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ORIGINAL ARTICLE

Effects of liver transplantation on the nutritional status of patients with cystic fibrosis*

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Summary

The long-term effects of liver transplantation on nutritional status, body composition and pulmonary function in patients with liver disease associated with cystic fibrosis (CF) are poorly defined. We studied 15 patients with CF-associated biliary cirrhosis and severe portal hypertension. Seven underwent liver transplantation (age: 14.8 ± 6.2 years), and eight were treated conservatively (age: 15.9 ± 6.7 years). All patients were evaluated at baseline and thereafter yearly for a median duration of 5 years. During follow-up, transplanted patients gained weight and showed a significant increment in body mass index ($P < 0.004$), whereas patients without transplantation remained stable ($P = 0.063$). Baseline bone mineral content (dual energy X-ray absorptiometry scan) was lower than normal in all patients (more in transplanted patients) and increased in transplanted patients ($P < 0.05$), but not in patients without transplantation. In both groups percent body fat did not change, whereas fat free mass increased only in the transplant group ($P = 0.06$) ($P < 0.03$ versus non-transplanted patients). Only in transplanted patients' plasma concentrations of vitamin E and A increased ($P < 0.05$ versus nontransplanted patients). Forced espiratory volume in 1 s and forced vital capacity showed similar deterioration in transplanted and in nontransplanted patients. Liver transplantation is associated with long-term beneficial effects on the nutritional status of CF patients and seems to favor bone mineralization.

Introduction

Orthotopic liver transplantation is the most remarkable innovation of the last two decades in the care of children with end-stage liver disease (LD) [1–3]. Because of development of innovative surgical techniques and improvement in postoperative care, including immunosuppression, 1-year survival rate for pediatric liver transplantation is now close to 90% and the range of its indications has expanded to include children with significant multi-organ diseases [3].

Up to 10% of patients with cystic fibrosis (CF) develop multilobular biliary cirrhosis [4,5] that is frequently complicated by severe portal hypertension and, later, by liver failure [6]. During the progression of LD, CF patients are at risk of developing serious variceal bleeding and a few extra-hepatic complications, including malnutrition, hepatic osteodistrophy [7] and deterioration of pulmonary status. Cirrhosis and portal hypertension can in fact negatively affect respiratory function because of organomegaly, ascites-induced diaphragmatic splinting and intrapulmonary shunting, leading to recurrent respiratory

infections from multiresistant bacteria and significant deterioration of quality of life.

In recent years liver transplantation has been performed in an increasing number of children and young adults with CF-associated end-stage LD [8–15], with a reported 1-year survival rate of 75–80% [16]. Although there are no established guidelines regarding selection and timing criteria for liver transplantation in CF [17], hepatic failure is seldom the unique indication and other important extra-hepatic parameters have to be taken into account, including deterioration of nutritional status despite adequate nutritional support and progressive deterioration of pulmonary function [14]. Information regarding the effects of liver transplantation in CF patients are generally limited to the first year after transplant.

In the assumption that liver transplantation may improve nutritional status and body composition in CF patients, we carried out a longitudinal study and compared the nutritional changes in a group of CF patients before and after liver transplantation, to those observed in a group of CF patients with portal hypertension who did not require transplantation.

Patients and methods

Patients

Of the 19 patients with multilobular biliary cirrhosis associated with CF considered for transplantation at the Transplantation Center of the University Hospital of Milan in the period January 1990 through March 2003, we have considered only those for whom a follow-up period of at least 2 years had been accomplished.

The genotype and clinical characteristics of the 15 CF patients included into the study are reported in Table 1. Five patients were already postpuberal at the time of first evaluation. All patients had severe genotype, pancreatic insufficiency and evidence of biliary cirrhosis with severe portal hypertension, esophageal varices (grade 3–4) and hypersplenism. Ascites was present in four patients and hepatic encephalopathy requiring protein restriction and lactulose administration in one, who also had renal failure. All were on pancreatic enzymes and on ursodeoxycholic acid (UDCA) therapy. With regard to pulmonary status, at the time of initial evaluation, pulmonary disease was negligible [forced espiratory volume in 1 s (FEV1) >90% of predicted] in three patients, of moderate severity (FEV1 between 65% and 90% of predicted) in seven, whereas it was severe (FEV1 <65%) in five. All patients except one were chronically infected with *Pseudomonas aeruginosa* (in 12), *Burkolderia cepacia* (in two) or *Stenotrophomonas malthophilia* (in five); fungal pathogens identified included *Aspergillus fumigatus* in four patients and *Candida* in seven. All *Pseudomonas* infected patients had received regular antibiotic treatment consisting in daily Colistin per aerosol and intravenous antibiotics every 4–6 months; patients with *Aspergillus* in sputum had been treated with oral itraconazole.

Indication for transplantation was established taking into account not only the severity of LD (in order of importance, progressive deterioration of hepatic function with hypoalbuminemia and increased prothrombin time, ascites, hypersplenism with leucopenia and thrombocytopenia, severe variceal bleeding), but also extrahepatic parameters including progressive deterioration of nutritional status and/or pulmonary function.

Most of these criteria have recently been included in a clinical assessment score for liver transplantation in CF by Noble-Jamieson *et al.* [18], a score higher than 10 establishing the need for transplantation. We therefore retrospectively evaluated patient status according to this score in our patients.

Patients undergoing orthotopic liver transplantation ($n = 7$)

Of the 10 CF patients who underwent liver transplantation according to our selection criteria, we have considered only the seven long-term survivors (>2 years).

Following transplantation, all patients were immunosuppressed with double therapy (cyclosporine plus steroids). Methylprednisolon was given at tapering doses from 200 to 20 mg within 5 days; maintenance dose was 20 mg/day of prednisone for 2 months tapering to 15 mg in the third month, 10 mg in the fourth, 5 mg in the fifth and 5 mg on alternate days in the sixth with suspension after 6 months. Cyclosporine was maintained at relatively low blood through levels (i.e. between 200 and 300 ng/ml during the first month post liver transplantation, between 150 and 100 ng/ml in the following 6 months and under 100 ng/ml thereafter) in order to avoid rejection, infections and other risks of immunosuppression. These therapeutic levels were achieved with oral cyclosporine (Neoral® (Novartis, Basel, Switzerland), 5–10 mg/kg/day), without relevant problems related to malabsorption.

Patients with portal hypertension not requiring liver transplantation ($n = 8$)

Patients with portal hypertension with relatively preserved hepatic function were not offered liver transplantation but regular follow-up at our center. Of the nine subjects in this group one was lost at follow-up.

All patients were informed about the purpose of the study and the experimental procedures and themselves or their parents gave their consent. The procedures were approved by the local ethical committee.

Table 1. Genotype and clinical characteristics of cystic fibrosis patients.

	Sex	Genotype	Symptoms	FEV1 (%)	FVC (%)	AST (U/ml)	ALT (U/ml)	GGT (mU/ml)	Bilirubin (mg/dl)	Cholesterol (mg/dl)	INR	Albumin (g/dl)	WBC (n/mm3)	PLT (n/mm3)	Bacteria/fungi	Follow-up
Transplanted																
1	M	DF508/UN	EV-A-H	45	87	60	52	175	0.40	51	1.2	4.1	2100	82 000	Pa	
2	F	N1303K/N1303K	EV-A-H-GI	62	63	20	23	33	0.60	70	2.4	3.6	2900	65 000	Xm, Pa, Sa, C	
3	M	R1162X/R1162X	EV-A-H	93	107	48	34	42	0.20	108	1.2	4.3	1600	38 000	Bc, Pa, Sa	Diabetes
4	M	DF508/G542X	EV-H	73	77	58	57	72	0.60	100	1.6	4.3	3000	34 000	Xm, Pa, Sa, C	Diabetes
5	M	N1303K/UN	EV-H	53	77	57	55	61	1.00	85	1.3	4.3	4580	56 000	Bc, C	Deceased 2 year after OLT
6	M	621+1G-T/UN	EV-A-H-E-R	77	89	26	24	130	0.74	78	1.7	3.5	1600	35 000	Pa, Sa	Diabetes
7	F	DF508/DF508	EV-H	85	88	76	39	85	1.20	107	1.3	2.6	4560	83 700	Xm, Pa, Sa, C, Af	PTLD, diabetes
Mean				70	84	49	41	85	0.68	86	1.5	3.8	2906	56 243		
SD				17	14	20	14	51	0.34	21	0.4	0.6	1265	21 498		
Portal hypertension																
8	M	N1303K/UN	EV-H	126	111	108	120	115	0.42	106	1.4	4.5	7760	82 300	C, Af	
9	F	DF508/UN	EV-H-D	66	66	40	49	306	1.36	153	1.1	4.3	8700	111 000	Pa	TIPS, diabetes
10	F	DF508/1717-1G-A	EV-H	122	116	35	37	189	0.33	166	1.2	4.3	4670	83 200	Pa, Sa	SPSS, diabetes
11	M	N1303K/711+1G-T	EV-H-D	48	78	32	28	33	0.41	79	1.5	4.5	3800	65 000	Pa	Diabetes
12	F	DF508/UN	EV-H-J	55	66	25	13	39	0.40	94	1.4	3.9	6440	56 000	Pa, Sa, Af, C	Diabetes
13	M	DF508/DF508	EV-H	73	77	57	98	184	0.21	157	1.2	4.4	3300	71 000	Pa	
14	M	DF508/3659delC	EV-H	68	72	88	96	248	0.58	124	1.2	4.9	1900	50 000	Xm, Sa, Af	TIPS
15	M	DF508/N1303K	EV-H	74	80	59	36	39	0.27	90	1.2	3.9	2910	76 000	Xm, Pa, Sa, C	SPSS, diabetes
Mean				79	83	56	60	144	0.50	121	1.3	4.4	4935	74 313		
SD				29	19	29	39	104	0.37	34	0.1	0.3	2443	18 958		
t-test (among groups)	–	–	–	ns	ns	ns	ns	ns	ns	0.032	ns	0.047	ns	ns	–	–

EV, esophageal varices; A, ascites; H, hypersplenism; J, jaundice; D, diabetes; GI, glucose intolerance; E, encephalopathy; R, renal failure; Pa, *Pseudomonas aeruginosa*; Bc, *Burkholderia cepacia*; Sa, *Staphilococcus aureus*; Xm, *Xenotrophomonas maltophilia*; C, *Candida*; Af, *Aspergillus fumigatus*; PTLD, post-transplant limphoprolypherative disorder; TIPS, transjugular intrahepatic portosystemic shunt after GI bleeding; SPSS, surgical portosystemic shunt after GI bleeding.

Follow-up

The median duration of follow-up was similar in the two groups of patients (transplanted: 5 years; nontransplanted: 4.6 years) and ranged from 2 to 12 years. Of the eight patients who did not undergo transplantation (Table 1), variceal bleeding occurred in four who therefore underwent portosystemic shunt: transjugular intrahepatic portosystemic shunt (TIPS) [19] was performed in patients no. 9 and 14, and surgical shunt in patients no. 10 and 15 [20]. This treatment led to decompression of portal hypertension and successful control of its severe complications in all patients, even if three of them showed transient deterioration of liver function.

Procedures

Patients in both group were regularly followed-up at our center, at least once a year; all the investigations performed at first evaluation were repeated during the follow-up.

In all patients initial evaluation included clinical examination, anthropometric assessment, laboratory determinations (routine hematology and biochemistry, including liver and renal function tests, plasma vitamin A and E levels), chest X-ray, pulmonary function tests [FEV1 and forced vital capacity (FVC) expressed as percent of predicted values for age and sex], sputum cultures and abdominal ultrasound; dual energy X-ray absorptiometry (DXA) scan was performed on total body to determine body composition [percent fat mass, fat-free mass, bone mineral content (BMC) and density], using Hologic QDR 2000 (Hologic Inc., Bedford, MA, USA).

Healthy controls

For interpretation of body composition data, each study subject was matched to a group of control healthy subjects ($n = 5$) with the same age and similar body mass index. The control subjects belonged to a cohort of healthy children, adolescents and young adults who had received a DXA scan with a procedure identical to the patients, at the International Center for the Assessment of Nutritional Status in the context of a study approved by the Institutional Ethical Committee. All subjects or their tutors gave their written consent after having been informed of the possible risks of the low-dose radiation exposure consequent to DXA examination. These subjects had been studied with the specific purpose of providing reference data for body composition in the Italian population, as the available reference data for DXA whole body scans are currently derived from a mixed European population [21,22].

Statistical analysis

For each variable, mean and standard deviation were calculated; for weight and height, *z*-scores were also calculated in order to compare our patients with an Italian group of healthy subjects of the same age and sex. Paired and unpaired *t*-tests were performed and values were considered significant when $P < 0.05$.

Results

At the time of first evaluation the two groups of patients were comparable with regard to age, serum liver enzyme values, and pulmonary function, however hepatic synthetic function was significantly more impaired in patients who underwent liver transplantation (albuminemia 3.8 ± 0.6 g/dl vs. 4.4 ± 0.3 g/dl, $P = 0.047$), who also showed significantly lower levels of plasma cholesterol (86 ± 21 mg/dl vs. 121 ± 34 mg/dl, $P = 0.032$) and a trend towards a more severe degree of hypersplenism (Table 1). Renal function was abnormal in one patient before transplantation (patient no. 6); two patients (no. 1 and 5) showed transient deterioration of renal function 9 months and 1 year after transplantation, respectively.

The clinical score according to Noble-Jamieson, and its individual components in our patients are shown in Table 2. Mean value in transplanted patients (16.86 ± 1.30) was significantly higher than that found in patients without transplantation (10.75 ± 2.30, $P = 0.045$). All patients who were transplanted had a score >10; in contrast, the score was ≤10 in all patients without transplantation except two, one of whom had not been transplanted for poor family compliance; in the other one the decision regarding transplantation was deferred despite two episodes of variceal bleeding and hypersplenism, because of preserved hepatic function and severe pulmonary disease.

Table 3 shows the relationship between age and Tanner stage between the two groups of patients. At entry, Tanner stage normalized for age was not different among groups. At the end of follow-up all subjects except two (one in each group) had completed their sexual development. Table 3 also shows that, at first evaluation, there was no significant difference between the two groups of patients neither in the absolute values of weight, height and body mass index (BMI), nor in the mean *z*-scores for weight and height. During follow-up, an increment in body weight occurred in transplanted patients (weight *z*-score at last visit -0.86 ± 0.72, $P = 0.37$ versus baseline; body mass index: from 16.7 ± 1.8 to $18.5 \pm 2.0\%$, $P < 0.004$), whereas no such effect was documented in nontransplanted patients (weight *z*-score at last visit:

Table 2. Clinical score in cystic fibrosis patients (for details see reference 18).

	Variceal bleeding	Ascites	BMI <16 (Kg/m^2)	Varices, not bleeding	Albumin	PT >19 s	WBC <4000 (10^3/mm^3)	PLT <100 000 (10^3/mm^3)		Total score
Transplanted										
1		6	6	4			2	2		20
2		6	6	4		2	2	2		22
3			6	4			2	2		14
4		6		4		2	2	2		16
5	8						2	2		12
6	8	6					2	2		18
7			6	4	2		2	2		16
n	2	4	4	5	1	2	7	7	Mean	16.86
									SE	1.30
Portal hypertension										
8			6	4						10
9	8									8
10				4				2		6
11	8						2	2		12
12				4				2		6
13	8	6	6		2		2	2		26
14	8							2		10
15				4			2	2		8
n	4	1	1	3	1	0	3	6	Mean	10.75
									SE	2.30
χ^2	0.398025	0.067278	0.067278	0.18883	0.919154	0.104377	0.010415	0.155318	*t*-test	0.044586

−0.90 ± 0.96, $P = 0.17$; body mass index: from 18.1 ± 2.6 to 18.5 ± 2.3%, $P = 0.48$) (Fig. 1).

With regard to body composition at baseline, transplanted patients had a greater reduction of BMC and a significantly higher percent body fat composition if compared with the other group. Figure 2 shows age-related changes in BMC in the two groups of CF patients in comparison to male and female controls [21,22]. In controls there is a clear increase of BMC up to the age of 18 years; although this physiologic increase of BMC in relation to age is recognizable also in most male and female CF patients, the majority of them are below the reference values for age. The increment in BMC was more pronounced after liver transplantation (from 1.1 ± 0.4 to 1.4 ± 0.3 kg, $P < 0.05$) compared with that observed in patients not undergoing transplantation (from 1.4 ± 0.6 to 1.5 ± 0.6 kg, $P = 0.23$) and occurred also after adolescence. Bone mineral density (BMD) *z*-score increased in transplanted patients, but showed a downward trend in nontransplanted patients ($P = 0.03$) (Fig. 2).

In both groups, no significant changes were observed in percent body fat, whereas fat-free mass increased only in the transplant group (from 30.1 ± 8.1 to 35.5 ± 7.9 kg, $P = 0.03$), compared with the other group (from 33.0 ± 12.1 to 35.6 ± 10.1 kg, $P = 0.12$).

Despite oral supplementation at recommended doses, at first evaluation plasma levels of vitamin E and A were lower in patients selected for transplantation (vitamin E 4.5 ± 1.96 mg/l; vitamin A 0.18 ± 0.08 mg/l), than in those not undergoing transplantation (vitamin E 6.64 ± 3.59 mg/l; vitamin A 0.24 ± 0.09 mg/l, $P = 0.23$ and 0.31, respectively); after liver transplantation there was an increase in plasma vitamin E (8.1 ± 2.0 mg/l, $P = 0.10$) and vitamin A (0.44 ± 0.27 mg/l, $P = 0.10$), which did not occur in patients without transplantation (vitamin E 5.94 ± 1.98 mg/l, $P = 0.34$; vitamin A 0.17 ± 0.04 mg/l, $P = 0.06$). For both vitamins, the difference between the increments observed in the two groups of patients was statistically significant ($P < 0.05$).

As shown in Fig. 3, four of six patients who underwent transplantation showed a deterioration of FEV1 in the year prior to transplantation, which indeed led to accelerate our decision for transplantation; although in four of seven transplanted patients FEV1 improved immediately after transplantation, a striking deterioration occurred in three of them after a few years. One patient with chronic *Burkholderia cepacia* infection died 2 years after transplantation for respiratory failure (patient no. 5).

Long-term follow-up of pulmonary function revealed similar and nonsignificant deterioration in transplanted (FEV1 from 64.7 ± 17.3 to 53.9 ± 20.0%, $P = 0.42$; FVC from 83.1 ± 14.0 to 73.1 ± 14.7%, $P = 0.31$) and in nontransplanted patients (FEV1 from 79.0 ± 29.1 to 69.4 ± 19.2%, $P = 0.16$; FVC from 83.3 ± 19.4 to 75.6 ± 13.3%, $P = 0.16$).

Table 3. Changes in weight, height and body composition in cystic fibrosis patients.

		Age (yr)		Weight (kg)		Height (cm)		Pubertal stage		BMI (kg/m^2)		FM (%)		FFM (kg)		BMD (g/cm^2)	
	Sex	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Liver transplantation																	
1	M	10.6	22.9	23.9	47.5	125	162	3	5	15.3	18.1		8		41.6		1.13
2	F	22.2	27.8	38.5	43.7	157	157	5	5	15.6	17.7		22		31.6	0.90	0.95
3	M	12.0	18.5	34.2	51.0	149	172	4	5	15.4	17.2	15	11	28.8	39.6	0.85	0.96
4	M	13.1	18.1	35.5	50.9	142	169	4	5	17.6	17.8	16	20	27.6	30.6	0.95	0.95
5	M	11.2	12.6	37.8	43.0	139	144	4	5	19.6	20.7	27	27	27.1	30.3	0.66	0.73
6	M	25.2	27.3	48.4	57.5	163	163	5	5	18.2	21.6	10	15	44.1	48.5	1.00	1.04
7	F	9.5	13.0	28.5	38.7	138	155	2	4	15.0	16.1	16	23	23.1	26.3	0.78	0.88
Mean		14.8	20.0	35.3	47.5	145	160	4	5	16.7	18.5	17	18	30.1	35.5	0.86	0.95
SD		6.2	6.2	7.8	6.3	13	9	1	0	1.8	2.0	6	7	8.1	7.9	0.12	0.12
t test (Pre versus Post)		–		0.003		0.029				0.004		ns		0.030		0.077	
Portal hypertension																	
8	M	5.5	8.7	17.0	22.4	104	121	2	2	15.7	15.3	12	9	12.8	15.9	0.79	0.83
9	F	21.4	26.4	48.7	47.0	163	163	5	5	18.3	17.7	9	24	33.7	33.1	0.98	0.90
10	F	17.0	19.6	48.8	48.5	151	152	5	5	21.4	21.0	11	28	30.3	33.4	0.90	0.97
11	M	19.7	23.8	57.0	57.5	165	166	5	5	20.9	20.9	10	12	45.8	46.8	1.17	1.19
12	F	12.1	20.0	44.0	60.3	164	174	4	5	16.4	19.9	9	26	40.5	40.2	0.92	1.00
13	M	10.4	15.8	29.1	44.8	139	162	3	5	15.1	17.2	9	10	22.5	34.2	0.76	0.83
14	M	26.6	32.1	55.5	54.0	164	164	5	5	20.6	20.1	11	8	49.2	48.0	1.21	1.14
15	M	14.5	16.7	34.7	36.2	147	151	5	5	16.2	15.9	9	12	28.9	33.1	0.90	0.90
Mean		15.9	20.4	41.9	46.3	150	157	4	5	18.1	18.5	10	16	33.0	35.6	0.95	0.97
SD		6.7	7.1	13.9	12.3	21	16	1	1	2.6	2.3	1	8	12.1	10.1	0.16	0.13
t test (Pre versus Post)		–		ns		ns				ns		ns		ns		ns	
t test (among groups)		ns	ns	ns	ns	ns	ns			ns	ns	0.010	ns	ns	ns	ns	ns
z-scores																	
Liver transplantation																	
Mean				−0.95	−0.86	−0.79	−0.71			16.67	18.50		−0.45	30.10	35.60		−2.73
SD				1.02	0.72	1.04	0.40			1.80	2.00		1.28	8.10	8.90		1.39
Portal hypertension																	
Mean				−0.70	−0.90	−0.67	−90.00			18.10	18.50		−0.42	33.50	35.60		−1.90
SD				0.69	0.96	1.33	1.41			2.60	2.30		0.55	12.10	10.10		1.56
t-test (among groups)				ns	ns	ns	ns			ns	ns		ns	ns	ns		ns

The table reports the body composition parameters in the two study groups. The mean *z*-score was calculated from the mean deviation of each subject from his individual control group ($n = 5$) matched for age, sex and BMI and recruited from the same geographic area.

Overall, none of the patients was diabetic at entry, but all those who underwent transplantation developed diabetes mellitus during the first stage of immunosuppression with steroids. At the end of follow-up four of seven had developed persistent diabetes requiring insulin therapy. However this figure was not different in patients on conservative management five of whom developed diabetes as well (Table 1).

Discussion

Liver transplantation is presently considered a potentially successful therapeutic option for CF patients with end-stage LD. The peculiar form of biliary cirrhosis associated with CF is characterized by long-term preservation of hepatic function but early development of portal hypertension. Despite the use of UDCA in recent years [23], in a few of these patients LD progresses and a negative impact on nutritional status, pulmonary function and quality of life is to be expected.

There is evidence that end-stage LD in CF patients can negatively influence nutritional status and that nutritional depletion, once present, can affect prognosis. In a recent report concerning liver transplantation in CF, poor growth and nutritional status were associated with a high post-transplant mortality rate [24].

A number of factors are involved in determining malnutrition in patients with end-stage LD, including cholestasis, impaired lipid digestion and absorption, malabsorption of liposoluble vitamins and micronutrient deficiency. Hepatic osteodystrophy may develop as a result of increased bone resorption and low bone formation, possibly because of the

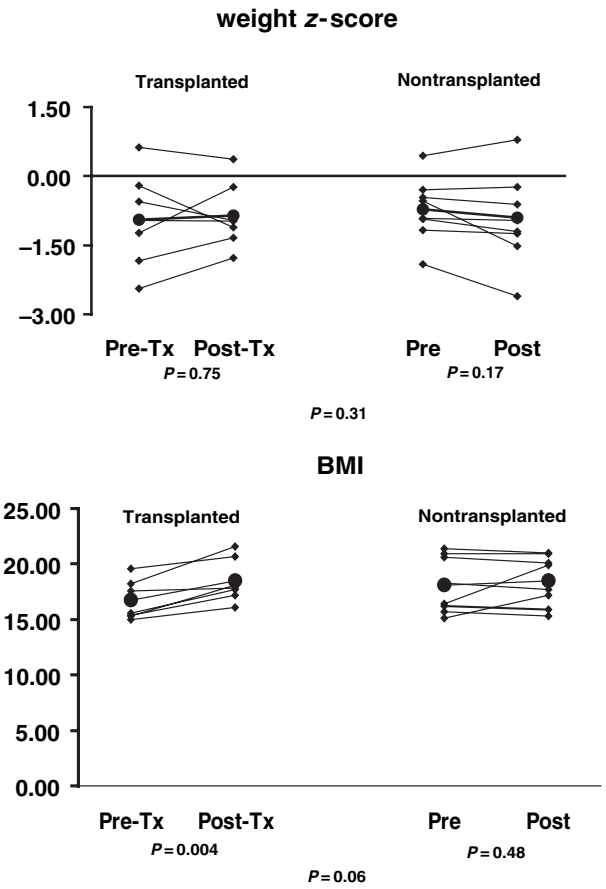

Figure 1 Changes in *z*-scores for weight and body mass index in transplanted and nontransplanted cystic fibrosis patients.

effect of a cholestatic factor (conjugated bilirubin or bile acids) [7]. All these factors may exert an even more detrimental effect in CF patients because of the nearly constant presence of pancreatic insufficiency in those with LD [5] and to the occurrence of osteoporosis, which is a frequent complication of CF [25].

Indeed at first evaluation most of our patients with end-stage LD (particularly those selected for transplantation) were underweight and were also severely osteopenic despite treatment with calcium and 25 OH-vitamin D at recommended doses. In this relatively small group of CF patients with severe cirrhosis and portal hypertension regularly followed at our Center, we could compare nutritional changes observed following liver transplantation to those observed in patients who received conservative treatment or elective surgical or transjugular porto-systemic shunt after gastrointestinal bleeding [19,20]. Criteria employed for deciding which patients should undergo liver transplantation were based not only on the severity of LD, but included also parameters of nutritional and pulmonary status. These criteria revealed to fit with the transplantation assessment score proposed by Noble-Jamieson [18]: only two of our patients with a score higher than 10 who were not transplanted were wrongly allocated (one as a result of poor compliance). Our data indicate that this score may be very useful in clinical practice not only to select patients who will benefit from transplantation but probably also in avoiding transplant in those who will not need it.

Liver transplantation in our patients was followed by a significant increment in BMI, bone mass and fat-free mass. None of these improvements were observed in patients with severe portal hypertension undergoing more conservative therapeutic intervention, who showed a consistent and progressive deterioration in bone mass. Thus, the liver transplant group was worse initially and hence had more capacity to catch up, whereas the group not requiring transplantation had relatively compensated nutritional status and remained stable. Our finding that in transplanted patients an initially worse nutritional status turned to be comparable or even better than in patients without transplantation at the end of follow-up, proves that liver transplantation had beneficial effects on the nutritional status of CF patients.

The beneficial effects of liver transplantation on the adverse nutritional changes of end-stage LD have been already reported in children with other chronic cholestatic LDs [26–28]. With regard to bone mineralization, the improvement is presumably linked to a combination of factors related to transplantation, including restoration of bile flow allowing better absorption of nutrients, improvement of protein anabolism, and increase in physical activity because of better quality of life [29]. In agreement with these findings, in our patients after transplantation we could document an increment in plasma liposoluble vitamin concentrations from abnormally reduced baseline levels, and also an increase in fat-free mass.

With regard to pulmonary function, after an initial improvement in the early post-transplant period, we observed similar deterioration in transplanted patients and in those who did not receive the liver allograft. Improvement in pulmonary function has been described shortly after liver transplantation in CF [9,10,14,30,31], probably because of better ventilation, disappearance of ascites, improved nutritional conditions and possibly to a direct anti-inflammatory effect of cyclosporine [32], but our data suggest that this effect may be lost in the long-term.

Our experience also indicates that liver transplantation can be successfully performed also in patients with significant pulmonary disease and is associated with a net improvement in quality of life. None of our patients was excluded from the waiting list because of extrahepatic manifestations of CF, including severe pulmonary disease (FEV1<65%), chronic *P. aeruginosa* or *B. cepacia*

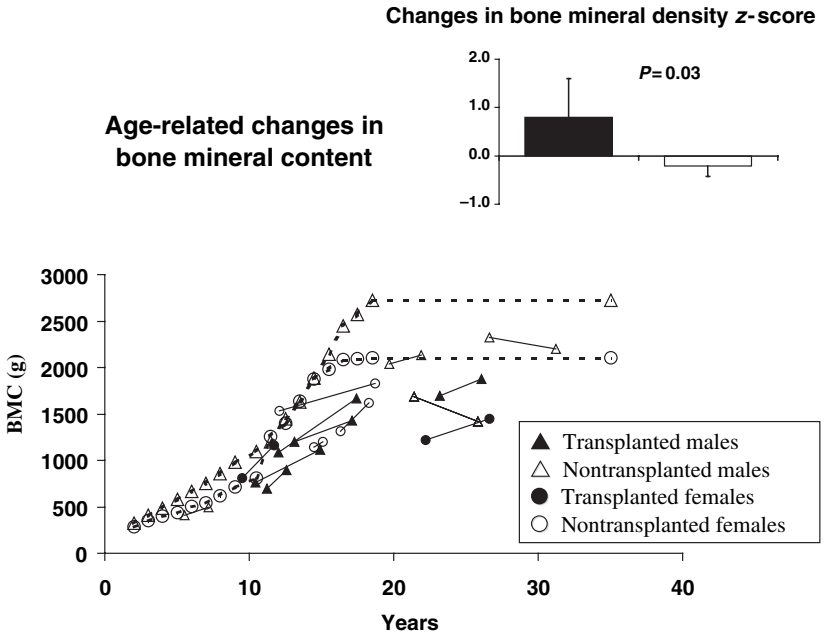

Figure 2 Changes in bone mineral content (BMC) during follow-up in CF patients who underwent liver transplantation (closed symbols) and in those who did not (open symbols). Males are indicated with triangle, female with circle. In the background, dotted lines represent age related bone mineral content values for male (triangle) and female (circle) reference population (see ref no 19 and 20). Changes in bone mineral density (BMD) *z*-score in the two groups of patients are also shown (top right panel).

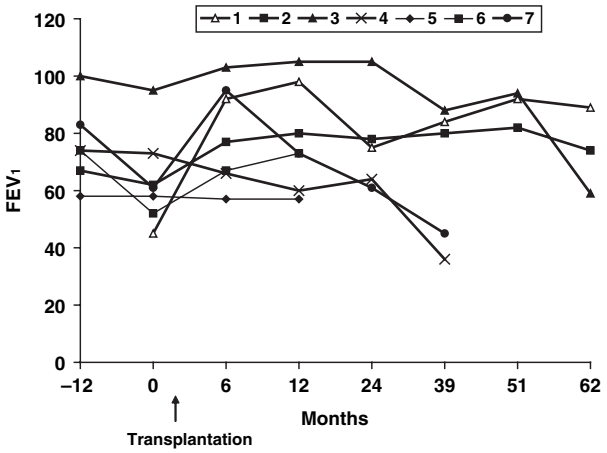

Figure 3 Time-related changes of FEV1 (percentage of predicted for height and sex) in transplanted patients before and after liver transplantation.

colonization and deterioration of pulmonary status was considered among criteria for anticipating transplantation.

Interestingly the majority of patients in both groups developed diabetes in their follow-up. It is well known that immunosuppressive regimens are important determinants of post-transplant diabetes mellitus [33]. This issue may be of special concern in patients with CF as the prevalence of diabetes strikingly increases with prolonged survival. It is noteworthy however that patients treated with conservative management had the same likelihood to develop diabetes suggesting that immunosuppression after liver transplantation was not an aggravating factor. Steroid-free immunosuppression after pediatric liver transplantation has been recently reported, with beneficial effects on growth and even better rejection-free survival [34]; future studies should assess the potential benefits of this regimen also in transplanted children with CF.

In conclusion, CF patients undergoing liver transplantation are nutritionally depleted, with significant abnormalities in body composition, particularly in bone mass. Liver transplantation has long-term beneficial effects on their nutritional status and seems to favor bone mineralization. CF patients may therefore benefit from early and elective liver transplantation, particularly those showing nutritional deterioration. Improvement in pulmonary function after transplantation may not be maintained in the long-term. However the improvement in nutritional status after liver transplantation may be particularly advantageous to the patients who develop an unfavorable pulmonary outcome.

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