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Cardiovascular Risk Factors in Patients Before and After Successful Liver Transplantation

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Background: Liver transplantation (LTx) is useful in the treatment of end-stage liver disease. Outcomes of transplantation are dependent upon graft survival and can also be affected by superimposed cardiovascular morbidities. The present retrospective study was performed to assess the prevalence of cardiovascular risk factors before and after LTx.

Material/Methods: A retrospective review of 130 patients undergoing liver transplantation between October 2005 and April 2014 was completed. The mean age of the patients was 49.3±11.9 years. The prevalence of cardiovascular risk factors was assessed before and 2 years after transplantation. The prevalence of cardiovascular risk factors was assessed using a comparison based upon the etiologies of liver disease resulting in transplantation including alcohol, viral, and autoimmune processes using a chi-square analysis.

Results: The prevalence of diabetes mellitus before and 2 years after liver transplantation (LTx) were 18% and 48% (P<0.001). Hypertension was documented in 24% of patients at baseline and 70% after 2 years of follow-up (P<0.001). The prevalence rates of diabetes mellitus before and 2 years after LTx were 18% and 48% (P<0.001). The prevalence of hypertriglyceridemia before and after LTx was 15% and 38%, respectively (P<0.001). Hypercholesterolemia was noted in 16% and 46%, respectively (P<0.001). Thirteen percent of patients before LTx and 18% after were obese (body mass index higher than 30 kg/m^2). The annual incidence of diabetes mellitus, hypertension, hypertriglyceridemia, hypercholesterolemia, and obesity during the first 2 years after LTx was 15%, 23.5%, 15%, 18.5%, and 6%, respectively. Twenty-four percent of patients before and 10% after LTx admitted to tobacco use (P<0.001). The prevalence of diabetes (38% vs 67%, P=0.02), hypertriglyceridemia (19% vs 63%, P<0.001), hypercholesterolemia (28% vs 67%, P=0.002), and obesity (9% vs 33%, P=0.02) was lower in patients with an autoimmune cause of liver cirrhosis in comparison to patients with alcoholic disease.

Conclusions: The prevalence of hypertension and glucose and lipid metabolism abnormalities may increase in patients after liver transplantation. The prevalence of cardiovascular risk factors in patients after LTx may be related to the cause of liver injury before LTx.

Keywords: **Cigarette Smoking • Diabetes Mellitus • Heart Disease Risk Factors • Hypertension • Liver Transplantation**

Abbreviations: **AIH** – autoimmune hepatitis; **ANOVA** – analysis of variance; **BMI** – body mass index; **PSC** – primary sclerosing cholangitis; **WOBASZ II** – Multi-Centre National Population Health Examination Survey

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Background

Liver transplantation is the only useful method in the treatment of end-stage liver disease. In the last decade in Poland, about 300 patients underwent liver transplantation every year [1]. The most common indications for liver transplantation in our population included end-stage liver disease caused by infectious hepatitis, autoimmune diseases, and alcoholic liver disease. Despite decreasing the risk of early graft failure, due to improving surgical techniques and immunosuppressive therapy, in the last 3 decades, long-time survival in liver transplant recipients has not improved [2]. The current focus of the transplant community has shifted to maximizing long-term survival after transplantation. Outcomes of transplantation are dependent upon graft survival and can be affected by superimposed cardiovascular morbidities. It has been shown that cardiovascular diseases are one of the most frequent causes of death in patients after liver transplantation [3,4]. New 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. Watt et al, in long-term follow-up of liver transplant recipients, has shown that some well-known cardiovascular risk factors like hypertension and diabetes mellitus were the risk factors for death in patients who survive 1 year after liver transplantation [4]. According to this observation, routine screening of cardiovascular risk factors seems to be an essential component of comprehensive post-transplant care of these patients.

Population studies in Poland have shown that 32-42.7% of people have hypertension [5,6]. Hypercholesterolemia, diabetes mellitus, and obesity are present in 61.1-64.3%, 6.0-6.7%, and 21.6-24.2% of the Polish adult population, respectively [5,7,8]. Moreover, 27.5% of subjects in Poland use tobacco [5].

The present retrospective study aimed to assess the prevalence of cardiovascular risk factors before and after successful liver transplantation were presented.

Material and Methods

This study involved 130 patients (52 female, 78 male) with age 49.3±11.9 years who underwent liver transplantation in the 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 a functioning transplanted liver for at least 24 months. Patients who died or had liver re-transplantation before 24 months of observation were excluded from 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. A retrospective analysis of patients' medical history was done.

In all patients, the following parameters were analyzed: body mass index (BMI), systolic and diastolic blood pressure, serum concentrations of glucose, cholesterol, and triglycerides, as well as doses of immunosuppressive drugs and tobacco use. Diabetes mellitus was diagnosed based upon 2 fasting serum glucose measurements of ≥7.0 mmol/L (126 mg/dL), random serum glucose or glucose concentration after 2 h of oral glucose tolerance test ≥11.1 mmol/L (200 mg/dL), or treatment with antidiabetic drugs. Systolic blood pressure 140 mmHg or diastolic blood pressure 90 mmHg or higher on 2 visits in the outpatient clinic or usage of antihypertensive agents were the criteria for hypertension. Hypertriglyceridemia was diagnosed when triglycerides serum concentration was ≥1.7 mmol/L (150 mg/dL).

Hypercholesterolemia was defined as a total cholesterol concentration ≥5.0 mmol/L (190 mg/dL). The prevalence of these cardiovascular risk factors was assessed a short time before liver transplantation (at the time of qualification, up to 6 months before the procedure) and 2 years after transplantation. Moreover, the annual incidence of these risk factors during the first 2 years after liver transplantation were analyzed.

Etiology of Liver Disease

Forty-nine patients of the transplanted group had viral hepatitis as a cause of liver failure (among them, 36 patients had hepatitis C, 12 had hepatitis B, 1 had hepatitis A). The cause of liver failure was alcoholic liver disease in 32 patients, autoimmune diseases in 30 patients (12 with primary sclerosing cholangitis, 9 with autoimmune hepatitis, 6 with primary biliary cirrhosis, and 3 with autoimmune hepatitis and primary sclerosing cholangitis overlapping syndrome), Wilson's disease in 2 patients, hemochromatosis in 1 patient, Budd-Chiari syndrome in 2 patients, iatrogenic biliary injures in 2 patients, and unknown cause of liver failure in 10 patients. Patients with liver transplantation due to hepatic cell cancer without liver failure were not included in the analysis.

Immunosuppressive Treatment

Two years after liver transplantation, most patients were using calcineurin antagonists. One hundred 5 patients (81% of all studied group) received tacrolimus, and 13 patients (10% of all studied group) received cyclosporine A. Twelve patients (9% of the studied group) were treated with everolimus. Oral prednisone was used in 120 patients (92% of the studied group), mainly in doses of 5-15 mg/day. Forty-six patients (35% of the studied group) were treated with mycophenolate. In 3 patients,

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the acute rejection of transplanted liver was diagnosed by clinical manifestation and treated by high-dose intravenous methylprednisolone. In another 3 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 performed using Statistica 13.3 software (StatSoft). The Shapiro-Wilk test was used to determine the normality of distribution. Mann-Whitney U, Q Cochrane, chi-square tests, ANOVA, Spearman's rank correlation, and multivariate regression analysis were used in this study. The results are presented as means with 95% confidence intervals.

Ethics

Because of the retrospective character of the study and use of results from blood tests performed as a routine in observation of patients after liver transplantation, ethics committee consent was not required.

Results

Diabetes Mellitus

Diabetes mellitus is a well-known complication associated with the use of steroids and tacrolimus. In the current study, diabetes had been diagnosed in 18% of the pre-transplant population (12% in females, 23% in males). Two years after transplant, diabetes mellitus was noted in 48% of female and 49% of male patients. Thirty percent of patients after liver transplantation developed new-onset diabetes (37% of females, 26% of males). The annual incidence of new-onset diabetes mellitus during the first 2 years after liver transplantation was 15%. As mentioned before, 92% of patients were treated after liver transplantation with prednisone. In the current study, there was no significant difference between the dose of prednisone in patients with and without diabetes mellitus (10.0 vs 10.3 mg/day) or new-onset diabetes mellitus (10.5 vs 10.0 mg/day) and no significant correlation between the dose of prednisone and fasting serum glucose concentration. In our study, the prevalence of diabetes mellitus and the incidence of a new-onset diabetes mellitus after liver transplantation in patients treated with immunosuppressive regimens based on tacrolimus, cyclosporine, and everolimus were similar (45%, 69%, 58% and 29%, 38%, 33%, respectively). A significant positive correlation was found between blood tacrolimus concentration and fasting serum glucose concentration 24 months after transplantation (R=0.25, P=0.02). The regression analysis model with diabetes mellitus 24 months after liver transplantation as a dependent variable and diabetes mellitus before the procedure, sex, immunosuppression regimen, age, and prednisone dose as independent variables showed that the prevalence of diabetes mellitus after liver transplantation depends on age (β=0.34) and diabetes mellitus before transplantation (β=0.42). In a similar model, it has also been shown that new-onset diabetes mellitus after liver transplantation depends on the patient's age (β=0.25).

Hypertension

Hypertension is a well-known complication associated with the use of steroids and tacrolimus. In the current study, 24% of patients (17% of females, 28% of males) had hypertension before liver transplantation. The prevalence of hypertension 2 years after liver transplantation was 70% (65% of females, 73% of males). The annual incidence of new-onset hypertension in the first 2 years after liver transplantation was 23.5%. In patients treated with an immunosuppressive regimen based on cyclosporine, hypertension 2 years after liver transplantation occurred more frequently than in patients treated with a regimen based on tacrolimus or everolimus (100%, 68%, 50%, respectively; cyclosporine vs tacrolimus [P=0.01] and cyclosporine vs everolimus [P=0.003]). Systolic blood pressure in patients treated with cyclosporine, tacrolimus, and everolimus was 145 (137-151) mmHg, 135 (131-139) mmHg, and 134 (121-146) mmHg, respectively. Systolic blood pressure in patients treated with cyclosporine tended to be higher than in patients treated with tacrolimus (ANOVA P=0.09, post hoc cyclosporine vs tacrolimus [P=0.09]). Diastolic blood pressure in patients treated with cyclosporine, tacrolimus, and everolimus was 91 (87-95) mmHg, 88 (86-90) mmHg, and 86 (78-94) mmHg, respectively, without significant differences between groups. There were no significant differences in the prevalence of hypertension in patients treated or not treated with glucocorticosteroids (69% vs 80%). A regression analysis model with hypertension 24 months after liver transplantation as a dependent variable and hypertension before the procedure, sex, immunosuppression regimen, age, and prednisone dose as independent variables showed that the prevalence of hypertension after liver transplantation depends on age (β=0.39), hypertension before transplantation (β=0.27), and immunosuppressive regimen (β=0.27).

Lipid Disorders

Dyslipidemia is a well-known complication associated with the use of steroids, tacrolimus, and everolimus. Hypertriglyceridemia before liver transplantation was found in 15% of patients. The prevalence of hypertriglyceridemia 2 years after liver transplantation was significantly higher, at 38% (37% in females, 38% in males) (P<0.001). The annual incidence of new-onset hypertriglyceridemia in the first 2 years after liver transplantation was 15%. Serum total cholesterol concentration was

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elevated above the normal range in 16% of patients before liver transplantation. After liver transplantation, 60 (46%) patients (50% of females, 42% of males) had hypercholesterolemia ($P<0.001$). The annual incidence of new-onset hypercholesterolemia in the first 2 years after liver transplantation was 18.5%. Our study showed no significant differences in the prevalence of hypertriglyceridemia in patients treated with tacrolimus, cyclosporine, and everolimus (38%, 38%, 42%, respectively). The prevalence of hypercholesterolemia in patients treated with everolimus was higher than in patients treated with tacrolimus or cyclosporine (75%, 42%, 46%, respectively [$P=0.09$]; everolimus vs tacrolimus [P=0.03]).

Body Mass Index and Obesity

Underweight was diagnosed when a body mass index was lower than 18.5 kg/m^2. Overweight was diagnosed when BMI was between 25.0 and 29.9 kg/m^2. Obesity was diagnosed when BMI was 30.0 and more. Before liver transplantation, 3% of patients (8% of females, none of the males) were underweight, 37% (23% of females, 46% of males) were overweight, and 13% were obese (6% of females, 18% of males). The prevalence of obesity was 18% (15% in females, 19% in males).

After liver transplantation, only one-third of patients had normal body mass index 2 years after liver transplantation. Four of the patients (3%, 3 females, 1 male) were underweight. Overweight occurred in 62 (48%) patients (42% of females, 51% of males). The prevalence of obesity was 18% (15% in females, 19% in males). The annual incidence of new-onset obesity in the first 2 years after liver transplantation was 6%. In patients treated with tacrolimus, cyclosporine, and everolimus, obesity occurred in 19%, 8%, and 17%, respectively, by 2 years after liver transplantation. Overweight occurred in 47%, 54%, and 50% of patients treated with tacrolimus, cyclosporine, and everolimus, respectively. There were no differences in the prevalence of obesity or overweight between groups. There were also no differences in the prevalence of obesity and overweight in patients treated or not treated with prednisone (17% vs 30% and 47% vs 60%, respectively).

Tobacco Use

Before transplantation, 31 (24%) patients used tobacco (17% of females 28% of males). At 24 months after liver transplantation, 13 (10%) patients (8% of females and 12% of males) reported using tobacco. Most patients who stopped tobacco use did so immediately after transplantation.

Etiology of Liver Failure and Cardiovascular Risk Factors

In an additional analysis, patients were divided into 3 liver disease etiology groups – alcohol, viral, and autoimmune causes – with the respective percentages. Diabetes mellites occurred in 38% of patients with an autoimmune cause of liver insufficiency, 49% due to viral disease, and 67% due to alcoholic liver disease (autoimmune vs alcohol [$P=0.02$]). Patients with the autoimmune disease had a lower prevalence of hypercholesterolemia than patients with alcoholic disease of the native liver (28% vs 67%, $P=0.002$). There was also a higher prevalence of hypertriglyceridemia in patients with alcoholic liver disease than in those with an autoimmune background (63% vs 19%, $P<0.001$). The annual incidence of new-onset hypertension (25%, 27.5%, 23.5%, NS); new-onset diabetes mellitus (12.5%, 16.5%, 20%; NS); new-onset hypertriglyceridemia (9.5%, 13.5%, 28.5%; $P=0.003$; autoimmune vs alcohol $P=0.002$, viral vs alcohol, $P=0.007$); new-onset hypercholesterolemia (12.5%, 18.5%, 26.5%, $P=0.06$; autoimmune vs alcohol, $P=0.02$), obesity (3%, 3%, 11.5%, $P=0.03$; autoimmune vs alcohol, $P=0.05$, viral vs; alcohol, $P=0.02$) were in autoimmune, viral, and alcoholic liver disease, respectively. Only 1 in 32 patients with autoimmune etiology of liver failure used tobacco, compared to 4 in 30 patients with alcoholic liver disease.

Discussion

The prevalence of cardiovascular risk factors increased over a 2-year survey of patients undergoing liver transplantation at our facility. Another essential piece of information is that the prevalence of the most cardiovascular risk factors 2-years after liver transplantation is higher than their prevalence in the adult population in Poland.

Diabetes mellitus is a well-known complication of liver transplantation [9]. It was shown that in the first and third year after transplantation, 25% and 32% of liver recipients, respectively, had diabetes mellitus [10,11]. In the current study, 2 years after liver transplantation, 44% of patients had diabetes mellitus. Other studies suggest that the incidence of post-transplant diabetes mellitus ranges from 3.3% to 30.8% yearly, with an incidence of 10.8% to 33% in the first year after liver transplantation [12]. Another study showed that the risk factors of post-transplant DM were male sex, pre-transplant DM, alcohol abuse, and mycophenolate treatment [13]. In the present study, it was found that new-onset post-transplant diabetes affects 37% of females and 26% of males. It was more common in patients with alcoholic liver disease than in other groups (autoimmune vs viral vs alcohol, 25%, 33%, 40%, respectively). Our results confirm that post-transplant diabetes depends on pre-transplant diabetic status, but not on the other above-quoted dependences. Small prednisone doses did not increase the risk of diabetes development or fasting serum glucose concentration after liver transplantation.

Two years after liver transplantation, 70% of liver transplant recipients developed hypertension. That is a remarkable

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difference compared to the general adult Polish population. The epidemiological study NATPOL 2011 has shown that 33% of the adult Polish population with comparable age have hypertension [5]. Another population study (WOBASZ II – Multi-Centre National Population Health Examination Survey) has shown that the prevalence of hypertension in the Polish population is 42.7% [6]. The present study results are similar to those obtained by Watt et al (2010), where hypertension was present in only 17% before liver transplantation, and it increased to 56% by 1 year after liver transplantation [13]. In the other study, which included 598 patients after liver transplantation, hypertension prevalence increased after liver transplantation and occurred in 30% before transplantation and in 34%, 44%, and 56% after 1, 4, and 7 years, respectively [10]. In another study, Hara et al (2015) found that the prevalence of hypertension increased from 19% before transplantation to 35% after transplantation [14]. A 2016 study showed that the prevalence of hypertension increases significantly during the first 24 months after liver transplantation [4]. The high prevalence of hypertension in these patients seems to be partially caused by the hypertensive properties of immunosuppressants. Our results agree with those of Hernandez et al (2003), who found that treatment with an immunosuppressive regimen based on cyclosporine, in comparison to tacrolimus, is associated with a higher risk of hypertension in liver transplant recipients (73% vs 63%) [15]. Moreover, the high prevalence of chronic kidney disease (CKD) has been shown in patients after successful liver transplantation. CKD occurred in 39% of patients 24 months after liver transplantation. CKD also may predispose to hypertension in liver transplant patients [16].

According to available data, the prevalence of dyslipidemia in liver transplant recipients differs greatly among studies, and it is present in 14-71% of patients [6,17,18]. In the current study, 46% of patients had hypercholesterolemia 2 years after transplantation, which is less than in the general adult Polish population (NATPOL 2011 – 61.1%, WOBASZ II – 64.3%) [5,7]. An opposite tendency is present for hypertriglyceridemia, as patients after liver transplantation present it more frequently than in the general population (38% vs 21% – NATPOL 2011) [5]. Another study (1996) showed that hypertriglyceridemia is even more common in the first year after liver transplantation than during long-term observation [18]. The prevalence of these abnormalities was significantly lower before liver transplantation – hypercholesterolemia 16% vs 46% and hypertriglyceridemia 15% vs 38% – but it may be influenced by the state of malnutrition in patients with end-stage liver disease qualified to liver transplantation. The effect of immunosuppressive therapy, especially steroids and cyclosporine A, may also impact these abnormalities [18,19].

It has been shown that 30-70% of liver transplant recipients are obese, and the risk of that disorder increases with time after transplantation [14,20]. In the current study, fewer patients were obese – 18% at 2 years after liver transplantation. Compared to the general Polish population, fewer liver transplantation recipients were obese. According to NATPOL 2011, 21.6% of people in Poland are obese [5], and in the WOBASZ II study, obesity was found in 24.2% [8]. Due to the retrospective nature of the current study – analysis of BMI, without examination of fluid retention and assessment of lipid tissue – the prevalence of overweight and obesity before liver transplantation seems to be overestimated. Ascites and peripheral edemas in patients with end-stage liver cirrhosis are more likely to have increased BMI than excess fat mass.

In the present study, 24% of patients before liver transplantation used tobacco, and it decreased to 10% after liver transplantation. In comparison, 27.5% of subjects of the general adult Polish population (NATPOL 2011) reported tobacco use [5]. In the WOBASZ II study, the prevalence of tobacco use was 29.9% in men and 20.5% in women [20]. According to a few studies, the prevalence of tobacco use after liver transplantation seems to be very different in various regions of the world and ranges from 15% to even 61% [17,21-23]. The low tobacco use rates may be related to better adherence to medical recommendations, which is essential after organ transplantation. Moreover, patients after liver transplantation have more frequent contact with a physician in the outpatient clinic, which may be an important factor that helps with cessation of tobacco use.

The current study also analyzed the impact of the etiology of liver cirrhosis on the prevalence of cardiovascular risk factors. In patients with an autoimmune background of liver cirrhosis, the prevalence of diabetes mellitus, hypertriglyceridemia, hypercholesterolemia, and obesity were lower. This may be due to younger age at liver failure diagnosis and generally healthier lifestyle. Patients with an alcohol abuse history seem to be less likely to have a healthy diet and regular physical activity, leading to an increased risk of developing diabetes mellitus and atherosclerosis.

We found that the prevalence of most of the analyzed cardiovascular risk factors increases after liver transplantation. Moreover, most of these factors are more frequent in a liver transplant recipient than in the general Polish population. Cardiovascular diseases are among the most common causes of death in these patients [2,4]. Available data suggest that the consequence of increased occurrence of cardiovascular risk factors is overall survival reduction after liver transplantation [4].

The present study has some limitations. Due to the retrospective character of the study, we cannot determine a cause-and-effect relationship between etiology of liver failure and incidence of the above-mentioned cardiovascular risk factors. The present study wa a single-center study in a Polish transplantation site, which is another limitation.

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Conclusions

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

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