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Cardiovascular assessment in liver transplant candidates

Ocena kardiologiczna kandydatów do przeszczepienia wątroby

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Abstract

Introduction. Liver transplantation (LT) is at high-risk for cardiovascular events. Therefore, candidates have pre-operative cardiological diagnostics to lower the risk of post-surgical complications. The purpose of this study was to analyse a cohort of liver recipients from one transplant centre in Poland, to evaluate the accuracy of pre-transplant cardiac assessment in the prediction of short- and long-term outcomes, and to investigate any correlation between cardiovascular events and patient characteristics.

Material and methods. This retrospective study was conducted among 141 consecutive patients evaluated for LT in 2017–2018. Recipients under the age of 40 were excluded. All candidates had electrocardiography, echocardiography and their functional capacity was assessed. Patients with metabolic equivalent < 4 or clinical indications were subjected to stress echocardiography. Patients underwent at least one year post-transplant follow-up to detect late cardiovascular complications.

Results. 141 patients were evaluated, and 116 patients were finally enlisted. Four recipients were disqualificated for cardiological reasons, and the remaining 21 were rejected for non-cardiological reasons. There were no early cardiovascular complications in a 30-day follow-up. Late cardiovascular complications were observed in four transplanted patients. Diabetes increases cardiovascular complications ($p = 0.001$).

Conclusion. The applied cardiological diagnostics allowed early cardiovascular events to be avoided. Very careful post-transplant monitoring is indicated, particularly in diabetes patients, due to the greater risk of long-term complications. Post-transplant immunosuppression and liver function recovery may contribute to this.

Key words: cardiovascular disease, cardiovascular events, liver transplantation, NODAT, NATPOL 2011

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Introduction

Cardiovascular disease (CVD) is a group of diseases that involve the heart and/or blood vessels. CVD includes coronary artery disease (CAD) which is a disorder resulting from impaired blood supply to the heart muscle caused by the narrowing of coronary vessels by the formation of atherosclerotic plaques. This leads to myocardial ischaemia because the delivery of oxygen and nutrients to the myocardium is insufficient [1]. Atherosclerotic changes in the vessels develop over the years. Their severity depends on genetic predispositions and the presence of risk factors for CAD: see Table 1 [2].

In patients with cirrhosis, cardiac complications develop and intensify with the progression of liver disease. Hyperdynamic circulation is the result of peripheral

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Table 1. Risk factors for coronary artery disease

Non-modifiable	Modifiable
Age	High blood pressure
Sex	Smoking
Family history	High lipid levels
History of thromboembolism	Diabetes
	Obesity
	Lack of exercise
	Chronic kidney disease
	Diseases of arteries (atherosclerosis of carotid arteries, arteries of lower limbs)

vasodilation after overproduction of nitric oxide due to portal hypertension. Reduced vascular resistance increases cardiac output. This leads to the development of hepatic cardiomyopathy due to impairment of left ventricle ejection fraction, or insufficient cardiac output in response to physical exertion, stress or pharmacological stimulation. Additionally, diastolic disorders appear as well as electrical dysfunction of the cardiac conduction system during the repolarisation period [QT prolongation in electrocardiography (ECG)]. Hepatic cardiomyopathy develops irrespective of underlying disease aetiology. Usually clinically silent cardiomyopathy manifests itself in response to stress, which in this case may be prolonged surgery [3, 4].

Therefore, patients with liver cirrhosis during evaluation for liver transplantation (LT), according to the European Cardiac Society (ESC) recommendations, undergo a detailed cardiac diagnostics due to the extent of surgery and the existence of multiple co-morbidities, which are also risk factors for CAD. Liver transplant candidates are in the high risk group of cardiovascular events in the perioperative period (a greater than 5% 30-day risk of myocardial infarction, cardiac arrest, life-threatening arrhythmias, stroke and death from cardiovascular causes) due to vascular changes after transplantation such as increased systemic vascular resistance, decreased cardiac output and increased pulmonary capillary wedge pressure [5–8].

Preoperative tests for high risk surgery, such as LT, include ECG and resting echocardiography [9]. Additionally, the patient's functional capacity, measured in metabolic equivalents (METs) of tasks, is taken into account. When METs are below 4, which in practice means an inability to walk up two flights of stairs, or when the clinical picture suggests the presence of CAD, extra stress tests are carried out.

Non-invasive tests, predicting long-term mortality (more than 30 days after surgery) from cardiac events include dobutamine stress echocardiography (DSE), cardiac magnetic resonance, and myocardial perfusion imaging (MPI). Patients with optimal exercise tolerance, even with CAD risk factors, have a good perioperative prognosis and do not require additional testing [8, 10].

Coronary angiography, the gold standard for coronary artery assessment, is rarely performed due to the invasive nature of the examination and the high risk of complications in patients with end-stage liver failure, such as the greater risk of bleeding than in the general population with a more frequent need for transfusion of blood products [11], infections and contrast-induced nephropathy, as well as the high sensitivity of non-invasive tests.

The aim of this study was to investigate the accuracy of pre-transplant cardiovascular assessment in predicting short- and long-term cardiovascular outcomes, and to analyse the correlation between cardiovascular events and patient characteristics.

Material and methods

The study group consisted of 141 consecutive cirrhotic patients aged from 40 to 70 years, who were hospitalised in 2017–2018 in one transplant centre for the purpose of qualifying for LT. Recipients under 40 years of age were excluded due to the low incidence of cardiovascular disease in this group.

In this retrospective assessment, the occurrence of CAD was analysed and risk factors were examined on the basis of medical tests (fasting lipids levels, glucose and creatinine levels) and cardiological studies. An ECG and an echocardiography with the evaluation of left ventricular ejection fraction (LVEF) and diastolic function were performed in all subjects. In addition, a DSE was performed in patients with a low functional capacity (assessed during the interview with the patient) or with clinical manifestation of CAD (ischaemic changes in ECG or segmental contractility abnormalities in the heart ultrasound) [12].

DSE was performed after stopping the β-blocker three days earlier to allow the target heart rate to be obtained. The baseline characteristics of the study cohort are set out in Table 2. The table excludes patients disqualified for non-cardiological reasons. Early cardiovascular complications (within 30 days post-op) and late complications (30+ days after surgery) were analysed.

Statistical analyses were carried out using the R program. All parameters are presented as mean (standard deviation) or counts (percentages) where appropriate. The effect of diabetes on the appearance of cardiovascular events was assessed using Fisher's test. Statistical significance level was assumed for p-value < 0.05.

Results

The main indication for liver transplantation was end-stage chronic hepatitis C.

Table 2. Baseline characteristics of study group

Parameter	All patients N = 120
Age at time of qualification	
Mean [years ± SD]	57 [± 6.91]
Median [range]	59 [40–70]
Female, N [%]	45 (37.5%)
Male, N [%]	75 (62.5%)
Aetiology of liver disease	
Hepatitis C	46 (38.33%)
Alcoholism	31 (25.83%)
Hepatitis B	15 (12.5%)
PBC/PSC	12 (10.0%)
Autoimmune	6 (5.0%)
Cryptogenic	3 (2.5%)
Other	7 (5.83%)
Risk factors of CAD	
Hypertension	46 (38.33%)
Diabetes mellitus	37 (30.83%)
Smoking	33 (27.5%)
Obesity	28 (23.33%)
Hyperlipidemia	24 (20.0%)
Chronic kidney disease	11 (9.17%)
Peripheral artery disease/history of thromboembolism	6 (5.0%)

SD — standard deviation; PBC — primary biliary cirrhosis; PSC — primary sclerosing cholangitis; CAD — coronary artery disease

Twenty one patients were excluded from the transplant list for non-cardiological reasons.

Among 120 patients included in the analysis, 62 (51,67%) had at least two risk factors for CAD. Among those patients were 42 men (67.74%) and 20 women (32.26%). Thirty one patients were burdened with more than two risk factors. The most frequent risk factors were hypertension, diabetes, smoking, and obesity.

During preoperative cardiological diagnosis, 24 dobutamine stress echo tests were performed. Four patients (two women and two men) were disqualified from LT for cardiological reasons. DSE was positive in two cases. One patient initially had a segmental contractility disorder in the resting echocardiography. In one case, severe aortic stenosis was diagnosed. The characteristics of these patients are set out in Table 3. It is worth noting that all of them suffered from diabetes.

There were no cardiovascular events during, or within 30 days after, transplantation. In four male patients, cardiovascular events in the form of myocardial infarction were revealed during long-term follow-up (all within the first year of observation). There were no cardiovascular incidents in women. The characteristics of patients who had a heart attack are set out in Table 4.

Among many risk factors in patients diagnosed with coronary artery disease during transplant qualification and in patients with late cardiovascular complications, diabetes deserves attention, because it occurred in 7/8 patients (87.5%).

Diabetes increases the risk of cardiovascular complications in patients with liver cirrhosis (p value = 0.001).

Table 3. Characteristics of patients disqualified from liver transplantation (LT)

Studied parameter	Patient 1	Patient 2	Patient 3	Patient 4
Age at time of qualifying for LT	64	56	63	67
Cause of liver cirrhosis	HBV	Alcoholism	Alcoholism	HCV
Risk factors	Diabetes	Diabetes Smoking	Diabetes Chronic kidney disease Hypertension Previous myocardial infarction Obesity	Diabetes Previous myocardial infarction Smoking
Dobutamine stress echo (DSE)	Positive	Not performed due to severe aortic stenosis in transthoracic ultrasound	Positive	Ischaemic negative, but new segmental contractility disorder in resting echocardiography
Coronary angiography	Multivessel coronary artery disease	No coronary artery stenosis	Not carried out (patient's decision)	Multivessel coronary artery disease

HBV — hepatitis B virus; HCV — hepatitis C virus

Table 4. Characteristics of patients with late cardiovascular complications

Studied parameter	Patient 1	Patient 2	Patient 3	Patient 4
Age at time of qualifying for LT	66	64	59	70
Cause of liver cirrhosis	HBV	HCV	Alcoholism	Other (haemochromatosis)
Risk factors	Smoking Chronic kidney disease	Hypertension Diabetes Smoking Hyperlipidemia Peripheral artery disease	Diabetes Chronic kidney disease	Diabetes Hypertension
Dobutamine stress echo (DSE) in preoperative period	Negative	Negative	Not performed due to good exercise tolerance	Not performed due to good exercise tolerance
Time from LT to cardiac death	6 months	42 days	3 months	10 months

LT — liver transplantation; HBV — hepatitis B virus; HCV — hepatitis C virus

Discussion

The pre-operative cardiological evaluation used in our study allowed us to avoid short-term cardiovascular complications, because 100% of patients survived the early perioperative period, and no cardiovascular events were noted.

Late cardiovascular complications occurred in a few patients despite correct results during preoperative tests, including negative DSE which has a confirmed high negative predictive value in the diagnosis of CAD [12, 13]. These cases mainly concerned patients with diabetes. Liver transplant recipients are at risk of worsening glucose levels after surgery among others because of immunosuppressive treatment (glucocorticosteroids, calcineurin inhibitors and mammalian target of rapamycin inhibitors) that increases liver gluconeogenesis after recovery and reduces tissue glucose catabolism [14–16]. For the above reasons, the risk of hyperglycaemia is also increased in non-diabetic patients (NODAT, new onset diabetes after transplantation) [17–19].

Another problem in liver transplant recipients is obesity. More than 40% of recipients become overweight or obese within the first year post-LT [17, 18]. Due to the changes in transplant indications observed in recent years (the increasing incidence of non-alcoholic fatty liver disease as a cause of liver cirrhosis), the risk of metabolic syndrome in liver recipients, and thus diabetes, increases [20].

We must underline that in our study group there were no clearly diagnosed cases of non-alcoholic steatohepatitis (NASH) as an indication for liver transplantation. However, we cannot rule out that so-called cryptogenic cirrhosis (three cases) or cirrhosis of unknown aetiology (seven cases) had been the result of burnt out steatohepatitis, but such an aetiology was not confirmed in the explant pathology. Lack of NASH cases in our series may partly explain the low incidence of CAD in the studied group.

The prevalence of diabetes increases from 15% before surgery to 40% after transplantation [21]. Therefore, a careful post-transplant observation towards CAD is mandatory, especially in patients with previously diagnosed diabetes, but also in patients with risk factors for diabetes or new-onset diabetes mellitus after transplantation (NODAT).

Likewise, lipid levels are lower in end-stage liver disease than in the general Polish population based on data from the NATPOL 2011 study [22]. In male patients from the study group, mean value of total cholesterol was 154.7 mg/dL versus 212.4 mg/dL in the general population, females 168.0 mg/dL vs. 214.4 mg/dL, respectively. After surgery, the liver regains its ability to produce cholesterol and thereby lipid levels significantly increase, and this phenomenon also requires further attention.

Therefore, the post-transplant assessment should always include regular monitoring of glucose level, HbA_{1c} and lipid parameters, as well as the performance of re-imaging tests (resting and stress echocardiography) if necessary.

Conclusions

The preoperative cardiological diagnostics before liver transplantation is effective because it allows the avoidance of short-term death and complications from cardiovascular causes in most instances. In this study, there were no cardiovascular events within 30 days of surgery. The presence of diabetes is associated with a higher risk of long-term cardiac deaths, and therefore requires a more accurate assessment, both before and after transplantation.

Conflict(s) of interest

The authors declare no conflict of interest.

Streszczenie

Wstęp. Transplantacja wątroby (LT) należy do operacji obarczonych dużym ryzykiem powikłań sercowo-naczyniowych, dlatego pacjenci kwalifikowani do przeszczepienia są poddawani ocenie kardiologicznej, by obniżyć ryzyko powikłań pooperacyjnych. Celem badania była analiza grupy potencjalnych biorców wątroby z jednego ośrodka transplantacyjnego w Polsce i ocena wpływu kwalifikacji kardiologicznej na występowanie wczesnych i późnych powikłań sercowo-naczyniowych. Badano również korelacje zdarzeń sercowo-naczyniowych z charakterystyką tych pacjentów.

Materiał i metody. Retrospektywnie analizowano 141 kolejnych pacjentów kwalifikowanych do operacji w latach 2017–2018. Z analizy wykluczono osoby poniżej 40. roku życia. U wszystkich kandydatów wykonano elektrokardiografię i echo serca oraz oceniano ich wydolność fizyczną. U pacjentów z małą wydolnością fizyczną, poniżej 4 ekwiwalentów metabolicznych, lub z kliniczną manifestacją choroby wieńcowej przeprowadzono echokardiografię obciążeniową z podaniem dobutaminy. Pacjentów poddano co najmniej rocznej obserwacji po przeszczepieniu w celu wykrycia późnych powikłań sercowo-naczyniowych.

Wyniki. Przeanalizowano dane dotyczące 141 chorych, spośród których ostatecznie 116 zostało zakwalifikowanych do operacji. Czterech chorych zdyskwalifikowano w toku diagnostyki kardiologicznej, a 21 odrzucono z przyczyn niekardiologicznych. Nie stwierdzono powikłań wczesnych. Późne komplikacje sercowo-naczyniowe wystąpiły u 4 biorców. Cukrzyca zwiększa ryzyko powikłań sercowo-naczyniowych ($p = 0{,}001$).

Wnioski. Zastosowana diagnostyka kardiologiczna pozwoliła uniknąć powikłań sercowo-naczyniowych w okresie okołooperacyjnych. Zaleca się dalszą dokładną obserwację biorców, szczególnie cierpiących na cukrzycę, ze względu na wyższe ryzyko odległych powikłań sercowo-naczyniowych. Odpowiadać za to może między innymi potransplantacyjna immunosupresja oraz powrót funkcji metabolicznej wątroby.

Słowa kluczowe: choroba układu sercowo-naczyniowego, zdarzenia sercowo-naczyniowe, transplantacja wątroby, NODAT, NATPOL 2011

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