Liver transplantation as a definitive treatment for familial hypercholesterolemia: A series of 36 cases


Abstract: FH is a genetic disorder characterized by an increase in serum LDL and total cholesterol values. The afflicted patients are at increased risk of premature atherosclerosis and myocardial infarction. Different treatment modalities are present, including pharmacological agents and surgical procedures. The most effective method of therapy in refractive cases is liver transplantation. Herein, we report our experience on 36 cases of patients with FH undergoing liver transplantation in our center, the main referral center of liver transplantation in Iran. The clinical findings, hospital courses, post-operative complications, and patient follow-up are also described.

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FH is an autosomal genetic disorder caused by different mutations in one of the two LDL receptor genes, APOB or PCSK9 (1–3). The function of the LDL receptor is to take LDL particles by endocytosis. Various degrees of defects are associated with different phenotypes of FH. In the most severe form (HoFH), bi-allelic mutation of LDL receptor gene leading to complete absence (<2%) or defective (2–25%) residual LDL receptor, or one mutation in each of the two different genes may also lead to severe hypercholesterolemia from early childhood. By contrast, the presence of one normally functioning gene in the HeFH is accompanied by less severe symptoms (1–3). The incidence of HeFH is about one in 500 persons worldwide, but HoFH is a rare disorder, afflicting only one of one million persons worldwide (1–8). Individuals with FH have an increased risk of developing premature atherosclerosis and coronary heart disease that may lead to early death from myocardial infarction, especially in severe forms if left untreated (1–8). The principles of treatment include a low-fat diet, lifestyle modification, pharmacotherapy, LDL apheresis, and surgical intervention (porto-caval shunting or ileal bypass surgery). However, in the HoFH, these treatment modalities rarely bring LDL cholesterol to the desired level because homozygous individuals cannot synthesize LDL receptors. Because 70% of LDL receptors are located in the liver, liver transplantation can be a treatment option in medical therapy refractive cases (1–9).

Abbreviations: CAG, coronary artery bypass grafts; CVD, cardiovascular disease; FH, familial hypercholesterolemia; HeFH, heterozygous form of familial hypercholesterolemia; HoFH, homozygous form of familial hypercholesterolemia; LDL, low-density lipoprotein.
Liver transplantation has been used as a treatment modality in different metabolic disorders such as Wilson’s disease, alpha 1-antitrypsin deficiency, tyrosinemia, primary hyperoxaluria type 1, congenital hemochromatosis, familial amyloidotic polyneuropathy, and Crigler–Najjar syndrome (type 1). Many case reports describe liver transplantation for FH (10). In this study, we report our experience with 36 patients with FH who underwent liver transplants. The clinical findings, hospital courses, post-operative complications, and follow-ups are precisely described.

Materials and methods

A retrospective review of the transplant center database at Namazi Hospital, affiliated with Shiraz University of Medical Sciences, Shiraz, Iran, from March 2008 to March 2014, revealed there were about 1880 liver transplantation cases. Among them, 36 patients received transplants due to FH. The demographic data, clinical presentation, laboratory data, post-transplant complications, and long-term follow-up of these patients were reviewed. The study was approved by the Ethics Committee of Shiraz University of Medical Sciences. Elevated LDL-C levels (more than 500 mg/dL in untreated patients and more than 300 mg/dL in treated patients) with cutaneous or tendon xanthomas before 10 yr of age and untreated elevated LDL-C levels consistent with HeFH in both parents are suggestive of HoFH. The LDL-C cutoff for the diagnosis of HeFH was >190 mg/dL in adults and was >160 mg/dL in children. Presence of premature coronary heart disease, arcus corneae, history of FH, high levels of LDL cholesterol, early-onset (i.e., age < 50 yr) coronary heart disease (especially premature myocardial infarction), and xanthomas were the additional findings associated with the diagnosis of FH.

Results

Demographic data

Of the 36 patients with FH, 20 (55%) were male and 16 were female with an age range of 2.5–28 yr. Patient weights varied from 10 to 72 kg. All the patients were diagnosed based on the clinical findings and cholesterol values. No genetic testing was performed. Based on our criteria, about 80% of the patients were homozygous and the rest were heterozygous. Eighteen (50%) patients were the offspring of consanguineous marriage, nine (25%) had partially related parents, and nine (25%) had unrelated parents (Table 1).

Clinical presentations

Cutaneous xanthoma was the most common clinical sign of FH and was identified in 33 (91%) patients. The most prevalent site of xanthoma was the elbow, followed by the natal cleft, the knee, extensor surfaces of the upper extremity, and the face. Eighteen patients (50%) had arcus of the cornea, which is a white-gray opaque ring around the iris.

Pretransplant cardiovascular evaluation

All the patients underwent trans-thoracic echocardiography with a GE Vivid 3 system (GE Vingmed, Horten, Norway) using a 3-MHz transducer. Echocardiographic study included two-dimensional, M-mode, and Doppler echocardiographic imaging. Coronary angiography was performed in all the patients before transplantation, and if the patient was hypertensive, aorto-renal angiography was performed.

Cardiovascular complications

Eighteen (50%) patients had premature coronary artery disease, needing intervention. Among them, 11 patients underwent CABG. Duration between CABG and liver transplantation was <3 months in two patients, 3–6 months in four patients, 6–12 months in two patients, and more than 12 months in two patients. All the patients were older than 14 yr when they underwent CABG. Seven patients were treated by percutaneous coronary stenting. Duration between coronary stenting and liver transplantation was 6–12 months. The age range of patients at the time of coronary stenting was 7–18 yr. One patient had thoracic aorta stenosis treated by stenting one yr prior to transplantation.

Table 1. Demographic, clinical features, cardiovascular complications, pretransplant LDL value, and type of graft of patients

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Clinical presentation</th>
<th>Cardiovascular complications</th>
<th>Pre-Tx LDL value mg/dL</th>
<th>Type of liver graft</th>
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<td>Pre-Tx</td>
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<td>Coronary artery disease</td>
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<td>&gt;500</td>
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<td>22</td>
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<tr>
<td>≥18 yr (11)</td>
<td>Male</td>
<td>6</td>
<td>5</td>
<td>11</td>
<td>11</td>
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<tr>
<td>Total (36)</td>
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<td>20</td>
<td>16</td>
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*Transplant.
One patient was diagnosed as having abdominal aortic coarctation (middle aortic syndrome) with severe calcification that was treated by surgical aortoplasty one yr before transplantation. Six (16%) of the patients had high blood pressure, requiring medical treatment. After transplantation, the percentage of patients with high blood pressure increased to 40%.

Pretransplant echocardiography findings

The echocardiographic findings of the patients were as follows: mild aortic stenosis in nine (25%) patients, mild aortic regurgitation in 17 (47%) patients, mild mitral regurgitation in seven (19%) patients, and mild tricuspid regurgitation in three (8%) patients. Left ventricular hypertrophy was seen in two (5%) patients. Ejection fraction was more than 60% in 33 (92%) patients, and three (8%) patients had ejection fraction between 40% and 60%.

Computed tomography angiography findings of thoracoabdominal vessels

Aortic arch and aortic valve calcification was seen in three patients and in one patient, respectively. Abdominal aortic calcification was observed in three patients and renal artery calcification in two patients.

Pretransplant cholesterol and LDL-C values

The majority of patients (24, 66.6%) had an LDL-C level of more than 500 mg/dL. Nine (25%) patients had an LDL-C level of 400–500 mg/dL and three (8.3%) patients had an LDL-C level of 300–400 mg/dL. All the patients were on a diet and medical treatment, and they received a maximum dose of antihypercholesterolemic drugs for at least six months.

Pretransplant medical treatment

Our institutional protocol for medical treatment of FH was as follows:

The children older than two yr of age were treated with low-fat diet and bile acid sequestrants (cholestyramine, 100 mg/kg/day) for about three months. If the LDL-C goal was not achieved, statin therapy (atorvastatin) was started, and if the response was not optimal, ezetimibe was then prescribed. Despite concern about the safety of statins before puberty and their adverse effect on growth, sexual, and central nervous system development, statins were prescribed for 11 patients younger than eight yr of age who had LDL-C values over 500 mg/dL for 3–6 months while on the waiting list for transplantation. All the parents were informed about the possible side effects of statins, and informed consent was obtained. No short-term atorvastatin side effect was seen in the patients. In spite of these treatments, none of the patients reached therapeutic LDL-C goals. Another modality of treatment of FH when pharmacotherapy is unsuccessful is LDL apheresis, especially in HoFH, but LDL apheresis is not available in our center, so liver transplantation was considered as a treatment option instead.

Liver transplantation

Twenty-eight (77%) patients received orthotopic deceased donation for whole liver transplantation. Five (13%) patients underwent living donor liver transplantation. These patients received a right liver lobe (one patient), a left liver lobe (three patients), or a left lateral segment (one patient). The donors were second-degree relatives to three patients because there is a possibility of heterozygote FH in patients’ parents, yet two patients received a liver from their father or mother. Three (8%) patients received split deceased donation liver transplants (left lateral segment). The duration between diagnoses of FH and transplantation was six months to 16 yr.

Post-transplant course

Duration of the patients’ follow-up was between six months and six yr after transplantation (mean ± s.d.: 24 ± 6 months).

Cutaneous xanthomas regressed after transplantation, but based on the size, their time to resolution differed. Generally, flat xanthomas smaller than 5 mm vanished after 1.5–2 yr. Nodular lesions larger than 5 mm resolved after three yr but may have left a hyperpigmentation area.

LDL-C levels reached the desired value in most patients 4–8 wk post-transplantation. In 14 patients (38%), LDL-C levels remained within normal limits, but in the rest of the patients, LDL-C levels rose after primary normalization. In three patients, the LDL-C value reached above 200 mg/dL. Among these three patients, two had biliary stricture and one had cellular rejection that with appropriate therapy, the LDL-C value declined (Table 2). For patients with a history of coronary artery disease, patients undergoing CABG or coronary stenting, and patients with an LDL-C level of more than 130 mg/dL, atorvastatin was started 3–4 wk post-transplantation (when the liver enzymes reached the normal values). The mainstay of immunosuppressive therapy consisted of corti-
corticosteroid with tacrolimus (double therapy) for children younger than five yr, and a combination of tacrolimus, mycophenolic acid (CellCept), and corticosteroid (triple therapy) for patients older than five yr. In the presence of complications or side effects, cyclosporine or sirolimus could replace the aforementioned drugs. Steroids were discontinued after six months, and other immunosuppressive drugs were tapered to minimum effective doses after 1–1.5 yr.

Post-transplant surgical complications

Biliary stricture was a surgical complication after liver transplantation found in two patients after 30–45 days. Both patients received split liver transplantation performed using duct-to-duct anastomosis. The strictures were treated by Roux-en-Y procedures. One patient experienced internal bleeding and the other a liver abscess; both complications were treated successfully.

Post-transplant medical complications

Five (13%) patients showed mild acute rejection in the first six months after transplantation that was treated successfully by immunosuppressive drugs. Septicemia (after undergoing three liver transplantations due to non-functioning livers), cytomegalovirus colitis, and convulsions were each seen in one patient. The hypertension rate among the sampled patients rose from 15% to 40% after surgery probably due to post-transplant immunosuppressive therapy.

Graft and patients’ survival

Based on the Kaplan–Meier survival curves, the one- and five-yr survival rates of the graft were 94% and 91%, respectively, and patient survival was 97% (Fig. 1a,b).

Post-transplant mortality

Of 36 patients with FH who underwent liver transplantation, three (8%) died.

The first patient had an unexplained cardiac arrest shortly after transplantation. His cardiac echocardiography showed mild aortic stenosis, and his coronary angiography was normal three months prior to transplantation. The second patient had coarctation of the abdominal aorta and underwent aortoplasty one yr prior to transplantation. The patient went through cardiac arrest before reperfusion of the transplanted liver. The third patient underwent transplantation three times. He first received a partial liver graft from his father, but due to non-function, he underwent a second deceased donation, whole organ transplantation. He acquired a non-functioning liver again, and he received another deceased donation, whole organ liver transplant. He was successfully discharged from the hospital, but after six months, he developed septicemia and died. All three patients who died were younger than four yr of age. One received a split liver donation from a deceased donor, and two received partial grafts (of the left lateral segment).

Discussion

FH is an autosomal, dominant disorder characterized by high levels of total and LDL cholesterol. The disease results from different mutations of the LDL receptor gene (1–3). Five classes of mutations have been identified (1–3). These mutations result in defective LDL-C endocytosis by a LDL receptor and subsequently lead to hypercholesterolemia. Recently, mutations in the alleles of three other genes were identified as causal in some cases with a severe phenotype resembling HoFH (1, 2).

Individuals with FH are at an increased risk of developing premature coronary vascular disease (1–9). Early detection and proper management of the patients will delay and prevent these lethal complications. Therefore, screening for FH is recommended if the following conditions are present: A family member has been diagnosed with FH, the patient has history of elevated LDL-C levels in two or more family members, premature coronary heart disease, xanthoma, sudden premature cardiac death, and a high LDL-C level (1–3). FH is classified into heterozygous and homozygous subtypes. In the HeFH, the onset of coronary vascular disease usually occurs within the fourth to fifth decade of a patient’s life. In the HoFH, the disease is more severe and aggressive, with early onset of CVD becoming evident in the first two decades of life. This type is usually unresponsive to lipid-lowering pharmacotherapy (1–3).
The treatment of patients varies according to the severity of hypercholesterolemia and the mode of inheritance. Lifestyle modifications including a low-fat diet, regular exercise, weight control, and pharmacotherapy are the principles of treatment (1–3).

Statins are the first choice of drug therapy that decreases CVD mortality as well. The Food and Drug Administration approved the use of statins in individuals older than eight yr of age (11). The use of statins in children younger than eight yr of age is not recommended because they may cause adverse effects on growth, sexual, and CNS development. We prescribed atorvastatin for 11 children <8 yr of age who persistently had LDL-C levels of more than 500 mg/dL. The atorvastatin was given for a short period before transplantation, and no short-term side effects were observed. Ezetimibe, which inhibits cholesterol absorption from the intestine, and bile acid sequestrates are other lipid-lowering agents that can be used in the treatment of FH. Their combination with statins decreases LDL-C levels and reduces the risk of CVD (3, 4, 12).

In spite of these treatments, some patients with severe HeFH, and most cases of HoFH, will not reach optimal LDL-C levels. Thus, some

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Fig. 1. Kaplan–Meier survival curve; (a) graft survival, (b) patient survival.
other modalities should be performed including LDL aphaeresis, portocaval shunting, ileal bypass surgery, and liver transplantation (1–9). Besides liver transplantation, other methods are only partially and transiently successful in reducing cholesterol levels in patients with HoFH, so liver transplantation is currently the most effective and definitive means of treatment in patients with HoFH. Because most of the LDL-C receptors are located in the liver, liver transplantation will compensate the lack of LDL-C receptors in patients with HoFH (3–9).

Liver transplantation as a treatment of FH was first performed in 1983 by Starzl on a six-yr-old girl who successfully underwent combined liver and heart transplantations (7). Since then, this procedure has been accepted in treating refractive cases of FH. Patients undergoing liver transplantation not only show fast and long-lasting resolution of hypercholesterolemia, but may also show the regression of cutaneous xanthoma and atherosclerotic plaques (6). In our study, most of the patients showed the regression of xanthomas and normalization of LDL-C. The post-transplant medical and surgical complications were minor, and all the patients were treated successfully. Only five patients developed mild acute cellular rejection in the first six months after transplantation.

The mortality rate after transplantation was about 8% in our study. Two patients included in this percentage died due to cardiac arrests. Because of the ongoing effects of hypercholesterolemia on vessel walls and the possible formation of accelerated atherosclerotic plaques, we recommend performing a coronary angiography within the three months before transplantation.

The timing of transplantation is still controversial. Some researchers assert that early transplantation reduces cardiovascular complications and mortality, arguing that aggressive medical therapy and apheresis, while not preventing CVD, will improve lipid profiles. Others express concern about the complications of immunosuppressive therapy and the scarcity of donor organs, implying that the best approach is monitoring the FH patient while on maximum-tolerated medical therapy, with liver transplantation warranted upon the onset of cardiovascular complications (13).

Conclusion
The study surveyed an acceptable number of patients who received genetically normal livers as a cure for FH and can be considered a unique experiment of its own kind. Despite the need for life-long immunosuppressive therapy, liver transplantation should be considered in patients with HoFH unresponsive to medical therapy, ideally before the onset of significant CVD.

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Authors’ contributions
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References
Liver transplant in familial hypercholesterolemia