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Regular paper

Lipid disorders before and after successful liver transplantation

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Introduction: Liver transplantation (LTx) is the only successful treatment for end-stage liver disease. The results of liver transplantation depend not only on graft survival but may be also affected by superimposed cardiovascular morbidities. The aim of this retrospective study was to assess the prevalence of lipid disorders as one of the important cardiovascular risk factors in patients before and after successful LTx. Material and Methods: One hundred eleven patients who underwent liver transplantation because of liver cirrhosis and survived at least 2 years with functioning graft between November 2005 and May 2014 were included in this retrospective analysis. The mean age of the patients at the time of liver transplantation was 49.7±12.2 years. The prevalence of dyslipidemia was assessed before and two years after liver transplantation. This was analyzed in relation to the etiology of liver disease, including alcohol toxicity, viral or autoimmune diseases. Results: The prevalence of hypertriglyceridemia before and after LTx was 13.5% and 40.5%, respectively (*P*<0.001). Similarly, hypercholesterolemia was noted in 17.1% and 51.4% respectively (*P*<0.001). The annual incidence of hypertriglyceridemia and hypercholesterolemia during the first two years after LTx was 16.2% and 20.7%, respectively. The prevalence of hypertriglyceridemia (18.5% *vs* 66.7%, *P*<0.001) and hypercholesterolemia (29.6% *vs* 70.0%, *P*=0.002) was significantly lower in patients with the autoimmune cause of liver cirrhosis in comparison to patients with the alcoholic liver disease. Conclusions: The prevalence of dyslipidemia is increased after liver transplantation. The prevalence of dyslipidemia may be related to the cause of liver injury before LTx.

Keywords: dyslipidemia, hypertriglyceridemia, hypercholesterolemia, cardiovascular risk factors, liver transplantation

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Abbreviations: BMI, body mass index; MELD, Model of End-Stage Liver Disease; LTx, liver transplantation

INTRODUCTION

Liver transplantation is the only successful method for the treatment of end-stage liver disease. In the last decade in Poland, about 300 patients underwent liver transplantation every year (Poltransplant, 2022). The most common indications for liver transplantation in our population included end-stage liver disease caused by infectious hepatitis, autoimmune or alcoholic liver disease. Despite decreasing the risk of early graft failure, due to improving surgical techniques and immunosuppressive therapy, in the last three decades, long-time survival in liver transplant recipients has not substantially improved (Rana *et al.*, 2019). Therefore currently transplant community focus has shifted to maximizing long-term survival after transplantation. The results of liver transplantation not only depend on graft survival but may be affected by superimposed cardiovascular morbidities. It has been shown that cardiovascular diseases are one of the most frequent causes of premature death in patients after liver transplantation (Berenguer *et al.*, 2002; Watt *et al.*, 2010). Current immunosuppressive drugs are very effective in preventing acute rejection of transplanted organs. However, it is well-recognized that some of these drugs, like tacrolimus or steroids, result in increased rates of hypertension, diabetes, and dyslipidemia (Gojowy *et al.*, 2016). Watt *et al.*, in long-term follow-up of liver transplant recipients, have shown that some well-known cardiovascular risk factors like hypertension or diabetes mellitus may be directly or indirectly involved in premature death in patients who survive one year after liver transplantation (Watt *et al.*, 2010). According to this observation, routine screening of cardiovascular risk factors seems to be an essential component of comprehensive post-transplant care for these patients. Population studies in Poland have shown that cardiovascular risk factors are common and hypercholesterolemia is present in 61.1-64.3% of the Polish adult population (Zdrojewski *et al.*, 2013; Stepniak *et al.*, 2016; Niklas *et al.*, 2018; Rutkowski *et al.*, 2020).

The current paper presents the results of a retrospective study which aimed to assess the prevalence of lipid disorders before and after successful liver transplantation.

MATERIAL AND METHODS

This retrospective, single-center study involved 111 patients (47 female, 64 male) aged 49.7±12.2 years who underwent liver transplantation because of liver cirrhosis in years 2005 to 2014 in the Department of General, Vascular and Transplant Surgery of the Medical University of Silesia in Katowice, Poland and who survived with functioning transplanted liver for at least 24 months. Patients who died or had liver re-transplantation before 24 months of observation were not included in the analysis. All transplantations were performed using cadaveric organs. After transplantation, patients were followed up in the Transplantation Outpatient Clinic of the Department of Nephrology, Transplantation and Internal Medicine Medical University of Silesia in Katowice, Poland. The median MELD score at the time of qualifica-

tion for liver transplantation was 14.0 (9.0;19.1). A retrospective analysis of the patients' medical history was performed.

In all patients, serum concentrations of total cholesterol and triglycerides, as well as doses and concentrations of immunosuppressive drugs were analyzed. Hypertriglyceridemia was diagnosed when triglycerides serum concentration was ≥1.7 mmol/L (150 mg/dL) or triglycerides-lowering treatment (i.e. one of the fibrates) was used. In such patients triglycerides serum concentration ≥1.7 mmol/L (150 mg/dL) was documented before initiation of this therapy. Hypercholesterolemia was defined as a total serum cholesterol concentration was ≥5.0 mmol/L (190 mg/dL) or cholesterol-lowering pharmacological treatment was used (i.e. one of statins or fibrates). In such patients, serum cholesterol concentration ≥5.0 mmol/L (190 mg/dL) was documented before initiation of this therapy. Because of the retrospective character of the current study due to the lack of data, the analysis of serum cholesterol fractions was not possible. Prevalence of lipid disorders was assessed a short time before liver transplantation (up to 6 months before the procedure) and two years after transplantation. Moreover, the annual incidence of these abnormalities during the first two years after liver transplantation was analyzed.

Etiology of liver disease

Thirty-seven patients had viral hepatitis as a cause of liver failure (among them, 28 patients suffered from hepatitis C, and 9 from hepatitis B infection); alcoholic liver disease was a cause of liver failure in 30 patients; autoimmune diseases in 27 patients (among them primary sclerosing cholangitis – 11 patients, autoimmune hepatitis – 9 patients, primary biliary cirrhosis – 5 patients, autoimmune hepatitis and primary sclerosing cholangitis overlapping syndrome – 2 patients) and others (17 cases).

Immunosuppressive treatment

Two years after liver transplantation, 90% of studied patients were treated with calcineurin inhibitors. Ninety-one patients (82% of all studied patients) received tacrolimus, and 9 patients (8% of all studied patients) received cyclosporine A. Eleven patients (10% of the studied patients) were treated with everolimus. Prednisone was used in 102 patients (92% of the studied patients), mainly in the dose of 5–15 mg/day. Thirty-seven patients (33% of the studied patients) were treated with mycophenolates. In three patients within 24 months after liver transplantation, the acute rejection of the transplanted liver was diagnosed only by clinical manifestation and treated with a high dose of intravenous methylprednisolone. None of these patients had a biopsy of the transplanted liver. In another two patients, it was necessary to transiently increase the prednisone dose to 60 mg/day in the early period after liver transplantation.

Statistical analysis

Statistical analysis was done using the Statistica 13.3 software (StatSoft). The Shapiro-Wilk test was used to determine the normality of distribution. Mann-Whitney U, chi-square tests, and Spearman's rank correlation were used in this study. The level of statistical significance is $\alpha=0.05$. Results were presented as a mean and standard deviation for the parametric distribution of variables and as a median with an interquartile range for the non-parametric distribution of variables.

Ethics

Because of the retrospective character of the study, ethics committee consent was not required.

RESULTS

Hypertriglyceridemia before liver transplantation was found in 13.5% of patients. The prevalence of hypertriglyceridemia two years after liver transplantation was significantly higher – 40.5% (36.2% in females, 43.8% in males) ($P<0.001$). The annual incidence of new-onset hypertriglyceridemia in the first two years after liver transplantation was 16.2%. It has been shown a significant positive correlation between serum triglycerides concentration and the age of liver transplant recipients ($R=0.27$, $P=0.003$). Serum total cholesterol concentration was elevated above the normal range in 17% of patients before liver transplantation. After liver transplantation in 57 (51.4%) patients (51.0% of females, 51.6% of males) hypercholesterolemia was found ($P<0.001$) (Table 1). The annual incidence of new-onset hypercholesterolemia in the first two years after liver transplantation was 20.7%. It has been shown a correlation between serum total cholesterol concentration and the age of liver transplant recipients ($R=0.25$, $P=0.008$).

There was no significant correlation between MELD score before LTx and serum triglycerides and total cholesterol serum concentration before and 24 months after LTx. There were also no significant differences in MELD score before LTx between patients with and without diagnosis of any type of dyslipidemias before and 24 months after LTx.

Before LTx, none of the patients were treated with lipid-lowering therapy. Only 7 patients were treated with lipid-lowering therapy two years after LTx (3 received statins, 3 received fibrates, and one patient was treated with both drugs from the above-mentioned group of agents). Patients were not treated with other lipid-lowering drugs (i.e. ezetimibe). Hypercholesterolemia was diagnosed in three patients with normal serum total cholesterol concentration at the time of examination (i.e. 2 years after LTx) treated with lipid-lowering therapy (1 with statin and 2 with fibrates). Hypertriglyceridemia was diagnosed in one patient with normal triglycerides serum concentration at the time of examination (i.e. 2 years after LTx) treated with fenofibrate.

Immunosuppressive drugs and lipid disorders

Our study showed no significant differences in the prevalence of hypertriglyceridemia in patients treated with tacrolimus, cyclosporine A, and everolimus (40%, 33%, and 55%, respectively). There was a significant difference in the prevalence of hypercholesterolemia in patients treated with everolimus, tacrolimus and cyclosporine (91%, 45%, and 66%, respectively, $P=0.01$; everolimus vs. tacrolimus $P=0.002$). Prevalence of hypercholesterolemia and hypertriglyceridemia in patients treated and not treated with mycophenolates was 46% *vs.* 54% and 35% *vs.* 43%, respectively (differences in the above-mentioned prevalence were not significant).

There were no significant correlations between serum total cholesterol as well as triglycerides concentration and blood tacrolimus concentration (Figs 1 and 2),

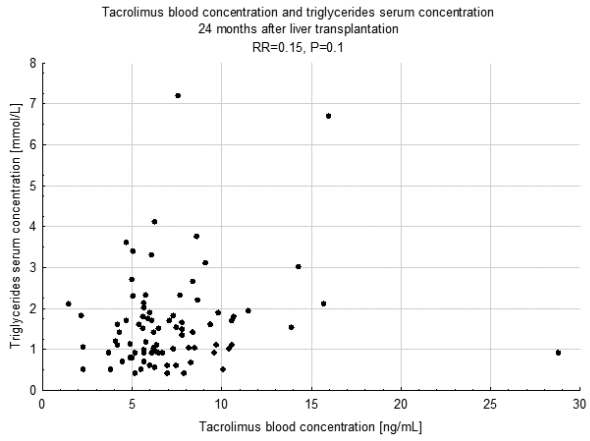

Figure 1. Tacrolimus blood concentration and triglycerides serum concentration 24 months after liver transplantation.

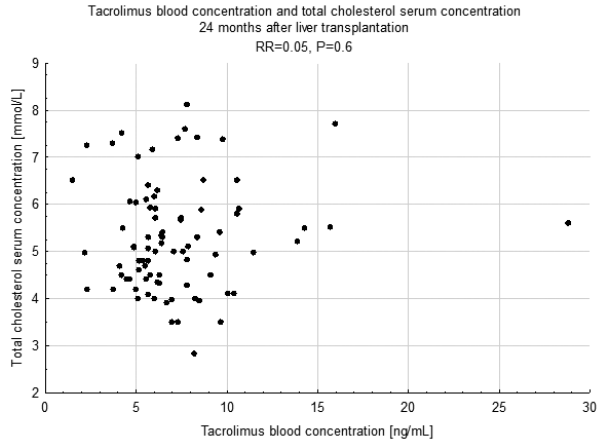

Figure 2. Tacrolimus blood concentration and total cholesterol serum concentration 24 months after liver transplantation.

as well as mycophenolate and prednisone dose in liver transplant recipients.

Etiology of liver failure and lipid disorders

In an additional analysis, patients were divided into three groups - alcohol, viral and autoimmune diseases. Patients with the autoimmune disease were characterized by a significantly lower prevalence of hypercholesterolemia than patients with alcoholic disease of the native liver (29.6% *vs.* 70.0%, P=0.002). There was also a significantly higher prevalence of hypertriglyceridemia in patients with alcoholic liver disease than in patients with an autoimmune background (66.6% *vs.* 18.5%, P<0.001). The annual incidence of new-onset hypertriglyceridemia (9.3%, 13.5%, 30.0%; P=0.001; autoimmune *vs.* alcohol – P=0.001, viral *vs.* alcohol P=0.006) and new-onset hypercholesterolemia (13.0%, 20.3%, 28.3%; P=0.06; autoimmune *vs.* alcohol – P=0.01), were in autoimmune, viral and alcoholic liver disease, respectively (Table 2).

There was a correlation between triglycerides serum concentration and body weight as well as triglycerides serum concentration and BMI in 24 months after liver transplantation (R=0.34, P<0.001 and R=0.32, P<0.001, respectively). There was also a correlation between gain of body mass as well as gain of BMI before and 24 months after liver transplantation and triglycerides serum concentration 24 months after LTx (R=0.22, P=0.02 and R=0.20, P=0.03, respectively). There was also a trend of correlation between total cholesterol serum concentration and body weight (R=0.19, P=0.05) and a correlation between total cholesterol serum concentration and BMI in 24 months after liver transplantation (R=0.20, P=0.03). There was also a trend of correlation between gain of body mass as well as gain of BMI before and 24 months after liver transplantation and total cholesterol serum concentration 24 months after LTx (R=0.16, P=0.09 and R=0.17, P=0.08, respectively). Patients with hypertriglyceridemia had higher BMI in comparison with patients without that disorder (28.1±5.4 *vs* 26.2±4.1 kg/m^2; P=0.03). There was no significant difference in BMI in patients with and without hypercholesterolemia (27.6±5.0 *vs* 26.3±4.5 kg/m^2).

DISCUSSION

The prevalence of lipid disorders increased over a 2-year survey of patients undergoing liver transplantation at our facility. According to available data prevalence of dyslipidemia in liver transplant recipients varies widely among studies, and it is present in 14–71% of patients

Table 1. Prevalence of lipid disorders before and after liver transplantation

	Before liver transplantation			After liver transplantation		
	All (n=111)	Male (n=64)	Female (n=47)	All (n=111)	Male (n=64)	Female (n=47)
Hypercholesterolemia	19 (17%)	7 (11%)	12 (25%)	55 (51%)*	33 (52%)	24 (51%)
Hypertriglyceridemia	15 (14%)	6 (9%)	9 (19%)	45 (41%)*	28 (44%)	17 (36%)

*P<0.001 *vs* before liver transplantation

Table 2. Lipid disorders prevalence and etiology of liver cirrhosis

Cardiovascular risk factor (24 months after LTx)	Autoimmune (n=27)	Viral (n=37)	Alcoholic (n=30)	P-value
Hypercholesterolemia	8 (30%)	20 (54%)	21 (70%)	P=0.05* P=0.02+ NS^X
Hypertriglyceridemia	5 (19%)	15 (41%)	20 (67%)	NS* P<0.001+ P=0.03^X

*autoimmune *vs*. viral; +autoimmune *vs*. alcoholic; ^{X}viral *vs*. alcoholic

(Clart *et al*., 1996; Gisbert *et al*., 1997; Kallwitz *et al*., 2012; Niklas *et al*., 2018). In the current study, 51.4% of patients presented hypercholesterolemia two years after liver transplantation. It is less than in the general adult Polish population (results of NATPOL 2011 61.1% and WOBASZ II – 64.3% studies) (Zdrojewki *et al*., 2013; Rutkowski *et al*., 2020). An opposite tendency is in the case of hypertriglyceridemia. In patients after liver transplantation hypertriglyceridemia is present in 40.5%. It is more frequent than in the general adult Polish population (21% – results of NATPOL 2011 study) (Zdrojewski *et al*., 2013). Results of previous studies suggest that hypertriglyceridemia is even more common during the first year after liver transplantation than in long-term observation (Clark *et al*., 1997, Gisbert *et al*., 1997). An important risk factor for developing hypertriglyceridemia after LTx is kidney dysfunction and greater body weight gain after LTx (Gispert *et al*., 1997). The prevalence of studied lipid abnormalities was significantly lower before liver transplantation – hypercholesterolemia 17.1% *vs*. 51.4% and hypertriglyceridemia 13.5% *vs*. 40.5%. This might be influenced by malnutrition in patients with end-stage liver disease qualified for liver transplantation. An observational study of 165 liver transplant recipients showed that living liver donation was related to a better lipid profile (lower triglycerides and higher HDL serum concentrations) two years after transplantation (Chu *et al*., 2017). In the current study, all transplanted livers were received from cadavers.

Dyslipidemia and immunosuppressive drugs

Dyslipidemia is a well-known complication associated with using steroids, tacrolimus, or everolimus.

Steroid therapy is a well-known risk factor for developing lipid disorders (Fatourou *et al*., 2019). Some observational studies suggest that withdrawal of steroids in the long term after liver transplantation may decrease serum cholesterol concentration (Punch *et al*., 1995; Stegall *et al*., 1997; Trouillot *et al*., 1999; Everson *et al*., 1999).

The effect of immunosuppressive therapy with calcineurin inhibitors (cyclosporine A or tacrolimus) may also induce lipid abnormalities (Clart *et al*., 1996; Stegall *et al*., 1997; Fatourou *et al*., 2019). Results of previous studies suggest that treatment with both calcineurin inhibitors predisposes to hyperglyceridemia. It has been shown that combined cyclosporine A and sirolimus therapy increase the risk of hypertriglyceridemia in liver transplant recipients (Trotter *et al*. 2001). Canzanello *et al*. suggest that the risk of hypertriglyceridemia in patients treated with cyclosporine A is higher than in patients treated with tacrolimus [Canzanell *et al*. 1997). Another study by Dehghani *et al*. presents opposite findings (Dehghani *et al*., 2007). In the observational study of 116 Spanish liver transplant recipients, Fernandez-Miranda *et al*. have shown a slight association between cyclosporine A and hypercholesterolemia in patients after LTx (odds ratio: 1.02; 95% CI: 1.00–1.03; P=0.01) (Fernandez-Miranda *et al*., 2002). Because of the low number of patients treated with cyclosporine A in the current study, such an analysis was impossible to perform. Orlando *et al*., in the interventional study of 42 liver transplant recipients with chronic toxicity of calcineurin inhibitors have shown that conversion of calcineurin inhibitors for mycophenolate leads to serum total cholesterol and triglycerides concentration reduction (Orlando *et al*., 2007).

It has been shown that treatment with mTOR inhibitors (everolimus or sirolimus) is associated with developing hypercholesterolemia in renal transplant recipients (Groth *et al*., 1999). Randomized trials have shown that immunosuppressive conversion from calcineurin inhibitors to mTOR inhibitors in a short time after liver transplantation increases total cholesterol and LDL-cholesterol concentration (Masetti *et al*., 2010; Fischer *et al*., 2012, De Simone *et al*., 2012; Teperman *et al*., 2013). Only one of these trials (with modification for everolimus and low tacrolimus dose regimen) has shown an additional increase in serum triglyceride concentration and an increase in HDL-cholesterol concentration (De Simone *et al*., 2012). Interestingly, the previously cited study has shown a hypertriglyceridemic effect of mTOR inhibitor on liver transplant recipients only in combination with cyclosporine A (Trotter *et al*., 2001). Also, in patients long time after liver transplantation, the conversion from calcineurin inhibitor regimen to mTOR inhibitor increases the rate of hypercholesterolemia (Shenoy *et al*., 2007; De Simeone *et al*., 2009; Abdelmalek *et al*., 2012). The current study's results align with the above data – the prevalence of hypercholesterolemia in patients treated with everolimus is higher.

A case-control analysis of 13 liver transplant recipients who withdrew all immunosuppressive drugs long-term after liver transplantation showed lower LDL-cholesterol concentration in patients within immunosuppressive therapy than in 22 patients who stayed with immunosuppressive treatment (Duizendstra *et al*., 2019).

García-Pajares and others (Garcia-Pajares *et al*., 2016) in an observational study of 204 Spanish liver transplant recipients have shown that hypertriglyceridemia in the first year after liver transplantation is an important risk factor for the development of metabolic syndrome in the next 5 years.

The current study also analyzed the impact of liver cirrhosis's etiology on dyslipidemia's prevalence. In patients with an autoimmune background of liver cirrhosis, the prevalence of hypertriglyceridemia and hypercholesterolemia was lower. This may be due to a younger age at liver failure diagnosis and a generally healthier lifestyle. Patients with an alcohol abuse history seem less likely to be on a healthy diet and their physical activity is presumably lower. This leads to an increased risk of diabetes mellitus and atherosclerosis.

In the current study, it has been shown that the prevalence of dyslipidemia increases after liver transplantation in comparison to the pre-transplant results. Moreover, hypertriglyceridemia is more frequent in a liver transplant recipient than in the general adult Polish population. Dyslipidemia is a risk factor for cardiovascular diseases, which are currently the most common causes of death in these patients (Watt *et al*., 2010; Rana *et al*., 2019). Available data suggest that the consequence of the increased occurrence of cardiovascular risk factors is overall survival reduction after liver transplantation (Watt *et al*., 2010).

Treatment with hypolipidemic drugs

Patients qualified for liver transplantation mostly had end-stage liver disease, where statins were contraindicated, therefore in most patients with dyslipidemias,only diet was recommended. In the past usage of hypolipidemic drugs in our center was limited. The safety and effectivity of statins after liver transplantation in previous years have not been well established. Nowadays there are some data suggesting the advantages of statin therapy for cardiovascular outcome and decreased risk of hepatocellular cancer recurrence after liver transplantation and us-

age of statins after LTx is more common (Becchetti *et al*., 2022; Kim *et al*., 2023).

Limitations

The presented study has some limitations because the retrospective nature of the study does not allow for establishinga cause-and-effect relationship between the etiology of liver failure and the incidence of dyslipidemia.

CONCLUSIONS

Our study has documented that the prevalence of dyslipidemia might increase after liver transplantation. Further research will be needed to assess if these changes result in associated cardiovascular mortality or morbidity. As these risk factors may be associated with cardiovascular disease that may limit survival, formalized efforts should be made to modify these risk factors and improve the long-term survival of patients undergoing liver transplantation. The incidence of lipid disorders in patients after LTx is related to the etiology of liver cirrhosis before liver transplantation.

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