High Frequency of Arterial Hypertension in Patients After Liver Transplantation

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ABSTRACT

Background. Cardiovascular diseases are among the most frequent causes of patient death after liver transplantation. The aim of this retrospective clinical study was to estimate the prevalence of arterial hypertension among patients after successful liver transplantation and the role of immunosuppressive drugs in the pathogenesis of hypertension in these patients.

Patients and Methods. A total of 88 patients (age 47 .5 ± 12.1 years; 33 women and 55 men) who had undergone successful liver transplantation and completed 24 months follow-up were studied. The results are presented as means with standard deviations.

Results. At 1, 12, and 24 months after liver transplantation, the prevalences of hypertension were 44.3%, 54.5%, and 62.5%, respectively. Systolic and diastolic blood pressure in these months were 124.1 ± 14.8, 132.8 ± 19.1, and 135.2 ± 17.3 mm Hg and 83.3 ± 12.0, 87.3 ± 11.1, and 87.9 ± 11.1 mm Hg, respectively. The estimated glomerular filtration rates were 77.8 ± 32.3, 80.3 ± 30.8, and 78.8 ± 29.1 mL/min/1.73 m^2, respectively. Arterial hypertension was significantly more frequent in patients treated with cyclosporine A than in those treated with tacrolimus ($P = .004$) or everolimus ($P = .005$). In patients treated with tacrolimus, a positive correlation was found between tacrolimus blood concentration and systolic blood pressure ($R = 0.34$; $P = .01$) and a negative correlation was found between estimated glomerular filtration rate and systolic blood pressure ($R = -0.28$; $P = .02$).

Conclusions. Based on study findings, the following conclusions were drawn: arterial hypertension occurs in more than 50% of patients after liver transplantation (significantly higher frequency than in the general population); calcineurin inhibitors may participate in the pathogenesis of arterial hypertension in patients after successful liver transplantation; and the clinical importance of these findings and the influence on cardiovascular outcome of the liver transplant recipients need further investigation.

ONE of the adverse effects of immunosuppressive therapy in patients after liver transplantation is an increase in blood pressure. The use of calcineurin inhibitors and glucocorticoids are the well-known risk factors for hypertension [1,2]. Moreover, cardiovascular diseases are a common cause of premature death in patients after liver transplantation [3,4]. The aim of this study was to estimate the prevalence of arterial hypertension in patients after successful liver transplantation and the role of immunosuppressive drugs in the pathogenesis of hypertension in these patients.

PATIENTS AND METHODS

The medical records of patients who underwent liver transplantation in our University Hospital treated at the Transplantation Outpatient were analyzed. A total of 88 patients (33 women and

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55 men) completed the 2-year follow-up. The mean age in the time of liver transplantation was 47.5 ± 12.1 years. All transplanted organs were obtained from deceased donors. The cause of liver failure in the studied group of patients were viral hepatitis in 25 patients (28%), including hepatitis C in 18 patients, hepatitis B in 6 patients, and hepatitis A in 1 patient; autoimmune liver disease in 24 patients (27%), including primary sclerosing cholangitis (PSC) in 10 patients, autoimmune hepatitis (AIH) in 6 patients, primary biliary cirrhosis in 5 patients, and AIH and PSC overlapping syndrome in 3 patients; cirrhosis caused by ethanol abuse in 16 patients (18%); hepatocellular carcinoma in 13 patients (15%); Wilson's disease in 2 patients; hemochromatosis in 1 patient; Budd-Chiari syndrome in 1 patient; and unknown in 6 patients (7%).

In the second year after the transplantation, 66 patients (75%) were treated with an immunosuppressive regimen that was based on tacrolimus, 12 patients (14%) based on cyclosporine A and 10 patients (11%) based on everolimus. A total of 81 patients (92%) received low doses (5–15 mg/d) of prednisone, and 35 patients (40%) received mycophenolate mofetil in doses 500–2000 mg/d. Clinically overt acute rejection treated by high doses of intravenous methylprednisolone occurred in 2 patients treated with an immunosuppressive regimen based on tacrolimus. In 1 patient treated with an immunosuppressive regimen based on tacrolimus and 1 patient with an immunosuppressive regimen based on cyclosporine A, it was necessary to transiently increase the dose of prednisone to 60 mg/d in the early period (ie, during the first 3 months) after liver transplantation.

The following parameters were analyzed in the study group: systolic and diastolic blood pressure, estimated glomerular filtration rate (eGFR; calculated with the Modification of Diet in Renal Disease [MDRD] formula), and doses of immunosuppressive drugs and tacrolimus blood concentrations. Systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg measured during 2 following appointments in the outpatient clinic or use of antihypertensive treatment were the criteria for hypertension diagnosis. The criteria for diabetes were fasting plasma glucose level ≥7.0 mmol/L twice, random plasma glucose level ≥11.1 mmol/L, or treatment with antidiabetic drugs. The prevalences of hypertension and diabetes mellitus before liver transplantation were based on the medical history of patients and available medical data.

The Shapiro-Wilk test was used to determinate whether the variables were distributed normally. The Student t test, Mann-Whitney U test, χ^2 test, analysis of variance (ANOVA), Cochran Q test, and Spearman correlation were used in the study. The results are presented as means with standard deviations.

RESULTS

Arterial hypertension 1, 12, and 24 months after liver transplantation occurred in 44.3%, 54.5%, and 62.5% patients, respectively (Fig 1). The prevalence of arterial hypertension increased significantly with the time after liver transplantation ($P < .003$; Cochran Q test). The mean systolic and diastolic blood pressure increased with the time after liver transplantation and in 1, 12, and 24 months after liver transplantation were 124.1 ± 14.8 mm Hg, 132.8 ± 19.1 mm, Hg, and 135.2 ± 17.3 mm Hg ($P = .0001$, ANOVA) and 83.3 ± 12.0 mm Hg, 87.3 ± 11.1 mm Hg, and 87.9 ± 11.1 mm Hg ($P = .007$, ANOVA), respectively. eGFR in the

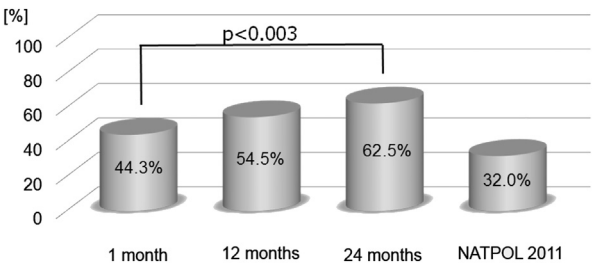

Fig 1. Prevalence of hypertension after liver transplantation and in general population of Poland (results of the NATPOL 2011 study) [3].

studied group 1, 12, and 24 months after liver transplantation were 77.8 ± 32.3, 80.3 ± 30., and 78.8 ± 29.1, respectively. Two years after liver transplantation, hypertension occurred in 57.6% of patients treated with an immunosuppressive regimen based on tacrolimus, in 50% of patients treated by immunosuppressive regimen based on everolimus, and in all patients (100%) treated with cyclosporine A. The incidence of hypertension was significantly higher in patients treated with cyclosporine A than in 2 other groups (cyclosporine A vs tacrolimus: $P = .004$; cyclosporine A vs everolimus: $P = .005$; χ^2 test). In patients treated with cyclosporine and tacrolimus, the prevalence of hypertension 24 months after liver transplantation was significantly higher than before liver transplantation (hypertension diagnosis before liver transplantation was based on medical history and available medical data; $P < .001$). The prevalence of diabetes after liver transplantation was significantly higher than before liver transplantation in patients treated with tacrolimus ($P < .001$). There were no significant differences in systolic and diastolic blood pressure and eGFR in patients treated with different immunosuppressive regimens (Table 1). Multivariate analysis in which the prevalence of hypertension 24 months after liver transplantation was the dependent variable and age, sex, prevalence of hypertension before liver transplantation, eGFR before and 24 months after liver transplantation, and immunosuppressive treatment regimen were independent variables showed that the prevalence of hypertension 24 months after liver transplantation depended on age ($P < .001$), prevalence of hypertension before liver transplantation ($P = .003$), and immunosuppressive regimen ($P = .007$).

Two years after liver transplantation in the group of patients treated with an immunosuppressive regimen based on tacrolimus, a negative correlation was found between eGFR and systolic blood pressure ($R = -0.28$; $P = .02$). Moreover, in this group of patients, a positive correlation was observed between tacrolimus blood concentration and systolic blood pressure ($R = 0.34$; $P = .01$). There was no significant correlation between tacrolimus blood concentration and eGFR 24 months after liver transplantation ($P = .06$). There was also no significant correlation between dose of mycophenolate mofetil or prednisone and systolic blood pressure.