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HEART TRANSPLANTATION IN DIABETIC RECIPIENTS

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Introduction. Heart transplantation (HT) in patients with preexisting type 2 diabetes (T2D) is associated with high risk of infectious and non-infectious complications (renal dysfunction, multifocal atherosclerosis, transplant coronary artery disease, etc.) that can negatively affect recipient survival in the early and late periods after HT. **Objective:** to assess the effect of pre-transplant T2D on early and long-term outcomes of HT based on a single-center retrospective study. **Materials and methods.** The study enrolled 891 recipients who underwent HT within the period 2011 to 2018, and were divided into two groups: main group (T2D) – recipients with pretransplant T2D (n = 80, 9.0%) and the control group (T2D-free) – recipients without T2D (n = 811, 91.0%). Recipients from both groups did not differ in terms of HT urgency (UNOS status) and the need for pre-transplant mechanical circulatory support (MCS). **Results.** At the time of the HT, recipients from the T2D group were older than the T2D-free recipients (54 [46; 59] years *vs* 48 [35; 56] years, $p < 0.001$), they had a higher weight ($p < 0.001$) and body mass index ($p < 0.001$), coronary heart disease was more often their main disease (65.0% *vs* 36.5%, $p < 0.001$), they had higher transpulmonary gradient (10.0 [7.0; 12.0] mmHg *vs* 9.0 [6.0; 12.0] mmHg, $p = 0.024$) and pulmonary vascular resistance (2.9 [2.2; 4.0] Wood units *vs* 2.5 [1.8; 3.4] Wood units, $p = 0.038$). In the pre-transplant period, the T2D group had pronounced manifestations of renal dysfunction and increased comorbidity. Recipients in both groups did not differ in terms of cardiac donor parameters, graft ischemia time, cardiopulmonary bypass time, and incidence of severe early heart graft dysfunction requiring MCS (12.5% *vs* 10.7%, $p = 0.74$). In the early post-transplant period, the T2D group had high requirements (100% *vs* 28.0%, $p < 0.001$) and higher doses of insulin therapy. More pronounced manifestations of renal dysfunction and a greater need for renal replacement therapy (51.4% *vs* 27.9%, $p = 0.003$) did not affect artificial ventilation and ICU duration (6 [5; 10] days *vs* 6 [5; 10] days, $p = 0.098$), as well as hospital mortality (8.8% *vs* 8.5%, $p = 0.895$). The presence of pre-transplant T2D had no negative effect on the incidence of acute cardiac graft rejection, progression of transmissible coronary atherosclerosis, incidence and severity of cardiac graft vasculopathy, structure and severity of distant infectious and non-infectious complications, and post-transplant survival. **Conclusion.** With correct selection of recipients and choice of optimal tactics for their post-transplant management, the presence of pre-transplant T2D has no negative effect on early and long-term outcomes of HT.

Keywords: heart transplantation, diabetes mellitus.

INTRODUCTION

Heart transplantation (HT) remains the most effective method of treating patients with end-stage congestive heart failure (CHF) developing against the background of various acquired or congenital heart conditions. Many patients with end-stage CHF have concomitant diseases that can act as an absolute or relative contraindication to HT or be a factor negatively affecting early and long-term HT outcomes [1; 2; 3].

Diabetes mellitus, especially type 2 diabetes (T2D), not only often contributes to the course of CHF, but also promotes its development and progression [4; 5]. There is a 12% prevalence of type 2 diabetes among CHF patients, reaching 24% among patients with its most severe clinical manifestations [4; 5]. Many patients considered as possible heart recipients have T2D, which is still considered a relative contraindication to HT [1; 2; 6; 7]. Surgeons are always extremely cautious in performing HT in patients with preexisting T2D due to increased risk of infectious and non-infectious complications (renal dysfunction, multifocal atherosclerosis, transplant coronary artery disease, etc.), as well as difficulties in selecting the optimal immunosuppressive therapy tactics for this carbohydrate metabolism disorder. In spite of the fact that some studies have shown satisfactory early and long-term post-transplant survival, effective implementation of HT in patients with concomitant T2D is still a challenging clinical task and is the subject of scientific discussion and research [1; 3; 8]. In recent years, development of an HT program at Shumakov National

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Medical Research Center of Transplantology and Artificial Organs is associated, among other things, with increased number of HT in recipients with comorbid diseases, including T2D [9; 10].

The **aim** of the study is to evaluate the early and long-term outcomes of HT in patients with end-stage CHF and concomitant T2D.

MATERIALS AND METHODS

Between 2011 and 2018, 891 heart transplantations were performed at the Shumakov National Medical Research Center of Transplantology and Artificial Organs. This included 80 (9.0%) recipients – 74 (92.5%) men and 6 (7.5%) women, median age 54 [46; 59] with pre-existing (pre-transplant) T2D. The weight of a recipient in this cohort was 85.0 [78.3; 95.0] kg, body mass index (BMI) 28.3 [25.2; 31.5] kg/m^2. There were 28 (35%) recipients with BMI ≥30.0 kg/m^2.

The main diseases leading to end-stage CHF were: ischemic cardiomyopathy (ICMP) in 52 (65.0%) recipients, dilated cardiomyopathy (DCM) in 27 (33.8%), decompensated atherosclerotic aortic valve disease in 1 (1.2%). The severity of clinical manifestations of CHF corresponded to the NYHA functional class 3.1 ± 0.4.

The urgency of performing HT corresponded to UNOS status 1A in 20 (25.0%), status 1B in 18 (22.5%), and status 2 in 42 (52.5%) recipients. Pre-transplant mechanical circulatory support (MCS) was used in 20 (25.0%): intra-aortic balloon counterpulsation (n = 1 (1.3%)), peripheral venoarterial extracorporeal membrane oxygenation (VA ECMO) (n = 19 (23.8%)). Pre-transplant MCS lasted for 4.1 [3.5; 5.5] days.

Correction of carbohydrate metabolism disorders in the pre-transplant period was achieved via diet therapy in 16 recipients (20.0%), via oral anti-diabetic medication in 44 (55.0%), and via insulin therapy in 20 (25.0%). At the time of HT, one oral anti-diabetic medication was used for T2D drug therapy in 27 (61.4%) of 44 recipients who did not need insulin therapy, a combination of two oral anti-diabetic medications was used in 15 (34.1%) recipients, and a combination of three oral anti-diabetic medications was used in 2 (%) recipients. The following oral medications were used for blood glucose-lowering therapy: glimeperide in 22 (27.5%) recipients, gliclazide in 6 (7.5%), vildagliptin in 43 (53.8%), sitagliptin in 2 (2.5%), metformin in 6 (7.5%), and empagliflozin in 2 (2.5%). Oral anti-diabetic medications were continued in all patients (20 (25.0%)), who needed insulin therapy. The level of glycated hemoglobin (HbA1c) at the time of HT was 7.4%, including 51 (63.8%) with less than 7.4%, and 29 (36.2%) with more than 7.4%. The structure of diabetes-related complications in recipients with pre-transplant T2D was as follows: atherosclerotic coronary artery disease in 53 (66.3%) recipients, chronic obliterating peripheral artery disease in 15 (18.8%), cerebral ischemia in 14 (17.5%), peripheral diabetic neuropathy in 10 (12.5%), and diabetic nephropathy in 9 (11.3%). Chronic kidney disease (CKD) stage 3A and higher was diagnosed in 9 (11.3%) recipients with T2D.

Management of recipients in early and late post-transplant periods was carried out in accordance with the ISHLT Guidelines (2010) [11]. To diagnose and determine the severity (0R, 1R, 2R and 3R degrees) of acute cellular rejection of a heart transplant, the 2004 ISHLT standardized morphological classification was used (Cardiac biopsy grading of cellular rejection revised and standardized International Society for Heart and Lung Transplantation (ISHLT)) [12]. To diagnose and determine the severity of histological and immunopathological manifestations (pAMR 0, pAMR 1 (H+), pAMR 1 (I+), pAMR 2, pAMR 3) of antibody-related (humoral) heart transplant rejection, the 2013 ISHLT working formulation for pathology diagnosis of cardiac antibody-mediated rejection) was used [13]. The paper presents the outcomes of cellular and humoral rejection of recipients who survived up to the first biopsy – 857 recipients (96.2% of 891) in two compared groups. The classification proposed by Gao S.Z. et al. in 1988 was used to determine the degree of damage in transplant coronary artery disease (TCAD) [14]. TCAD was diagnosed based on the 2010 ISHLT Guidelines for the care of heart transplant recipients [11]. CKD diagnosis and severity were established by the degree of decrease in glomerular filtration rate according to the KDIGO 2012 classification [15].

Research data was statistically processed using Microsoft Excel spreadsheets and SPSS Statistics 20 software. All the studied parameters were tested for normal distribution using the Kolmogorov–Smirnov test. Arithmetic mean and standard deviation (M ± SD), upper and lower bounds, were used to represent parametric data. Median and interquartile range (interval between 25% and 75% percentiles) were used to describe nonparametric variables. Significance of differences in quantitative parameters in the two groups was determined via Fisher's exact test. Mann–Whitney U test and the Student's t test were used to compare variables in the study groups. Survival analysis was performed using the Kaplan–Meier estimate. Differences were considered statistically significant if the probability of error was less than 0.05 ($p < 0.05$).

STUDY RESULTS

Analysis of the pre-transplant examination data that was included in the study of heart recipients revealed that patients in the diabetes group were older ($p < 0.05$) by age (Table 1). Weight and body mass index were significantly ($p < 0.05$) higher in the study group.

Table 1

Comparative preoperative clinical characteristics of diabetic and nondiabetic heart recipients (n = 891)

Indicator	T2D in recipients		p
	T2D (n = 80)	T2D-free (n = 811)	
Age	54 [46; 59]	48 [35; 56]	**<0.001**
Height	175 [170; 180]	175 [170; 180]	0.969
Gender men (n/%) women (n/%)	 74/92.5 6/7.5	 683/84.2 129/15.9	 0.067
Weight, kg	85.0 [78.3; 95.0]	75.0 [65.0; 89.0]	**<0.001**
BMI, kg/m²	28.3 [25.2; 31.5]	24.7 [22.0; 28.4]	**<0.001**
BMI≥30.0, kg/m² (n/%)	28/35.0	163/20.1	**0.004**
DCM (n/%)	27/33.8	464/57.2	**<0.001**
ICMP (n/%)	52/65.0	296/36.5	**<0.001**
MAP, mmHg	79.5 [73.0; 89.5]	78.0 [69.0; 87.0]	0.144
RAP, mmHg	8.0 [6.0; 12.8]	8.0 [5.0; 12.0]	0.140
mPAP, mmHg	32.0 [25.0; 42.0]	28.0 [20.0; 37.0]	**0.004**
PWP, mmHg	22.5 [16.0; 29.8]	19.5 [13.0; 28.0]	**0.010**
CI, l/min/m²	1.9 [1.5; 2.2]	2.0 [1.6; 2.2]	**0.047**
TPG, mmHg	10.0 [7.0; 12.0]	9.0 [6.0; 12.0]	**0.024**
PVR, Wood units	2.9 [2.2; 4.0]	2.5 [1.8; 3.4]	**0.038**
PVR >4.0, Wood units (n/%)	25/31.3	122/15.0	**<0.001**
HT urgency by UNOS Status 1A (n/%) Status 1B (n/%) Status 1A–1B (n/%) Status 2 (n/%)	 20/25.0 18/22.5 38/47.5 42/52.5	 151/18.6 194/23.9 345/42.5 467/57.5	 0.216 0.888 0.456 0.456
Total bilirubin, μmol/L	20.3 [13.3; 36.5]	25.0 [15.6; 50.0]	**0.042**
Urea, mmol/L	8.3 [6.0; 10.0]	6.7 [5.6; 10.2]	**0.036**
Creatinine, μmol/L	105.2 [82.4; 110.0]	90.0 [77.0; 112.8]	**0.042**
GFR, mL/min	67.5 [62.7; 88.7]	79.9 [60.4; 95.7]	**0.046**
Total protein, g/L	72.0 [68.5; 76.3]	71.8 [65.5; 76.3]	**0.020**
ALT, U/L	21.0 [14.0; 35.0]	24.0 [15.6; 42.2]	0.147
AST, U/L	24.0 [19.0; 30.0]	27.0 [20.0; 39.0]	0.145
Prothrombin index, %	84.0 [69.0; 91.5]	78.0 [65.0; 88.0]	**0.025**
INR	1.2 [1.0; 1.6]	1.4 [1.1; 1.7]	**0.047**
White blood cells	7.8 [6.7; 9.4]	7.5 [6.0; 8.9]	0.095
Platelets	188.5 [142.0; 237.0]	192.0 [134.0; 243.0]	0.694
Glucose level (at any time), mmol/L	7.9 [6.4; 9.2]	6.1 [5.4; 6.9]	**<0.001**

Note: BMI – body mass index, DCM – dilated cardiomyopathy, ICMP – ischemic cardiomyopathy, mAP – mean arterial pressure, RAP – right atrial pressure, mPAP – mean pulmonary artery pressure, PWP – pulmonary wedge pressure, CI – cardiac index, TPG – transpulmonary gradient, PVR – pulmonary vascular resistance, HT – heart transplantation, GFR – glomerular filtration rate, ALT – alanine aminotransferase, AST – aspartate aminotransferase, INR – international normalized ratio.

The ratio of recipients with DCM and ICMP was multidirectional between the main and control groups. Recipients diagnosed with pretransplant ICMP (65.0%) prevailed in the main group ($p < 0.001$), while those diagnosed with DCM (57.2%) predominated in the control group. Hemodynamic manifestations of CHF and concomitant pulmonary hypertension (PH) were pronounced in the main group, as manifested by lower ($p < 0.05$) cardiac index (CI), higher ($p < 0.05$) mean pulmonary artery pressure (mPAP), transpulmonary gradient (TPG) and pulmonary vascular resistance (PVR). The proportion of patients with pre-transplant PVR level >4 Wood units (27.5%) was also higher ($p < 0.05$) in the main group. Recipients in both groups did not differ in terms of urgency of performing HT. Biochemical manifestations of pre-transplant renal dysfunction (urea, blood creatinine, glomerular filtration rate (GFR)) were more ($p < 0.05$) pronounced in the main group, hepatic dysfunction (total bilirubin, prothrombin index (PI) and international normalized ratio (INR)) – in the main groups. Naturally, pre-transplant blood glucose level was higher ($p < 0.05$) in the main group.

The nature and incidence of coexisting conditions at the time of HT in the main and control groups are presented in Table 2.

The main group was characterized by a larger proportion (3.8% to 17.5%) of recipients with stage 2/3 hypertension, stage 2/3 dyscirculatory encephalopathy, multifocal atherosclerosis, urolithiasis, subclinical hypothyroidism, and CKD stage 3 and higher ($p < 0.05$). In the control group, incidence of the same concomitant diseases ranged from 0.6% to 5.5%.

There were no differences in the main clinical, laboratory and imaging parameters of heart donor between the main and control groups, except for the "donor/recipient body weight ratio" indicator (Table 3).

The main and control groups did not differ in terms of incidence of early graft dysfunction, requiring post-transplant MCS – 12.5% versus 10.7%, respectively ($p = 0.764$) (Table 4). Clinical and biochemical manifestations of acute kidney injury in the early post-transplant period were more ($p < 0.05$) pronounced in the main group, which led to 1.8 times greater ($p < 0.05$) need for renal replacement therapy (RRT). The duration of the use of continuous RRT methods (continuous veno-venous hemofiltration (CVVH)) was longer ($p < 0.05$)

Table 2

Preoperative morbidity in diabetic and nondiabetic heart transplant recipients (n = 891)

Comorbidities (n/%)	T2D in recipients		Chi-square	p
	T2D (n = 80)	T2D-free (n = 811)		
Arterial hypertension, stage 2/stage 3	14/17.5	45/5.5	14.979	**<0.001**
DEP, stage 2/stage 3	11/13.8	19/2.3	23.767	**<0.001**
Multifocal atherosclerosis	11/13.8	10/1.2	44.349	**<0.001**
CKD, stage 3 and above, (n/%)	9/11.3	11/1.4	28.175	**<0.001**
Brachiocephalic artery atherosclerosis with carotid stenosis >50%	8/10.0	9/1.1	26.225	**<0.001**
Non-drug-induced clinical/subclinical hypothyroidism	7/8.8	14/1.7	12.731	**<0.001**
Obliterating atherosclerosis of the lower extremities	6/7.5	10/1.2	12.881	**<0.001**
Kidney stone disease	3/3.8	5/0.6	4.909	0.027

Note. DEP – dyscirculatory encephalopathy, CKD – Chronic kidney disease.

Table 3

Clinical characteristics of heart recipients (n = 891)

Indicator	T2D in recipients		p
	T2D (n = 80)	T2D-free (n = 811)	
Age (years)	45.0 [34.0; 55.5]	44.0 [34.0; 53.0]	0.441
Sex Female, (n/%) Male, (n/%)	 15/18.8 65/81.2	 160/19.7 652/80.3	 0.955
Female donor/male recipient pair (n/%)	13/16.3	124/15.3	0.945
Donor weight (kg)	85 [75; 90]	80 [70; 90]	0.143
Donor/recipient body weight ratio	0.95 [0.85; 1.1]	1 [0.86; 1.2]	**0.010**
Non-traumatic brain injury in the donor, (n/%)	48/60	522/64.4	0.523
Cardiopulmonary resuscitation, (n/%)	3/3.8	32/3.9	0.828
MV (days)	2 [1; 3]	2 [1; 3]	0.562
Hemoglobin, g/L	120 [92; 142]	113 [89; 138]	0.168
Total protein, g/L	60 [52; 70]	60.5 [52; 67]	0.542
Blood sodium, mmol/L	148 [141; 157]	147 [140; 156]	0.298
Blood sodium >160 (mmol/L), (n/%)	13/16.3	82/10.1	0.131
Sympathomimetic therapy, (n/%)	63/78.8	572/70.5	0.156
Norepinephrine (n/%, ng/kg/min) (max.)	44/55 300 [167; 550]	458/56.5 340 [180; 600]	0.902 0.194
Dopamine (n/%, μg/kg/min) (max.)	19/23.8 6 [3.5; 13.5]	279/34.4 7 [4; 12]	0.073 0.184
Troponin T, (pg/ml)	0.17 [0.1; 0.7]	2 [0.2; 62.1]	**0.049**
CK-MB, ng/mL	37 [32; 65]	33 [5.5; 54.5]	0.161

Note. MV – mechanical ventilation, CK-MB – creatine kinase-MB.

Table 4

Early posttransplant clinical characteristics of diabetic and nondiabetic recipients (n = 891)

Indicator	T2D in recipients		P
	T2D (n = 80)	T2D-free (n = 811)	
Graft ischemia, min.	154 [133; 185]	159 [131; 194]	0.597
AC duration, min.	119 [100; 142]	120 [93; 152]	0.878
Dopamine			
n/%	76/95.0	632/78.0	**<0.001**
μg/kg/min (max.)	6 [4;10]	6 [4; 8]	0.184
Dobutamine			
n/%	54/67.5	457/56.4	0.072
μg/kg/min (max.)	4.0 [3.5; 6.0]	5.0 [4.0; 6.0]	0.769
Adrenalin			
n/%	78/97.5	625/77.1	**<0.001**
ng/kg/min (max.)	40.0 [60.0; 80.0]	43.0 [60.0; 80.0]	0.299
Post OHT – MCS, n/%	10/12.5	87/10.7	0.764
Post-transplant MCS (days)	3.5 [1.5; 5.5]	3 [2; 5]	0.524
Postoperative MV, hours	8.5 [6; 13]	9 [6; 14.5]	0.831
Total bilirubin (max.), (mmol/L)	43 [31.7; 69.4]	47 [30.7; 77.8]	0.888
ALT (max.), U/L	42 [30; 54]	42 [31; 81]	0.770
AST (max.), U/L	129 [98; 236]	108 [143; 193]	0.585
Urea (max.), (mmol/L)	16.7 [12.2; 22.2]	14 [10.1; 18.8]	**0.022**
Creatinine (max.), (mmol/L)	151.2 [115.6; 218.7]	133.9 [100.1; 174]	**0.019**
Total protein (min.), G/l	58 [54; 62]	66 [63; 68]	**<0.001**
PT (min.), %	67 [60; 74]	71 [63; 77]	**0.016**
White blood cells (max.)	20.2 [17.4; 23]	18.1 [15.2; 22.3]	**0.028**
Platelets (min.)	76 [56; 103.5]	74.5 [51; 107]	0.871
Procalcitonin (max.)	8.8 [2.7; 23.9]	6.4 [2.6; 17.7]	0.159
Postoperative delirium, n/%	19/27.1	101/12.5	0.008
Renal replacement therapy: CVVH, (n/%)	36/51.4	226/27.9	**0.003**
Start of CVVH, days after surgery	1.5 [1; 2]	4 [2; 12]	**0.002**
Transition from CVVH to intermittent HDF, (n/%)	13/18.6	85/10.5	0.165
Number of patients receiving insulin pump therapy after HT, n/%	80/100	227/28.0	**<0.001**
Intravenous insulin, units/day	66.7 [50; 89.3]	50 [33.3; 66.7]	**<0.001**
Intravenous insulin, duration of days	2 [1; 5]	1 [0.5; 2]	**<0.001**
ICU (days)	6 [5; 10]	6 [4; 8]	0.098
Hospital survival, n/%	73/91.2	742/91.5	0.895

Note. AC – assisted circulation, OHT – orthotopic heart transplantation, MCS – mechanical circulatory support, MV – mechanical ventilation, ALT – alanine aminotransferase, AST – asprat aminotransferase, PT – prothrombin time, CVVH – continuous veno-venous hemofiltration, HDF – hemodiafiltration, HT – heart transplant, ICU – intensive care unit.

in the study group. Recipients in the main group were characterized by a more frequent (2.2 times) occurrence of postoperative delirium (27.1% versus 12.4%). The leading in-hospital infectious complications in both the main and control groups were pneumonia (mainly of bacterial etiology) and purulent mediastinitis, whose incidence was, respectively, 18.8% (T2D group) versus 19.0% (T2D-free group) (p = 0.919) and 2.5% (T2D group) versus 2.1% (T2D-free group) (p = 0.86). There were no significant differences in the incidence of these infectious complications among both groups.

In the early periods after HT, the need and average daily doses of insulin were higher (p < 0.05) in the main group (Table 5). In the control group, 227 patients (28%) received continuous intravenous insulin infusion via a medication dispenser. In our study, the target blood glucose level was 5–10 mmol/L.

77 (96.3%) of 80 recipients from the T2D group and 780 (96.2%) of 811 recipients from the T2D-free group survived up to the first endomycardial biopsy. The groups did not differ significantly in terms of incidence of acute cellular rejection: (1) grade 1R rejection – 45.5% (T2D group) versus 42.9% (T2D-free group) (p = 0.76); (2) grade 2R rejection – 0.0% (T2D group) versus 1.0% (T2D-free group) (p = 1.00); (3) grade 3R rejection – 2.6% (T2D group) versus 2.1% (T2D-free group) (p = 0.92). In terms of incidence of antibody-mediated rejection, there were no significant differences between reci-

Table 5

Daily intravenous insulin doses (U/day) at early postoperative period in diabetic and non-diabetic recipients (n = 307)

Study phase (after HT)	Recipient group		Chi-square / Fisher's exact test	p
	T2D group (n = 80)	T2D-free group (n = 227)		
12 hours	115.5 ± 47.1	110.3 ± 35.5	1.1871	0.236
Day 1	89.3 ± 33.7	55.3 ± 29.3	9.6193	0.0001
Day 2	63.9 ± 25.1	47.1 ± 15.3	8.5071	0.0001
Day 3	52.3 ± 17.1	37.5 ± 12.1	9.7958	0.0001
Day 4	48.9 ± 16.3	23.3 ± 7.1	25.3178	0.0001
Day 5	35.7 ± 15.0	14.4 ± 5.3	26.2307	0.0001

Note. HT – heart transplantation.

Table 6

Causes of post-transplant in-hospital mortality (n = 76)

Cause of death	Pre-transplant T2D in recipients who died in the early post-HT period		Chi-square / Fisher's exact test	p
	T2D (n = 7)	T2D-free (n = 69)		
Multiple organ failure not associated with primary graft dysfunction	4/57.1	28/40.6	0.273	0.603
Multiple organ failure associated with primary graft dysfunction	2/28.6	19/27.5	0.148	0.701
Acute rejection crisis	1/14.3	15/21.7	0.004	0.951
Other reasons	0	7/10.1	0.039	0.843

pients from both groups. In all cases, antibody-mediated rejection pAMR 2 was diagnosed – 3.9% (T2D group) versus 4.7% (T2D-free group), respectively (p = 0.96).

The presence of pre-transplant T2D had no adverse effect on length of stay in intensive care unit (ICU) and hospital mortality, which was, respectively, 8.8% (T2D group) versus 8.5% (T2D-free group) (p = 0.895). There was no difference in hospital mortality between the groups (Table 6).

In the long term post-HT period, the leading infectious complication in both groups was community-acquired pneumonia (mainly of mixed bacterial-viral etiology), whose incidence was 12.5% (T2D group) versus 10.9% (T2D-free group) (p = 0.793).

The incidence of donor-transmitted coronary atherosclerosis (DTCA) (developed during the lifetime of the heart donor) in both groups of recipients did not differ significantly – respectively 22.5% (T2D group, n = 18) versus 26.1% (T2D-free group, n = 212) (p = 0.569), as well as the number of initially detected affected coronary arteries – respectively 1.4 ± 0.4 (T2D group) versus 1.3 ± 0.5 (T2D-free group, n = 212) (p = 0.071). The groups also did not differ significantly in the frequency of percutaneous coronary intervention in the early post-HT period in recipients with DTCA – respectively 45.0% (9 of 20, T2D group) vs. 63.1% (159 of 252, T2D-free group) (p = 0.173). In the late posttransplant period, repeated coronary angiographic studies in 14 (70%) of 20 recipients of the T2D group revealed the progression of DTCA, which required additional percutaneous coronary intervention. In the T2D-free group, additional percutaneous coronary intervention was required for 177 (70.2%) of 252 patients with identified DTCA (p = 0.817).

There was no significant difference in the incidence of TCAD diagnosed at different times after HT in recipients from both groups discharged from the hospital – respectively 45.2% (33 out of 73, T2D group) versus 39.6% (294 out of 742, T2D-free group) (p = 0.417). According to the classification by Gao S.Z. et al. (1988), the groups did not differ significantly in terms of frequency of detection of various types of stenotic coronary artery lesions in TCAD: (1) type A – 39.4% (T2D group) versus 54.8% (T2D-free group) (p = 0.136); (2) type B1/B2 – 42.4% (T2D group) versus 33.0% (T2D-free group) (p = 0.373); (3) type C – 18.2% (T2D group) versus 12.2% (T2D-free group) (p = 0.489).

Outpatient renal replacement therapy by long-term hemodialysis was required in 11 (1.3%) out of all the 816 recipients discharged from the hospital after HT. Recipients in both groups did not differ in the incidence of "chronicity" of renal failure requiring outpatient long-term hemodialysis – respectively 1.4% (1 out of 73, T2D group) versus 1.3 (10 out of 743, T2D-free group) (p = 0.606).

During the analyzed period, 145 of 816 heart recipients who were discharged from the hospital died, including 13 (17.8%) of 73 (T2D group) and 132 (17.8%) of 743 (T2D-free group). There were no significant diffe-

rences in the structure of long-term mortality in recipients discharged after HT (Table 7).

The presence of pre-transplant T2D did not significantly affect both early and long-term survival of heart recipients (Fig.).

DISCUSSION

Frequent combination of cardiovascular conditions and carbohydrate metabolism disorders accounts for the high prevalence of T2D among patients with heart diseases, accompanied by development of CHF [4; 5]. This, in turn, explains the presence of T2D in many patients with end-stage CHF, some of whom are indicated for HT [3; 4; 5; 16; 17]. Despite the fact that many years of experience with HT in patients with concomitant T2D have been accumulated abroad, the intervention continues to be associated with increased risk of early and long-term complications that may negatively affect the post-transplant survival of recipients [2; 6; 7; 18]. According to a single-center study, Ram E. et al. (2020), the presence of pre-transplant T2D in heart recipients increases the risk of post-HT death by 1.8 times [19].

According to multicenter studies, the proportion of HT in recipients with pre-transplant T2D ranges from 13.6% to 28.2% [20; 21]. In our study, the proportion of HT in recipients with pre-transplant diabetes was 9.0% of the total number of heart transplants performed during the analyzed 8-year period. The initiation of regular HT in recipients with pre-transplant T2D since 2011 coincided with an increase in the number of heart transplants performed annually over 30 per year. An increase in the proportion of HT in recipients with pre-transplant diabetes was also associated with increased proportion of heart transplants in older patients, which led to an increase in the average age of the heart recipient [22].

A comparative study revealed that pre-transplant T2D recipients were older in age, had a higher weight and BMI compared to recipients without pre-transplant

Table 7

Causes of long-term post-transplant post-discharge mortality (n = 145)

Cause of death	T2D in recipients		Chi-square / Fisher's exact test	p
	T2D (n = 13)	T2D-free (n = 132)		
Infectious complications	5/38.5	22/16.7	2.411	0.121
Rejection	3/23.1	32/24.2	0.060	0.806
CAV	2/15.4	25/18.9	0.004	0.953
Sudden death	1/7.6	30/22.7	0.823	0.365
Cancer	0	8/6.1	0.076	0.783
Unknown cause	2/15.4	15/11.4	0.000	0.983

Note: CAV – cardiac allograft vasculopathy.

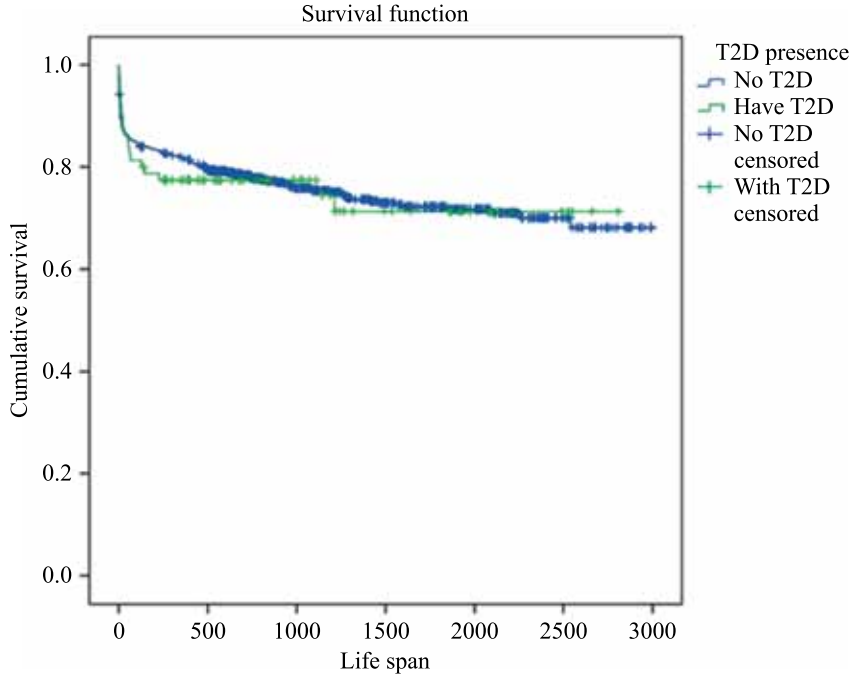

Fig. The effect of pre-transplant T2D on early and long-term survival in heart recipients

carbohydrate metabolism disorders. Coronary heart disease (CHD) was the leading cause of end-stage CHF in recipients with pre-transplant T2D. Predominant impairment of left ventricular (LV) systolic and diastolic function resulted in more pronounced manifestations of pre-transplant PH in this cohort of heart recipients. Nearly 1/3 were recipients with pre-transplant PVR levels above 4 Wood units. In addition, as this study has shown, when preparing and performing HT in recipients with pre-transplant T2D, it is necessary to take into account more pronounced manifestations of preoperative renal dysfunction and the presence of concomitant conditions (arterial hypertension (AH), multifocal atherosclerosis, CKD stage 3 and higher, etc.), which can negatively affect the course of early and long-term post-transplant periods.

Almost half of patients with pre-transplant T2D required urgent HT. This included 25% with pre-transplant MCS using peripheral venoarterial extracorporeal membrane oxygenation (VA ECMO), which could negatively affect the course of the perioperative period and be a risk factor for adverse outcomes in the early post-transplant period.

The median age of the heart donor did not differ significantly between the two studied groups of recipients – within 44–45 years – which fully corresponds to the median age of the heart donor in Europe and reflects the current trends towards an increase in the age of the heart donor due to pronounced reduction in the pool of donors under 40 years old [23]. In both groups, heart donors, whose cause of death was irreversible non-traumatic brain injury, which is considered a possible risk factor for early graft dysfunction, prevailed (60.0–64.4%) [24; 25]. Significantly lower need and doss of sympathomimetic support, as well as the value of the marker for myocardial injury troponin T during cardiac donor conditioning could positively affect the nature of restoration of initial cardiac graft function in the main group [24; 26].

Despite the absence of differences in the frequency of MCS use in the early post-transplant period, the intensity of sympathomimetic therapy, and the duration of postoperative mechanical ventilation, the main group showed more pronounced manifestations of multiple organ failure, mainly kidney-liver failure. Moreover, postoperative delirium was 2.2 times more frequent. Renal replacement therapy was used 1.8 times more often. These features are worth considering when managing recipients with pre-transplant T2D in the perioperative period. It is expected that this category of patients had a significantly greater need for insulin therapy. At the same time, as our study showed, the above facts did not have a negative impact on the duration of postoperative treatment of recipients with T2D in the ICU and on hospital mortality. In both study groups, the leading cause of death was multiple organ failure syndrome.

The study revealed no negative effect of pre-transplant T2D on the incidence of early and late infectious complications, which we attribute to a "more aggressive" postoperative antimicrobial chemoprophylaxis (early complications) and a personalized approach in determining the optimal immunosuppressive therapy scheme (early and late complications) [27; 28; 29].

Our study did not find any significant negative effect of pre-transplant T2D on DTCA in the post-transplant period, as well as on incidence and severity of TCAD. Early studies demonstrate the ambiguous effect of pre-transplant T2D on development and progression of pre-existing or de novo emerging transplant coronary artery disease [16; 19; 30]. The presence of pre-transplant T2D did not negatively affect the incidence and severity of TCAD, which was also revealed in other studies [27].

There was no significant effect of pre-transplant T2D on the incidence and severity of other non-infectious non-lethal and lethal complications (chronic renal failure, oncopathology, acute graft rejection, etc.).

Early and long-term survival rates in recipients with and without T2D were comparable, indicating that with the correct selection of recipients and choice of an optimal management strategy in the post-transplant period, high HT outcomes are achieved even in recipients with a high risk of early and long-term complications [6; 17; 31]. A possible explanation for the results obtained in the study is that HT in recipients with pre-transplant T2D was performed in the absence of significant manifestations of diabetes-dependent and diabetes-associated complications that could affect the survival of recipients. Besides, the presence and significance of the influence of other comorbidities on HT outcomes were taken into account [7].

CONCLUSION

With the correct selection of recipients and choice of an optimal management strategy in the post-transplant period, pre-transplant type 2 diabetes does not have a negative effect on early and long-term outcomes of heart transplantation.

The authors declare no conflict of interest.

REFERENCES

1. *Mehra MR, Canter CE, Hannan MM, Semigran MJ, Uber PA, Baran DA et al.* The 2016 international society for heart lung transplantation listing criteria for heart transplantation: A 10-year update. *The Journal of Heart and Lung Transplantation.* 2016; 3: 1–23.
2. *Marelli D, Laks H, Patel B, Kermani R, Marmureanu A, Patel J et al.* Heart transplantation in patients with diabe-

tes mellitus in the current era. *The Journal of Heart and Lung Transplantation.* 2003; 22 (10): 1091–1097.
3. *Mehra MR, Kobashigawa J, Starling R, Russel S, Uber PA, Parameshwar J et al.* Listing criteria for heart transplantation: international society for heart and lung transplantation guidelines for the care of cardiac transplant candidates – 2006. *The Journal of Heart and Lung Transplantation.* 2006; 25 (9): 1024–1042.
4. *Obrezan AG, Kulikov NV*. Chronic Heart Failure and Diabetes Mellitus: Pathogenesis and Possibilities of Treatment. *Kardiologiia*. 2018; 58 (7): 85–94. (In Russ.). doi: 10.18087/cardio.2018.7.10156.
5. *Pochinka IG, Strongin LG, Botova SN, Razumovsky AV, Baranova AA, Dvornikova MI et al*. Effect of Type 2 Diabetes Mellitus on Five-Year Survival of Patients Hospitalized Because of Acute Decompensated Heart Failure. *Kardiologiia*. 2017; 57 (9): 14–19. doi: 10.18087/cardio.2017.9.10027.
6. *Schulze PC, Jiang J, Yang J, Cheema FH, Schaeffle K, Kato TS et al.* Preoperative assessment of high-risk candidates to predict survival after heart transplantation. *Circulation: Heart Failure.* 2013; 6: 527–534.
7. *Gomis-Pastor M, Mingell EU, Perez SM, Loidi VB, Lopez LL, Bassons AD et al.* Multimorbidity and medication complexity: New challenges in heart transplantation. *Clinical Transplantation.* 2019; 33: 1–14.
8. *Morgan JA, John R, Weinberg AD, Colletti NJ, Mancini DM, Edwards NM.* Heart transplantation in diabetic recipients: a decade review of 161 patients at Columbia Presbyterian. *The Journal of Thoracic and Cardiovascular Surgery.* 2004; 127 (5): 1486–1492.
9. *Gautier SV, Shevchenko AO, Kormer AY, Poptsov VN, Shevchenko OP*. Prospects to improve long-term outcomes of cardiac transplantation. *Russian Journal of Transplantology and Artificial Organs*. 2014; 16 (3): 23–30. (In Russ.) https://doi.org/10.15825/1.
10. *Meboniya NZ, Poptsov VN.* Transplantatsiya serdtsa u retsipientov 60 let i starshe. *Transplantology: results and prospects*. Vol. X. 2018 / Ed. by S.V. Gautier. M.–Tver: Triada, 2019: 504, 335.
11. *Costanzo MR, Dipchand A, Starling R, Anderson A, Chan M, Desai S et al.* ISHLT Guidelines for the care of heart transplant recipients. *The Journal of Heart and Lung Transplantation.* 2010; 29 (8): 914–956.
12. *Stewart S, Winters GL, Fishbein MC, Tazelaar HD, Kobashigawa J, Abrams J et al.* Revision of the 1990 working formulation for the standartization of nomenclature in the diagnosis of heart rejection. *The Journal of Heart and Lung Transplant.* 2005; 24 (11): 1710–1720.
13. *Berry GJ, Burke MM, Andersen C, Bruneval P, Fedrigo M, Fishbein MC et al.* The 2013 international society for heart and lung transplantation working formulation for the standartization of nomenclature in the pathologic diagnosis of antibody-mediated rejection in heart transplantation. *The Journal of Heart and Lung Transplantation.* 2013; 32 (12): 1147–1162.
14. *Gao SZ, Alderman EL, Schroeder JS, Hunt SA*. Accelerated coronary vascular disease in the heart transplant patient: coronary arteriographic finding. *Journal of the American College of Cardiology.* 1988; 12: 334–340.
15. *Eknoyan G, Lameire N, Eckardt K-U, Kasiske BL, Wheeler DC, Abboud OI et al.* KDIGO 2012 Clinical practice guideline for the evaluation and management of chronic kidney disease. *Official Journal of the International Society of Nephrology.* 2013; 3 (1): 1–150.
16. *Chen JM, Russo MJ, Hammond KM, Mancini DM, Kherani AR, Fal JM et al.* Alternate waiting list strategies for heart transplantation maximize donor organ utilization. *The Annals of Thoracic Surgery.* 2005; 80 (1): 224–228.
17. *Hong KN, Iribarne A, Worku B, Takayama H, Gelijns AC, Naka Y et al.* Who is the high-risk recipient? Predicting mortality after heart transplant using pretransplant donor and recipient risk factors. *The Annals of Thoracic Surgery.* 2011; 92: 520–527.
18. *Szabo Z, Hakanson E, Svedjeholm R.* Early postoperative outcome and medium-term survival in 540 diabetic and 2239 nondiabetic patients undergoing coronary artery bypass grafting. *The Annals of Thoracic Surgery.* 2002; 74 (3): 712–719.
19. *Ram E, Lavee J, Sternik L, Segev A, Peled Y.* Relation of age of major rejections, allograft vasculopathy, and long-term mortality in a contemporary cohort of patients undergoing heart transplantation. *Israel Medical Association Journal.* 2020; 22: 486–490.
20. *Lund LH, Khush KK, Cherikh WS, Goldfarb S, Kucheryavaya AY, Levvey BJ et al.* The registry of the international society for heart and lung transplantation: thirty-fourth adult heart transplantation report – 2017; focus theme: allograft ischemic time. *The Journal of Heart and Lung Transplantation.* 2017; 26 (10): 1037–1046.
21. *Cehic MG, Nundall N, Greenfield JR, Macdonald PS.* Management strategies for posttransplant diabetes mellitus after heart transplantation: a review. *Journal of Transplantation.* 2018: 1–14.
22. *Poptsov VN, Spirina EA, Ukhrenkov SG, Ustin SYu, Aliev EZ, Masyutin SA et al.* Early Postoperative Period After Orthotopic Heart Transplantation in Recipients of 60 Years and Older. *Russian Journal of Transplantology.* 2016; 18 (4): 56–65. (In Russ.) doi: 10.15825/1995-1191-2016-4-56-65.
23. *Khust KK, Cherikh WS, Chambers DC, Harhay MO, Hayers DJ, Hsich E et al.* The international thoracic organ transplant registry of the international society for heart and lung transplantation: thirty-sixth adult heart transplantation report – 2019; focus theme: donor and recipient size match. *The Journal of Heatr and Lung Transplantation.* 2019; 38: 1056–1066.
24. *Peled Y, Kassif Y, Raichlin E, Kogan A, Har-Zahav Y, Nachum E et al.* Improved long-term outcomes after heart transplantation utilizing donors with traumatic mode of brain death. 2019; 14 (138): 1–9.
25. *Samsky M, Patel CB, Owen A, Schulte PJ, Jentzer J, Rosenberg PB et al.* Ten year experience with extended criteria cardiac transplantation. *Circulation: Heart Failure.* 2013; 6 (6): 1230–1238.

26. *Nakamura Y, Saito S, Miyagawa S, Yoshikawa Y, Hata H, Yoshioka D et al.* Perioperative ischaemic reperfusion injury and allograft function in the early post-transplantation period. *Interactive CardioVascular and Thoracic Surgery.* 2019; 29: 230–236.
27. *Russo MJ, Chen JM, Hog KM, Stewart AS, Ascheim DD, Argenziano M et al.* Survival after heart transplantation is not diminished among recipients with uncomplicated diabetes mellitus (an analysis of the United Network of Organ Sharing database). *Circulation.* 2006; 114: 2280–2287.
28. *Subramanian S, Trence DL.* Immunosuppressive agents: effects on glucose and lipid metabolism. *Endocrinology and MetabolismClinics of North America.* 2007; 36: 891–905.
29. *Pirsch JD, Henning AK, First MR, Fitzsimmons W, Gaber AO, Reisfield R et al.* New-onset diabetes after transplantation: results from a double-blind early corticosteroid withdrawal trial. *American Journal of Transplantation.* 2015; 20: 1–9.
30. *Ram E, Lavee J, Tenenbaum A, Klempfner R, Fishman EZ, Maor E et al.* Metformin therapy in patients with diabetes mellitus is associated with a reduced risk of vasculopathy and cardiovascular mortality after heart transplantation. *Cardiovascular Diabetology.* 2019; 18 (118): 1–8.
31. *Chambers DC, Cherikh WS, Goldfarb SB, Hayers JD, Kucheryavaya AY, Toll AE et al.* The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-Fifth Adult Heart Transplantation Report – 2018; Focus Theme: Multiorgan Transplantation. *Journal of Heart and Lung Transplantation.* 2018; 37 (10): 1169–1183.

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