease (CVD) including dyslipidemia, has received part of the post-transplant management strategy in this population. Excess weight gain, hypertension, diabetes mellitus and hyperlipidemia are common complications after liver transplant most likely due to multiple causes. These components of metabolic syndrome can increase the risk of CVD that is a common cause of mortality after liver transplantation. Understanding the prevalence and predisposing factors of CVD in liver transplant recipients and a comprehensive prevention and treatment strategy is very important to minimize cardiovascular morbidity and mortality after liver transplant. Weight reduction and control of metabolic syndrome are the mainstay to any prevention and management strategy. (2, 3)

The prevalence of hyperlipidemia in liver transplant recipients is high and is estimated to range

from 27 to 71%. (4–6) In our previous study over the 20-year period, on 391 pediatric liver transplant recipients the rates of posttransplant hyperlipidemia, hyperglycemia, and hypertension were 7.5%, 22%, and 9.6%, respectively and the rate of metabolic syndrome was 50.2%. On that study the pretransplant rate of metabolic syndrome was 10.5%. (7)

The development of hyperlipidemia is related to various factors, as is the case with liver transplants. Immunosuppressive drugs after liver transplantation may lead to abnormalities of lipid metabolism and hyperlipidemia. (8)

A meta-analysis study collected from population-based and case-control studies showed that in recipients after liver transplantation, the risk of CVD is approximately 64% higher than in the general population. However, the increased risk of atherosclerosis-related diseases in transplant recipients indicates that all of these patients are prevented with lipid-lowering drugs, drug interactions, and other side effects. In practice, many transplant physicians are cautious about treating liver transplant recipients with lipid-lowering drugs (9).

Optimal follow-up of these patients should include continuous follow-up and management of cardiovascular risk factors such as dyslipidemia. Therefore, it is essential to consider recommendations for managing lipid levels in liver transplant recipients, including considering the risk factors of CVD and the effects of immunosuppressive agents. (10)

While research on post liver transplant dyslipidemia has focused on patient factors and immunosuppressive regimens, the role of liver donors in the development or prevention of this complication are not investigate properly.

The purpose of this study was to compare the lipid profiles and prevalence of dyslipidemia in children underwent living-related (LR) or deceased donor (DD) liver transplant.

Methods

The present study is a retrospective cross-sectional study that was performed to evaluate and compare the status of lipid profiles in pediatric patients receiving liver transplant from LR and DD during 2005–2018. The study population consisted of all patients younger than 18 years who underwent transplant surgery in Shiraz as the main Pediatric Liver Transplant Center in Iran and were followed up in clinics affiliated to Shiraz University of Medical Sciences.

Exclusion criteria were patients who died within two years of transplantation, patients with any pre-transplant dyslipidemia such as familial hypercholesterolemia, and patients who did not receive regular follow-up after transplantation. Included patients were divided into two groups of LR donor and DD according to the source of transplanted graft. Then demographic information, indications of liver transplant, graft type, immunosuppressive drugs, clinical and paraclinical findings were collected using their medical records. The American College of Sports Medicine report the normal triglyceride (TG) levels

for children under 18 years of below 150 mg/dL, borderline high values of 150–199 mg/dL, high and very high values of 200–499 mg/dL and greater than 500 mg/dL. The American Academy of Pediatrics expresses that normal total cholesterol (TC) levels for children less than 18 years less than 170 mg/dL and borderline level and high are 170–199 mg/dL and more than 200 mg/dL. Normal low density lipoprotein (LDL) cholesterol levels are expressed less than 110 mg/dL and borderline level and high are 110–129 mg/dL and more than 130 mg/dL. The fasting blood sugar (FBS) lower than 100 mg/dL was considered as normal and prediabetes and diabetes were defined as FBS 100–125 mg/dL and ≥ 126 mg/dL, respectively.

In the present study, high density lipoprotein (HDL) cholesterol levels above 50 mg/dL, after two years of transplant were considered to be optimal lipid profile in patients. Statistical analyzes were performed to determine the predictive factors of this marker. Statistical analysis of fasting lipid and glucose profiles was performed on average with 95% confidence interval.

After collecting data and entering into SPSS 18 software, it was analyzed and then descriptive indices such as mean and standard deviation, minimum and maximum as well as frequency and percentage were used. In inferential analysis to investigate the relationship between two categorized factors, the chi-square test was used. Independent t-test or its nonparametric equivalent, Mann-Whitney U test, was used to compare the mean of a quantitative factor between the two groups. Also, One-way ANOVA was used to compare the mean of a quantitative factor between the three groups. Pearson correlation test was used to examine the correlation between the two quantitative factors. The level of significance at all tests was 0.05.

Results

This study was performed on 397 liver transplants recipients during 13 years. The mean age of transplant day was 8.4 ± 4.7 years (range: 1 to 18 years). 182 (46%) of them were girls with mean age of 8.4±5.3 year and 215 (54%) of them were boys with mean age of 8.4±2.2 year (p=0.504).

Of the total population, 234 (58.9%) had received their transplant from DD and 161 (40.6%) from LR donors. The mean BMI in the LR and DD groups were 16.25 ± 3.29 and 17.51 ± 5.49, respectively (p = 0.05). The mean time elapsed after transplant in all 397 patients was 2.45±5.74 years.

The most common underlying diseases were biliary atresia (22%) and autoimmune hepatitis (15%).

The frequency of any of the post-transplant complications in individuals is as follows: hepatic artery thrombosis in 8 (2%), hepatic vein thrombosis in 17 (4.3%), one of them has portal vein thrombosis, graft rejection in 65 (16.4%), biliary complications in 16 (4%), infections in 17 (4.3%), ascites in 3 (0.8%), convulsion in 27 (6.8%), renal problems in 4 (1%), pulmonary heart problems in 4 (1%), PTLD in 3 (0.8%), and bowel perforation in 1 (0.3%). The rate of post-transplant complications was not related to sex and age groups (p > 0.05).

Table 1 presents the results of the independent t-test for comparing the mean values of lipid profile and FBS between girls and boys. The results show no significant differences between them in any of the relevant factors.

Table 1
Comparison of mean Lipid profile and blood sugar between gender groups

Lipid profile factors	Gender	Number	Mean ± SD	Minimum	Maximum	p-value
FBS	Female	179	86.88 ± 20.89	56.33	312	0.37
	Male	204	88.61 ± 17.22	63.33	203	
TG	Female	179	13.47 ± 58.53	57.67	570	0.06
	Male	204	12.55 ± 45.57	46.67	289	
Total cholesterol	Female	179	16.45 ± 39.8	55	331.33	0.37
	Male	204	16.11 ± 51.97	59	570	
HDL	Female	156	50.14 ± 21.89	6	259	0.7
	Male	185	49.08 ± 28.22	19	386	
LDL	Female	156	87.5 ± 33.39	28	222.67	0.78
	Male	184	88.83 ± 50.46	11	595	

Table 2 is shown the results of one-way variance analysis for comparing the mean lipid profile and FBS between different age groups. There is a significant difference between the mean FBS and HDL in different age groups ($p < 0.05$). On the other words, with increasing the age the mean value of FBS is increased and the mean value of HDL is decreased.

Table 2
Comparison of mean Lipid profile and fasting blood sugar in different age groups

Age group Lab	Age group	Number	Mean ± Standard deviation	Minimum	Maximum	p-value
FBS	Under 6	150	84.13 ± 15.34	56.33	203	0.001
	7–12	140	87.88 ± 10.31	65.67	161	
	13–18	92	93.74 ± 30.2	65.33	312	
TG	Under 6	150	123.95 ± 56.48	53.67	570	0.13
	7–12	140	124.6 ± 48.3	57.67	317.3	
	13–18	92	136.88 ± 49.99	46.67	293.33	
Total cholesterol	Under 6	150	166.7 ± 49.99	96.67	532.67	0.33
	7–12	140	159.09 ± 31.04	55	268	
	13–18	92	159.86 ± 59.28	59	570	
HDL	Under 6	126	52.35 ± 22.68	21	259.5	0.04
	7–12	130	50.6 ± 32.64	6	286	
	13–18	84	43.78 ± 12.63	19	129.5	
LDL	Under 6	126	87.24 ± 35.59	37	286	0.797
	7–12	129	87.75 ± 31.24	11	203	
	13–18	84	91.14 ± 65.05	23.5	595	

Table 3 presents the chi-square test to investigate the frequency distribution of post-liver transplant complications based on transplanted graft donor (LR vs DD). There is no significant difference in the rate of post-transplant complications regarding the donor type. ($P < 0.05$)

Table 3
Comparison of post transplant complications between two groups

Donor Complication	Deceased n = 234	Living n = 161	p-value
Hepatic artery thrombosis	5(1.3)	3(0.8)	1
Hepatic vein thrombosis	9(2.3)	8(2)	0.62
Hepatic vein thrombosis	0(0)	1(0.3)	0.41
Graft rejection	39(9.9)	26(6.6)	0.89
Bilirubin complications	8(2)	8(2)	0.45
Infection	7(1.8)	10(2.5)	0.14
Ascites	2(0.5)	1(0.3)	1
Marrow inhibition	0(0)	0(0)	-
convulsion	18(4.6)	9(2.3)	0.42
Renal problems	4(1)	0)0)	0.15
Pulmonary heart problems	1(0.3)	3(0.8)	0.31
PTLD	1(0.3)	2(0.5)	0.57
Intestine rupture	1(0.3)	0(0)	1
Vascular problems	0(0)	2(0.5)	0.17
Diabetes	1(0.3)	0(0)	1

The rate of pre-diabetes, diabetes, and various dyslipidemia are shown in Table 4.

Table 4
The rate of pre-diabetes, diabetes, and various types of dyslipidemia after liver transplant regarding graft type

Profile	Living-related Donor	Deceased Donor	Total
Normal FBS	92.3%	92%	92.2%
Pre-diabetes	5.6%	6.5%	6.1%
Diabetes	2.2%	1.5%	1.7%
Normal TG	84.5%	70.8%	76.3%
Borderline High TG	11%	19.2%	15.7%
High TG	4.5%	10%	8%
Normal Cholesterol	64.3%	64.7%	64.5%
Borderline High Cholesterol	27.3%	21.7%	24.1%
High Cholesterol	8.4%	13.6%	11.4%
Normal LDL	88.2%	76.9%	80.9%
Borderline High LDL	5.9%	11.5%	9.6%
High LDL	5.9%	11.5%	9.6%
Normal HDL	54.9%	22.8%	34.4%
Low HDL	45.1%	72.2%	65.6%

Hypertriglyceridemia and hypercholesterolemia were seen in 23.7% and 35.5% of the patients, respectively. Totally 19.2% of the cases had abnormal LDL and 65.6% had low HDL.

Comparing the mean lipid profile and FBS between the two donor groups (Table 5) showed that the mean TG and HDL levels were significantly different between the two groups of DD and LR donors with more favorable in the LR donor group ($p < 0.05$).

Table 5
Comparison of Lipid Profile factors and fasting blood sugar based on donor (deceased or living)

Donor Drug	Donor	Number	Mean	Standard deviation	Minimum	Maximum	p-value
FBS	deceased	223	88.89 ± 20.63		56.33	312	0.2
	living	158	86.31 ± 16.56		63.33	203	
TG	deceased	223	133.13 ± 49.51		46.67	336.33	0.006
	living	158	118.19 ± 54.69		53.67	570	
Total cholesterol	deceased	223	163.09 ± 48.43		55	570	0.64
	living	158	160/81 ± 44.57		100	532/67	
HDL	deceased	207	46.27 ± 19.23		6	259/5	0.003
	Living	132	54.63 ± 32.59		21	386	
LDL	deceased	207	91.07 ± 48.25		11	595	0.15
	Living	131	84 ± 34.49		28	286.5	

There is no significant difference regarding the use of immunosuppressant drugs between the two groups. ($p > 0.05$) (Table 6).

Table 6
Immunosuppressive medications based on donor type (deceased or living-related)

Donor Drug	deceased = 224	Living n = 158	p-value
Cyclosporine	25(6.5)	7(1.8)	0.09
Tacrolimus	221(57.9)	153(40.1)	0.22
Sirolimus	44(11.5)	26(6.8)	0.42
Cell cept	197(51.6)	104(27.2)	0.07
Prednisolone	204(53.4)	136(35.6)	0.12
Steroid pulse	53(13.9)	29(7.6)	0.21

Discussion

In recent years, advances in surgical techniques as well as immunosuppressive drugs have increased the success of transplant surgery and the longevity of patients after liver transplant. The majority of liver

transplant recipients need lifelong immunosuppression, mostly based on tacrolimus, cyclosporine or sirolimus with or without steroids which are associated with increasing risk of metabolic syndrome components like hypertension, diabetes mellitus, and hyperlipidemia and also increased risk of CVD. (11) Therefore, the prevention and management of long-term complications have become increasingly important in the success of liver transplant. Weight gain beyond normal levels, obesity and impaired lipid profiles are known to be common complications after surgery in patients with liver transplant. Post liver transplant diabetes is a well-known disorder is associated with impaired graft tissue function, increased risk of infection and CVD. (12,13)

Post-transplant metabolic disorder can lead to CVD and is associated with increased post-transplant mortality. In their study, Laish et al., reported a 59.1% prevalence of post-transplant metabolic disorders that was twice that in the normal population (13). In our center the rate of metabolic syndrome after liver transplant in children was 50.2% (7). Therefore, identifying the risk factors associated with these syndrome is recognized as an important issue in patients' long-life span.

In the Husing study, hyperlipidemia was observed in 45% of patients with or without immunosuppressive drugs. (15) In our center the rate of hypertriglyceridemia and

hypercholesterolemia in a combine pediatric and adult series were 70% and 15.3%, respectively. Age, sex, BMI, and underlying liver disease were not predictors of hypertriglyceridemia or hypercholesterolemia. Post-transplant hypertriglyceridemia was significantly more common in patients receiving tacrolimus than in those receiving cyclosporine (p=0.040), but post-transplant hypercholesterolemia had no significant correlation with type of immune suppression. (16)

In the present study, the most common immune suppressive medication was tacrolimus followed by prednisolone, mycophenolate and sirolimus. Immunosuppressive drugs usage in the present study in both gender, different age categories, as well as type of graft didn’t show any difference.

A recent study in pediatric liver transplant recipients showed that post-transplant metabolic syndrome and its components were common as 28% of children and young adults were overweight or obese, and 35% have pre-hypertension or hypertension, 44% have pre-diabetes, and 37% have low HDL. (17) In the present study prediabetes and diabetes were seen in 6.1% and 1.7% of the patients, respectively and 65.6% of them had low HDL.

Pinto et al. evaluated the effect of diet on reducing lipid profiles in 53 patients with liver transplant, and their results showed that post-transplant TC, LDL and TG profiles were significantly decreased by dietary intervention. The mean of each of these profiles was 160, 84.2 and 150 mg/dL for boys and 169, 95.8 and 123.5 mg/dL for girls, respectively (10).

In a study on 165 adults liver recipients the lipid profiles were compare between the two groups of recipients (LD and DD) and showed that LDLT recipient had lower fasting glucose (4.85 vs. 7.21 mmol/L,

p < 0.001) and TG (0.87 vs. 1.22 mmol/L, p = 0.016) but higher HDL (1.58 vs. 1.39 mmol/L, p = 0.022) and the authors concluded that LDLT recipients had better lipid profiles than DDLT recipients. (18)

The results of this study showed that the mean levels of FBS, TG, TC and LDL were higher in patients with transplant from DD, and the mean HDL level was lower in these patients, whereas these differences were significant only in TG and HDL profiles. FBS and HDL levels increased and decreased with age, respectively. Also, the levels of TG and HDL factors were significantly correlated with the type of tissue graft used. Patients who received a transplanted organ from a LR donor have a significantly lower TG and higher HDL and a lower risk of CVD.

According to results of this study we can suggest that DDLT recipients need more closely lipid profile monitoring.

Conclusion

Patients who received liver from a living-related donor have a significantly lower TG and higher HDL and a lower cardiovascular risk than patients who receive liver from deceased-related donor.

Abbreviations

LFT liver function test

CVD cardiovascular disease

DD Deceased donor

LD Living donor

Declarations

Conflict of interest: Authors of this manuscript had no conflict of interest

Ethics approval and consent to participate: All procedures performed in this study were in accordance with the ethical standards of the “Research Ethics Committee of Shiraz University of Medical Sciences” and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. **This study was submitted to and** approved by the “Research Ethics Committee of Shiraz University of Medical Sciences” with Ethics code IR.sums.med.rec.1396.s336

Consent for publication: This manuscript does not contain any personal data, and the consent for publication is applicable.

Ethical approval and consent to participate: The study was explained for the patients or guardians and informed consent forms were signed by them.

Availability of Data and Materials: We state that the data used and/or analyzed during the current study are **available from the corresponding author on reasonable request.** Data sharing is applicable to this article and datasets were generated and analyzed during the current study and data sharing is allowed.

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Author contributions:

SM.D design and analysis and manuscript preparation

NM writing and preparation of the manuscript

R.N collecting data

H.M data analysis

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