Research Article

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Results of liver transplantation due to celiac

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Long-term results of celiac disease patients who underwent liver transplantation

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Abstract

Background and Aim: Although there are a few studies reporting transplantation for celiac disease (CD), there are no studies reporting long-term outcomes after transplantation in CD patients. Therefore, we aimed to report the long-term outcomes of patients who underwent liver transplantation (LT) for CD in our high-volume liver transplantation center.

Materials and Methods: Our study was a single-center, retrospective study and included 28 CD patients who underwent LT at Inonu University. CD diagnosis was made based on anti-tissue transglutaminase or anti-endomysium antibody positivity and/or duodenal biopsy results.

Results: The 1-, 3-, 5-, and 10-year survival rates after transplantation were 92.9%, 92.9%, 84.4%, and 75%, respectively. The most striking finding in the study was the high frequency of biliary complications. Another important finding was the significant difference in body mass index (BMI) between pre-transplant and post-transplant ($p<0.001$). The incidence of rejection and recurrence was 39.1% and 25%, respectively. The number of patients with high anti-tissue transglutaminase (anti-TTG) levels after transplantation decreased significantly ($p<0.001$).

Conclusion: Our study suggests that the frequency of post-transplant biliary complications is very high in CD patients and that LT had positive effects on BMI and anti-tissue transglutaminase levels.

Keywords: Celiac disease; liver; transplantation.

Introduction

Celiac disease (CD) is a T-cell autoimmune disorder of the small intestine characterized by malabsorption resulting from the ingestion of gluten, the main protein fraction in wheat, rye, and barley, in genetically predisposed individuals. The prevalence in the general population varies between 0.5% and 2%, with an average of around 1%.[1] Although CD is defined as a disease with malabsorption in the small intestine, untreated cases also affect other organs, including the liver. Liver involvement may progress to end-stage liver failure in patients who do not adhere to a gluten-free diet.[2] There is also a close relationship between celiac disease and autoimmune liver disease. Studies have found the prevalence of celiac disease to be 3–7% in patients with primary biliary cirrhosis, 3–6% in patients with autoimmune hepatitis, and 2–3% in patients with primary sclerosing cholangitis.[3–5]

In liver transplant patients with end-stage liver disease from different causes, the prevalence of CD varies between 3% and 4.3%.[2] Although there are a few studies reporting transplantation for CD,[6] there are no studies reporting long-term outcomes after transplantation in CD patients. Therefore, we aimed to report the long-term outcomes of CD patients who underwent liver transplantation in our high-volume liver transplantation center.

Materials and Methods

Our study was a single-center, retrospective study and included 28 CD patients who underwent liver transplantation at Inonu University between January 2004 and December 2023. Celiac disease diagnosis was made based on anti-tissue transglutaminase or anti-endomysium antibody positivity and/or duodenal biopsy results. Among patients who underwent transplantation due to cryptogenic cirrhosis, patients with positive anti-tissue transglutaminase or anti-endomysium antibody were also considered as celiac patients. Clinical and laboratory data of patients were obtained by reviewing the patients' electronic files. This study was carried out with the permission of the Inonu University Ethics Committee with the decision number 2024/5649. The study was conducted in accordance with the Declaration of Helsinki.

Pre-Transplant Parameter

Patients' age, gender, blood group, concomitant diseases, transplantation type (living donor-cadaveric), Model End Stage Liver Disease-Na

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(MELD-Na) scores at the time of transplantation, anti-tissue transglutaminase level before and after transplantation, presence of iron deficiency anemia and osteoporosis, body mass index, transplantation indication, donor's age, gender, blood group, consanguinity between the donor and the recipient, presence of Rh-incompatible transplantation, and presence of hepatocellular carcinoma were recorded.

Post-Transplant Parameters

Presence of hepatocellular carcinoma after transplantation, immunosuppressive treatment used after transplantation, use of ursodeoxycholic acid or steroids after transplantation, survival time, causes of death, presence of diarrhea after transplantation, presence of portal vein thrombosis, hepatic vein thrombosis, hepatic artery thrombosis after transplantation (if any), duration, development of recurrence and rejection, relationship with other malignancies, presence of second and third transplantation, cytomegalovirus infection, biliary complication frequency and feature, type of bile duct anastomosis (duct-to-duct anastomosis/hepaticojejunal anastomosis), treatment of post-transplant biliary complications, and liver biopsy results (acute rejection, chronic rejection, antibody-mediated rejection, disease recurrence, if any) were recorded.

Statistical Analyses

The analyses were evaluated using SPSS (Statistical Package for Social Sciences; SPSS Inc., Chicago, IL) version 22. In the study, descriptive data were shown as n, % values for categorical data and as mean ± standard deviation (mean±SD) values for continuous data. Chi-square analysis (Pearson Chi-square) was applied to compare categorical variables between groups. The Kolmogorov-Smirnov test was used to evaluate the compliance of continuous variables with normal distribution. Student t-test was used to compare binary groups. In the analyses, the statistical significance level was accepted as $p<0.05$.

Results

A total of 28 patients were included in the study: 12 (42.9%) male and 16 (57.1%) female. The mean age of the patients was 21.3±14.1 years. Eight patients were younger than 18 years old. Two (7.1%) of the transplants were deceased donor, and 26 (92.9%) were living donor liver transplantation. The mean follow-up period of the patients was 73.3±46.1 months. Table 1 shows demographic characteristics of patients undergoing liver transplantation due to CD.

The results of all patients after liver transplantation are summarized in Table 2. One of the six patients who died had a deceased donor transplant. Half of the deaths were biliary and the other half were secondary to rejection. The 12-month and 36-month survival rates were 92.9%; the 60-month survival rate was 84.4%, and the 120-month survival rate was 75% (Fig. 1). Factors affecting mortality were analyzed, and only age was found to be a significant factor. The average age of those who died was significantly lower than the average age of those who did not die ($p=0.041$). Other parameters had no significant effect on mortality ($p>0.05$) (Table 3).

The most striking finding in the study was the high frequency of biliary complications. Biliary complications were found to develop in one of two deceased donor transplants (50%) and in 73% of living donor transplants. Biliary complications occurred in 3 of 4 patients (75%) with HJ and 17 of 24 patients (70.8%) with duct-to-duct anastomosis. Of the

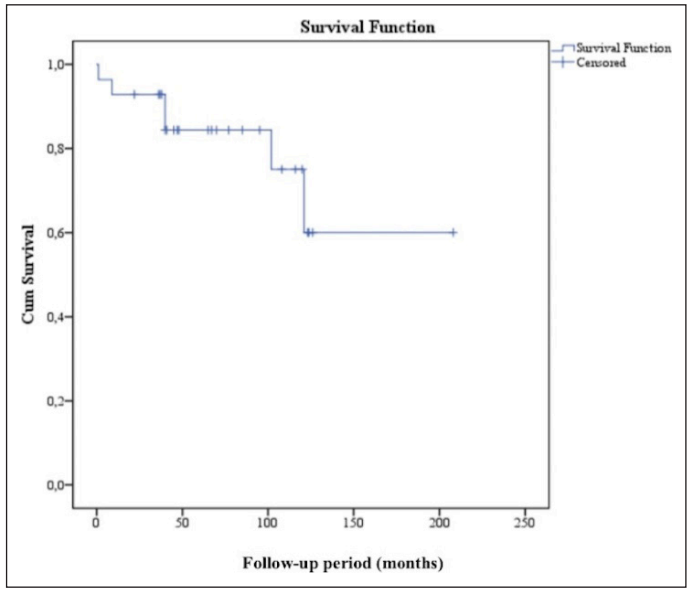

Figure 1. Kaplan–Meier survival curve of celiac disease patients after liver transplantation.

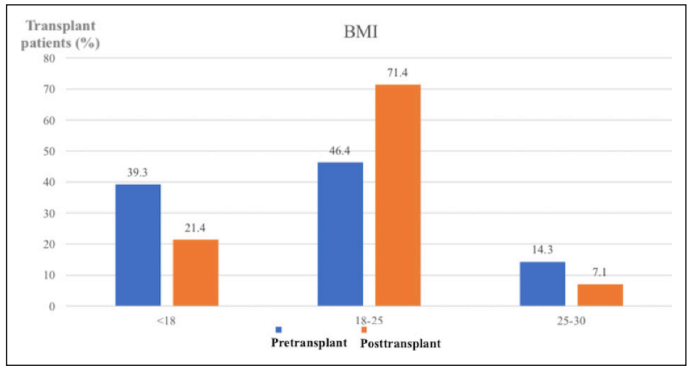

Figure 2. Comparison of body mass index (BMI) before and after liver transplantation in celiac disease patients.

patients with duct-to-duct anastomosis, 11 had biliary stricture, 3 had stricture and leakage, and 3 had stricture and stones. Of the patients with HJ, 2 had stricture and 1 had leakage. All patients with HJ and biliary complications (100%) were successfully treated with percutaneous transhepatic biliary interventions (PTBI). ERCP was performed in 16 patients with duct-to-duct anastomosis and biliary complications, and biliary problems were resolved in 9 patients with ERCP. The endoscopic success rate was 56.2%. PTBI was performed in 7 patients with duct-to-duct anastomosis. One patient with duct-to-duct anastomosis and biliary complications recovered with medical treatment without the need for any interventional treatment. All patients with duct-to-duct anastomosis and biliary complications (100%) were successfully treated with ERCP + PTBI. Surgery was not performed in any patient with biliary complications.

Another important finding was the significant difference in BMI between pre-transplant and post-transplant ($p<0.001$, Fig. 2). While 39.3% of the patients had a BMI of <18 before transplantation, 46.4% had a BMI of 18–25 and 14.3% had a BMI of 25–30. After transplantation, 21.4% of the patients had a BMI of <18, 71.4% had a BMI of 18–25, and 7.1% had a BMI of 25–30.

Table 1. Demographic characteristics of patients undergoing liver transplantation due to Celiac disease

	Cadaveric (n=2)		Living donor (n=26)		Total (n=28)	
	n	%	n	%	n	%
Gender						
Male	0	0	12	46.2	12	42.9
Female	2	100	14	53.8	16	57.1
Age, Mean±SD (median)	18.0±17.0 (18.0)		21.6±14.2 (19.50)		21.3±14.1 (19.50)	
Follow-up period, Mean±SD (months)	58.5±26.2		74.4±47.5		73.3±46.1	
Dietary compliance before transplantation						
Yes	1	50	4	15.4	5	17.9
No	1	50	22	84.6	23	82.1
HCC before transplantation						
Yes	1	50	2	7.7	3	10.7
No	1	50	24	92.3	25	89.3
Associated disease						
Yes	0	0	18	69.2	18	64.3
No	2	100	8	30.8	10	35.7
Associated disease						
Type 1 diabetes mellitus	0	0	1	5.6	1	5.6
Primary biliary cholangitis+Crohn	0	0	1	5.6	1	5.6
Irritable bowel syndrome	0	0	1	5.6	1	5.6
IgA nephropathy	0	0	1	5.6	1	5.6
Autoimmune hepatitis	0	0	13	72.2	13	72.2
Fibrocystic liver disease	0	0	1	5.6	1	5.6
Transplant indication						
High MELD score	1	50	19	73.1	20	71.4
Persistent pruritus	0	0	1	3.8	1	3.6
Portal Hypertension-related complications	0	0	6	23.1	6	21.4
HCC	1	50	0	0	1	3.6
Bile duct anastomosis						
HJ	1	50	3	11.6	4	14.3
Duct-to duct	1	50	23	88.4	24	85.7

SD: Standard deviation; MELD: The model for end-stage liver disease; HCC: Hepatocellular carcinoma; HJ: hepaticojejunostomy.

Celiac recurrence developed in 7 patients, and these patients had living donor transplants except for one patient. Six of these patients had no dietary compliance after transplantation. Among the patients who underwent living donor transplantation, 2 developed acute rejection, 4 developed chronic rejection, and 3 developed antibody-mediated rejection. It was found that half of deceased transplant patients (1/2, 50%) developed chronic rejection. A total of 11 patients (39.3%) developed rejection.

While 77.8% of the patients had high anti-tissue transglutaminase levels before transplantation, this rate became 10.5% after transplantation, and the rate of normality increased significantly ($p<0.001$). Iron deficiency anemia, osteoporosis, and duodenal biopsy results of the patients before and after transplantation did not change significantly ($p>0.05$). The frequency of iron deficiency anemia was 35.7% (10/28) before transplantation and 46.4% (13/28) after transplantation. The frequency of osteoporosis was 10.7% (3/28) before transplantation and 17.9% (5/28) after transplantation. Findings compatible with celiac disease in duodenal biopsy were 32.1% (9/28) before transplantation and 25% (7/28) after transplantation.

Table 2. The results of all patients after liver transplantation

	Cadaveric (n=2) n (%)	Living donor (n=26) n (%)	Total (n=28) n (%)
Drugs after transplantation			
Tacrolimus	0 (0)	2 (7.7)	2 (7.1)
Everolimus+Tacrolimus+MMF	1 (50)	8 (30.8)	9 (32.1)
Tacrolimus+MMF	1 (50)	7 (26.9)	8 (28.6)
Tacrolimus+Cyclosporine+Everilumus+MMF	0 (0)	7 (26.9)	7 (25.0)
Unknown	0 (0)	1 (3.8)	1 (3.6)
Tacrolimus+Everilumus+Cyclosporine	0 (0)	1 (3.8)	1 (3.6)
Corticosteroid	0 (0)	4 (15.4)	4 (14.3)
UDCA	1 (50)	3 (11.5)	4 (14.3)
Corticosteroid+UDCA	1 (50)	18 (69.2)	19 (67.9)
Death			
Yes	1 (50)	5 (19.2)	6 (21.4)
No	1 (50)	21 (80.8)	22 (78.6)
Cause of death			
Biliary sepsis	1 (50)	2 (7.6)	3 (10.7)
Rejection	0 (0)	3 (11.5)	3 (10.7)
Recurrence			
Yes	1 (50)	6 (23.1)	7 (25)
No	1 (50)	20 (76.9)	21 (75)
Rejection			
Var	1 (50)	10 (38.5)	11 (39.3)
Yok	1 (50)	16 (61.5)	17 (60.7)
Biliary complication			
Yes	1 (50)	19 (73)	20 (71.4)
No	1 (50)	7 (27)	8 (28.6)
Second transplantation			
Yes	0 (0)	3 (11.5)	3 (10.7)
No	2 (100)	23 (88.5)	25 (89.3)
Portal vein thrombosis			
Yes	0 (0)	2 (7.7)	2 (7.1)
No	2 (100)	24 (92.3)	26 (92.9)
Hepatic arthery thrombosis			
Yes	0 (0)	1 (3.8)	1 (3.6)
No	2 (100)	25 (96.2)	27 (96.4)
Hepatic vein thrombosis			
Yes	0 (0)	1 (3.8)	1 (3.6)
No	2 (100)	25 (96.2)	27 (96.4)

Table 2 (cont). The results of all patients after liver transplantation

	Cadaveric (n=2) n (%)	Living donor (n=26) n (%)	Total (n=28) n (%)
Surgery for biliary complication			
Yes	0 (0)	0 (0)	0 (0)
No	2 (100)	26 (100)	28 (100)
ERCP			
Yes	1 (50)	15 (57.7)	16 (57.1)
No	1 (50)	11 (42.3)	12 (42.9)
PTBI			
Yes	1 (50)	9 (34.6)	10 (35.7)
No	1 (50)	17 (65.3)	18 (64.3)
CMV			
Yes	1 (50)	2 (7.7)	3 (10.7)
No	1 (50)	24 (92.3)	25 (89.3)
HCC after transplantation			
Yes	0 (0)	0 (0)	0 (0)
No	2 (100)	26 (100)	28 (100)
Diarrhea after transplantation			
Yes	1 (50)	6 (23.1)	7 (25.0)
No	1 (50)	20 (76.9)	21(75.0)

MMF: Mycophenolate mofetil; UDCA: Ursodeoxycholic acid; ERCP: Endoscopic cholangiopancretaography; PTBI: Percutaneous transhepatic biliary intervention; CMV: Cytomegalovirus; HCC: Hepatocellular carcinoma.

Discussion

In our study, we found the 1-, 3-, 5-, and 10-year survival rates in CD patients who underwent transplantation to be 92.9%, 92.9%, 84.4%, and 75%, respectively. The mean age of patients who died after transplantation was significantly lower than that of survivors. We also found that liver transplantation had positive effects on BMI and anti-tissue transglutaminase levels. One of the most striking findings in our study was the high frequency of biliary complications.

Since there are very few publications in the literature on liver transplantation outcomes due to CD, we had to compare our results, especially regarding survival, with the results after liver transplantation due to autoimmune diseases. In a study conducted by Mottershead et al.[7] in 2008 on patients who underwent liver transplantation due to autoimmune hepatitis, 1- and 5-year survival rates were found to be 87% and 80–90%, respectively. In two different studies, post-transplant survival rates in patients with autoimmune hepatitis were also reported as 85–97% and 78.4%, respectively.[8,9] In the European Liver Transplant Registry, the 5- and 10-year survival rates for PSC were 80% and 83% after transplantation.[10] In a study conducted by Egawa et al.[11] on 444 patients who underwent transplantation due to PBC, 5-year survival was found to be 76.6%. The survival rate of CD patients who underwent liver transplantation in our center is similar to liver transplantations performed due to other autoimmune diseases worldwide. Our results suggest that survival rates after liver transplantation are quite satisfactory in patients with end-stage liver disease due to CD, for which no other treatment options are available.

In our study, recurrence was observed in 7 (28%) patients who underwent liver transplantation due to CD. In a study conducted by Alabraba et al.,[12] recurrence was observed in 259 (18.5%) of 1,399 patients who underwent liver transplantation due to PSC. In two studies, the recurrence rate after liver transplantation in patients with AIH was 17.9% and 41%, respectively.[9,13] Khettry et al.[14] reported that 18.6% of 43 PBC-related transplant patients developed recurrence. Our results suggest that the recurrence rate after liver transplantation due to CD is similar to other autoimmune diseases.

Since CD is an autoimmune disease, it may be accompanied by other autoimmune diseases. The prevalence of autoimmune hepatitis in celiac disease is 1.6%.[15] Lawson et al.[16] reported the prevalence of PBC as 0.1% in a study of 4,732 CD patients. In a study including a very large number (136,735) of CD patients, the prevalences of AIH, PBC, and PSC were 0.32%, 0.15%, and 0.004%, respectively.[17] Kaukinen et al.[18] reported that CD was detected in 8 of 185 liver transplant patients. Among the patients with CD, 3 had primary biliary cirrhosis, 1 had autoimmune hepatitis, 1 had primary sclerosing cholangitis, 1 had congenital liver fibrosis, and 1 had secondary sclerosing cholangitis.

In our study, in patients who underwent transplantation due to CD, 46% had autoimmune hepatitis, 3.5% had PBC, 3.5% had IgA nephropathy, and 3.5% had Type 1 DM. All these data and our results suggest that the frequency of AIH and PBC is higher in CD patients with liver transplantation and that autoimmune liver diseases may coexist in CD patients with liver transplantation.

Table 3. Factors affecting mortality

	Death				p*
	Yes		No		
	n	%	n	%	
Gender					0.673
Male	2	16.7	10	83.3	
Female	4	25	12	75.0	
Biliary complication					0.871
Yes	5	21.1	15	78.9	
No	1	22	7	78	
Type of biliary complications					0.247
Stricture	3	23	10	76.9	
Leak	1	100	0	0	
Stricture + leak	0	0	3	100	
Stricture + stone	1	33	2	66	
MELD before LT					0.640
0–15	1	12.5	7	87.5	
>15	5	25.0	15	75.0	
Bloood group					0.880
A	3	30.0	7	70.0	
B	1	12.5	7	87.5	
0	2	22.2	7	77.8	
AB	0	0	1	100	
BMI before LT					0.696
<18	3	27.3	8	72.7	
18–25	3	23.1	10	76.9	
25–30	0	0	4	100	
BMI after LT					0.130
<18	3	50.0	3	50	
18–25	3	15.0	17	85.0	
25–30	0	0	2	100.0	
Dietary compliance before LT					0.932
Yes	1	20.0	4	80.0	
No	5	21.7	18	78.3	
Dietary compliance after LT					0.549
Yes	0	0	4	100	
No	6	25.0	18	75.0	
Donor gender					0.653
Male	3	27.3	8	72.7	
Female	3	17.6	14	82.4	
Age, Mean±SD	29.5±10.5		41.2±16.1		**0.041**

Table 3 (cont). Factors affecting mortality

	Death				p*
	Yes		No		
	n	%	n	%	
Donor blood group					0.826
A	2	20.0	8	80.0	
B	0	0	4	100.0	
0	4	28.6	10	71.4	
Donor degree of kinship (1st degree)					0.064
Yes	2	10.5	17	89.5	
No	4	44.4	5	55.6	
Rh incompatibility					0.443
Yes	0	0	2	100.0	
No	6	23.1	20	76.9	
HCC before LT					0.107
Yes	2	66.7	1	33.3	
No	4	16.0	21	84.0	
HCC after LT					–
Yes	0	0	0	0	
No	6	21.4	22	78.6	
Associated disease					0.891
Yes	4	22.2	14	77.8	
No	2	20.0	8	80.0	
PVT after LT					0.443
Yes	0	0	2	100.0	
No	6	23.1	20	76.9	
HAT after LT					0.214
Yes	1	100.0	0	0	
No	5	18.5	22	81.5	
HVT after LT					0.595
Yes	0	0	1	100.0	
No	6	22.2	21	77.8	
CMV					0.338
Yes	0	0	3	100.0	
No	6	24.0	19	76.0	

MELD: The model for end-stage liver disease; BMI: Body mass index; HCC: Hepatocellular carcinoma; PVT: Portal vein thrombosis; HAT: Hepatic artery thrombosis; HVT: Hepaitc vein thrombosis; CMV: Cytomegalovirus; LT: Liver transplantation.

In our study, it was observed that the number of patients with high anti-TTG levels after transplantation decreased significantly. In a study conducted by Rubio-Tapia et al.[2] on patients who underwent liver transplantation due to CD, it was reported that the rate of patients with pre-transplant anti-TTG positivity decreased significantly after transplantation and even became negative. One study suggested that there may be two reasons for the decrease in anti-TTG levels after transplantation in CD patients. The first reason is that removal of the diseased liver reduces the level of anti-TTG antibodies, as it may be a target organ. The second reason is that immunosuppressive drugs used

after transplantation affect the production of autoantibodies.[19] In addition, correction of intestinal barrier dysfunction caused by cirrhosis after transplantation may also reduce the antigenic environment and B-cell activation and lead to normalization of anti-TTG.[2] Our results are similar to the study by Rubio-Tapia et al.,[2] suggesting that liver transplantation has a positive effect on anti-TTG levels in CD patients who underwent liver transplantation.

In our study, post-transplant acute and chronic rejection rates in CD patients were 7% and 21.4%, respectively. In the study conducted by Rubio-Tapia et al.,[2] it was reported that 3 (30%) of 10 double (anti-TTG and EMA) positive patients developed rejection. In a study conducted by Chouik et al.[20] on a large number of patients who underwent liver transplantation due to autoimmune hepatitis, acute rejection was detected in an average of 23.5%, and this rate decreased from 45.7% in the early years of liver transplantation to 13.4% over the years. The AASLD AIH guideline reported the incidence of chronic rejection as 16% for AIH, 5.2% for PSC, and 8.2% for PBC.[21] In a study conducted by our group at our center on patients who underwent liver transplantation due to PSC, the incidence of acute and chronic rejection was 13.3% and 10%, respectively.[22] Our results suggest that the rate of post-transplant rejection in patients with CD in our center is higher than liver transplants performed for other autoimmune diseases worldwide. In addition, although the number of studies reporting the frequency of post-transplant rejection in CD patients is very small, the results of Rubio-Tapia et al.[2] and ours suggest that post-transplant rejection is common in CD patients.

In our study, the frequency of post-transplant biliary complications was found to be quite high. Biliary complications occurred in 50% of deceased donor liver transplants and 73% of living donor liver transplants. There are studies reporting the frequency of biliary complications after transplantation in AIH and PSC patients as 25.3% and 36.1%, respectively.[20,23] In a study including a large number of patients, biliary complications were reported in 11.1% of 6,471 deceased donor liver transplant patients and in 20.8% of 389 living donor liver transplant patients.[24] It has been reported that ERCP was applied to 283 (18.7%) of 1,506 LDLT patients with duct-to-duct anastomosis in our institute between 2015 and 2021.[25] The majority of the patients in our study had living donor LT. Therefore, it is possible that our results are related to technical reasons associated with living donors. However, because of the small number of patients in our study, it is not easy to interpret whether the high frequency of biliary complications is related to celiac disease or technical reasons. Although our case number is small, our results suggest that the frequency of post-transplant biliary complications in CD is higher than in other autoimmune diseases.

Another important finding in our study was the significant difference in BMI before and after transplantation. Our results suggest that liver transplantation provides significant benefits on weight gain in CD. In this study, no significant change was detected in the iron deficiency anemia (IDA), osteoporosis, and duodenal biopsy results of the patients before and after transplantation. The lack of change in the frequency of osteoporosis may be related to the side effects of immunosuppressive drugs used after transplantation on the bones. Our result regarding iron deficiency anemia can also be explained by the lack of positive change in small intestine histology after transplantation.

Conclusion

Our results suggest that the frequency of post-transplant biliary complications is very high in CD patients and that LT had positive effects on BMI and anti-tissue transglutaminase levels.

Ethics Committee Approval: The Inonu University Clinical Research Ethics Committee granted approval for this study (date: 05.03.2024, number: 2024/5649).

Informed Consent: The requirement for individual informed consent was waived due to the retrospective nature of the study.

Conflict of Interest: The authors have no conflict of interest to declare.

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