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CLINICAL STUDY

Metformin therapy and risk of cancer in patients after heart transplantation

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ABSTRACT

BACKGROUND: Diabetes mellitus (DM) and malignancy are recognized among the most common complications increasing mortality in patients after heart transplantation (HTx). Clinical trials have shown a higher risk for different types of tumours in diabetic patients. This risk is potentiated by immunosuppressive therapy in transplant patients. Biguanide metformin has been shown to exhibit anti-tumour activity and we tried to find out whether this effect is valid for heart transplant patients.

METHODS: We retrospectively analysed a group of 497 patients, who undergone HTx in our centre between 1998 and 2019. The primary outcome was any malignancy during the 15-year follow-up period and patient's survival.

RESULTS: Out of the 497 patients enrolled in the study, 279 (56 %) had diabetes and 52 (19 %) were treated with metformin. Fifteen-year survival in treated patients without malignancy was 93 %, the remainder for the DM patients was 56 %, with survival in non-DM patients being 74 %. Untreated diabetic patients had 4.7 times higher chance of malignancy than those on metformin (p = 0.01). Fifteen-year survival in metformin treated patients was 53 %, in other DM patients 44 %, and in non-DM patients 51 %.

CONCLUSION: Our study showed a significantly lower incidence of malignancies in metformin-treated patients and slightly better overall survival *(Tab. 2, Fig. 3, Ref. 19)*. Text in PDF *www.elis.sk*

KEY WORDS: biguanide, heart graft, malignancy, diabetes mellitus, survival.

Introduction

Diabetes mellitus and heart transplant. These diagnoses increase the risk of tumour development, even more so, when both are present in one patient. Several clinical trials have confirmed a higher incidence of various tumours in patients with diabetes mellitus (DM). In transplant patients, the risk is even higher due to immunosuppressants. Metformin - one of the most prescribed oral drugs to treat DM – has been shown to have anti-tumour effects. Currie's retrospective study of more than 60,000 DM patients showed that metformin significantly reduces the risk of developing a tumour and the risk is even lower than in the non-DM population. Insulin, on the other hand, increases the risk. The combination of insulin and metformin reverses the risk to a normal level. It is, therefore, important to administer insulin combined with metformin in type 2 DM patients (1). Once the malignancy develops and is being treated, combining metformin with chemotherapy has a synergistic effect which allows for dose reduction and thus the chemotherapy's adverse effects can be reduced (2, 3, 4) The aim of our study was to ascertain whether the systemic effect of metformin occurs in patients after heart transplant (HTx).

Material and methods

We performed a retrospective analysis of 497 subjects, who underwent HTx at our hospital between the years 1993 and 2016 and who survived one month after the transplant. We analysed data on malignancy incidence and patients' long-term survival rate from the 15-year period. All the patients were managed in compliance with our immunosuppressive protocol: induction treatment with anti-interleukin-2 receptor monoclonal antibody basiliximab or polyclonal antibody anti-thymocyte globulin, followed by a combination of three drugs comprising cyclosporine A or tacrolimus, mycophenolate mofetil, and corticosteroids. The present study was approved by the local Ethical Committee, conforms with "WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI: Ethical Principles for Medical Research Involving Human Subjects" (updated in Fortaleza, Brazil 2013) and orders of GCP European community. The informed consent was not required because this study was retrospective.

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Tab. 1. Baseline characteristics of patients by diabetes status.

Before Htx	Non-DM n=218; 44 %	DM n=279; 56 %	p
Recipient age (years)	46±15	54±9	<0.01
median	51	57	
Donor age (years)	38±14	37±13	0.77
median	39	38	
Etiology ischemic	54 (24.8)	126 (45.2)	<0.01
Recipient gender (male)	176 (80.7)	226 (81.0)	0.99
Donor gender (male)	156 (71.6)	224 (80.3)	0.02
Recipient BMI	24,0±4.0	26.9±3.9	<0.01
median	24.2	27.2	
Hypertension	77 (35.3)	169 (60.6)	<0.01
Past smoker	69 (31.7)	139 (49.8)	<0.01
Recipient blood type			
0	55 (25.2)	70 (25.1)	0.92
A	85 (39.0)	130 (46.6)	0.08
B	52 (23.9)	47 (16.8)	0.07
AB	24 (11.0)	31 (11.1)	0.99
Dyslipidaemia	68 (31.2)	141 (50.5)	<0.01
	0.35±0.30	0.32±0.26	
median	0.19	0.17	0.12
	2.3±1.8	2.2±1.2	
median	1.8	1.8	0.2
Inotropic	64 (29.4)	61 (21.9)	0.06
LVAD bridge to Htx	18 (8.3)	33 (11.8)	0.23
Ischemic time (min)	154±58	153±52	0.77
median	160	159	

Tab. 2. Baseline Characteristics of Patients by Using Metformin in the Diabetes Group.

Before Htx	Non-metformin n=227; 81 %	Metformin n=52; 19 %	p
Recipient age (years)	54±9	55±10	0.37
median	57	59	
Donor age (years)	37±14	38±12	0.67
median	38	39	
Etiology ischemic	102 (44.9)	24 (46.2)	0.88
Recipient gender (male)	183 (80.6)	43 (82.7)	0.85
Donor gender (male)	184 (81.1)	40 (76.9)	0.58
Recipient BMI	26.9±4.0	27.3±3.2	0.47
median	27.2	27.7	
Hypertension	130 (57.3)	39 (75)	0.02
Past smoker	111 (48.9)	28 (53.8)	0.54
Recipient blood type			
0	58 (25.6)	12 (23.1)	0.86
A	106 (46.7)	24 (46.2)	0.99
B	34 (15.0)	13 (25.0)	0.10
AB	28 (12.3)	3 (5.8)	0.22
Dyslipidaemia	108 (47.6)	33 (63.5)	0.045
Recipient bilirubin (mg/dl)	0.32±0.26	0.32±0.24	0.66
median	0,15	0,22	
Recipient creatinine (mg/dl)	2.2±1.2	2.2 ±1.2	0.99
median	1,8	2	
Inotropic	55 (24.2)	6 (11.5)	0.06
LVAD bridge to Htx	24 (10.6)	9 (17.3)	0.23
Ischemic time (min)	153±52	153±55	0.99
median	159	156	

Statistical analysis

Basic recipient and donor characteristics were presented using descriptive analysis methods. Results were expressed as the mean with standard deviation (SD) and the median with continuous variables, using absolute and relative numbers with categorical variables. Categorical variables were compared using the Fisher's test. For continuous variables, which showed a normal distribution pattern, the parametric t-test was used and those, which did not show a normal distribution pattern, we applied the non-parametric Mann–Whitney test to compare inter-group parameters. Comparing the survival between the two groups was calculated using Kaplan-Mayer survival analysis. The hazard ratio was calculated using the Cox proportional hazard model. All analyses were conducted at a level of significance of 5 % (i.e., $p < 0.05$ were considered statistically significant), using statistical software Statistica 12, (StatSoft, USA).

Results

Out of the 497 patients enrolled in the study, 279 (56 %) had DM type 2, out of which 52 (19 %) were treated with metformin. DM developed in 151 patients (67 %) not treated with metformin after HTx, and in 22 (42 %) patients, who were treated with metformin. The basic characteristics of the cohort (Tab. 1) showed that non-DM patients were statistically significantly younger than DM patients.

DM patients were statistically significantly more obese, presented more often with hypertension and hyperlipoproteinemia prior to the transplant, and included more cigarette smokers. Regarding the diagnosis, transplant indication was based on, the group of DM patients included a significantly higher number of patients with ischemic heart disease (IHD) compared to the non-

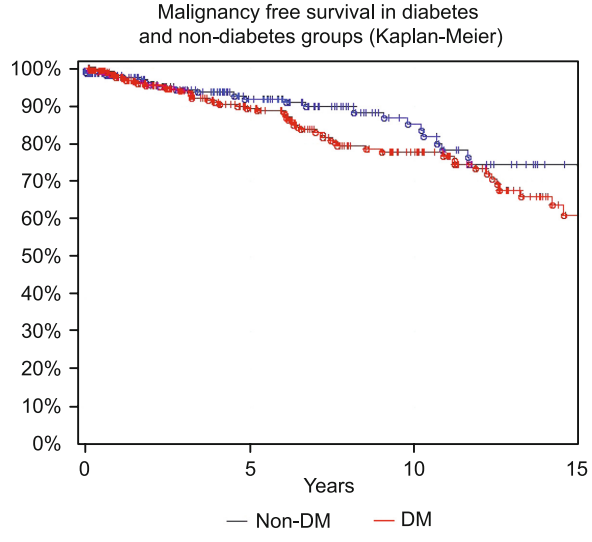

Fig. 1. Kaplan–Meier curves showing the malignancy free survival in Metformin and Non-metformin groups during the 15-year follow-up.

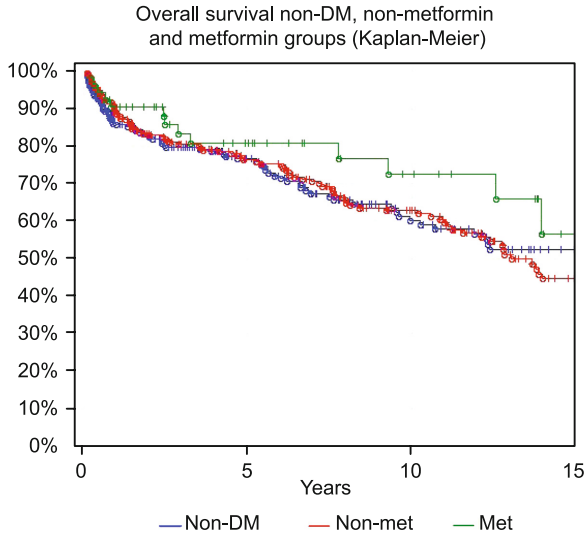

Fig. 2. Kaplan-Meier curves showing the malignancy free survival in Diabetes and Non-diabetes groups during the 15-year follow-up.

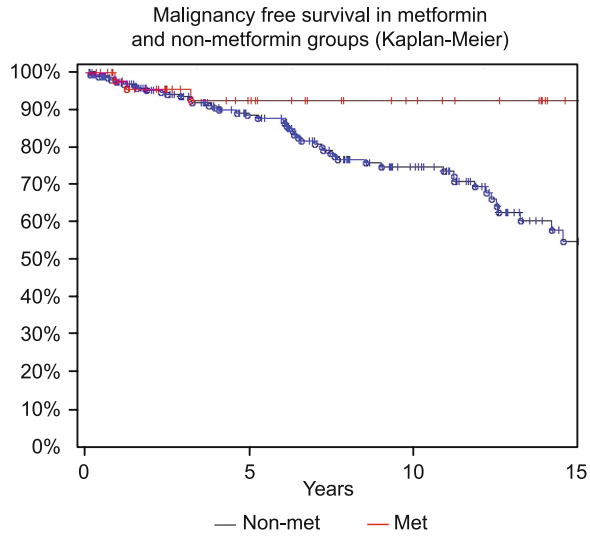

Fig. 3. Kaplan-Meier curves showing the overall survival in Non-diabetes, Non-metformin and metformin groups during the 15-year follow-up.

DM group. Regarding other parameters, there were no statistically significant differences between the groups. We ascertained a statistically significant difference in the respective graft donors between the groups. When comparing both groups of DM patients (Tab. 2), there was a significant difference only in the higher incidence of hypertension and hyperlipoproteinemia in the metformin group.

After HTx, there were more newly diagnosed DM cases in the non-metformin group than in the metformin group. Fifteen-year survival in metformin treated patients without malignancy was 93 %, in the remainder for the DM patients was 56 %, survival in non-DM patients was 74 % (Figs 1, 2). According to the Cox regression analysis, diabetics not treated with metformin had 4.7 times higher chance of malignancy than those on metformin ($p=0.01$). 15-year survival in metformin treated patients was 53 %, in other DM patients 44 %, in non-DM patients 51 % (Fig. 3).

Discusion

The main factor affecting the long-term survival rate in patients after HTx is cancer. Based on Youn and Stehlík's analysis of over 17 thousand patients from the ISHLT registry, the risk of developing new solid tumours within 1 to 5 years after transplant between 2000 and 2005 was 10.7 %, and the incidence increased between 2006 and 2011 to 12.4 %, which was statistically significant ($p<0.0001$) (5). The incidence of skin tumours increased from 6.4 % to 8.4 %, and the incidence of solid tumours (excluding skin tumours) increased from 4 % to 4.5 % ($p = 0.004$) (5). This increase did not occur in lymphoproliferative disorders. The survival rate of the patients with new malignancies was significantly lower than in patients without malignancies ($p<0.0001$). In skin tumours, the five-year survival rate decreased from 90 % to 50 %, and in solid tumours from 90 % to only 40 % (5). Several clinical trials demonstrated a higher risk of developing various solid tumours in patients with DM. A meta-analysis of clinical trials showed a link between DM and the risk of malignant tumours in two key internal organs: the liver and pancreas. A high insulin concentration in the portal vein was considered as one of the causes for DM patients to be at a 2.5 times higher risk of developing hepatocellular carcinoma (6). Obesity, which occurs in up to 80 % of type 2 DM patients and is often accompanied by hepatic steatosis, may be one of the causes. DM patients are more often at a risk of cirrhosis and hepatitis B and C infections. The carcinogenesis itself is associated with inflammation and reparative processes. The risk of developing a pancreatic tumour is 1.7 times higher in DM patients than in non-DM patients. The risk is even higher in elderly DM patients, it is eight times higher. Laboratory and clinical findings indicate that DM induced by a pancreatic tumour develops through cytokines produced by the tumour, rather than due to direct endocrine pancreatic tissue destruction by the tumour. This is consistent with the observation that hyperglycaemia occurs in early pancreatic carcinomas and does not correspond to their size and stage. A biological relationship between pancreatic carcinoma and DM is unclear. The expected reason is higher exposure to insulin released from the pancreas' endocrine component and secreted into the blood in higher concentrations (7). A higher incidence and mortality in DM patients in relation to a kidney tumour is probably associated with obesity, frequent hypertension, and diabetic nephropathy. In addition to hyperinsulinemia, the higher incidence of urinary tract infection in DM patients can also be an important factor

in bladder cancer incidence. In DM patients, the risk of kidney carcinoma is 1.5 times higher (8), and the risk of a bladder tumour is 1.4 times higher (9). In female DM patients, malignant tumour incidence in reproductive organs is independent of obesity; however, obesity is a significant risk factor in breast cancer and endometrial cancer. Hyperinsulinemia also increases oestrogen levels and decreases plasma globulin levels, which free oestrogen binds to. At the same time, it can stimulate the androgen secretion in the ovaries. In female DM patients, the risk of breast cancer is 1.2 times higher (10). The increased risk does not apply only to prostate tumours. In several studies, a lower incidence of prostate cancer by 16 % on average was observed in a subpopulation of male DM patients, which was probably related to the decreased testosterone levels in these patients (11). Based on the International Society of Heart and Lung Transplantation (ISHLT) registry from 2019, the survival rate of DM patients after HTx was lower than in non-DM patients. More specifically, the 12-year survival rate in non-DM patients after HTx was 63 %, whereas in DM patients it was only 40 % ($p < 0.0001$) (12). Data from the same registry also showed that the patients' long-term survival rate after HTx without cancer was 72.3%, compared to patients, who were diagnosed with some type of malignant tumour and whose 10-year survival rate was 27.7 %. Due to these significant differences in patients' long-term survival rate with these diagnoses, it is important to take advantage of any option that could reduce possible tumour development. One option is to switch to mTOR inhibitors, which are proven to have an anti-tumorous effect (13, 14). A significantly better strategy would be to prevent tumour development after HTx. This could be possible with metformin. In a study of 237 patients, Peled et al (2017) confirmed that metformin could lower the risk of developing malignancies in patients after HTx. The total of 56 % of DM patients in this study were managed with metformin. The incidence of malignancies within 15 years post-transplant was only 4 % in DM patients managed with metformin, as opposed to 62 % of malignancies in DM patients, who did not receive metformin. In non-DM patients, the incidence of malignancies within 15 years post-transplant was 27 % ($p < 0.0001$) (15). The second most serious factor, associated with the long-term survival rate after HTx, was cardiac allograft vasculopathy (CAV). The ISHLT registry reports a high incidence of CAV after HTx: up to 50 % by 10 years post-transplant and ~ 30 % by 5 years post-transplant (16,17). Ram et al., in the study of 298 transplanted patients with DM, proved that the combined risk of CAV or cardiovascular mortality was lower in the metformin-treated patients than in those not receiving metformin (32 vs 68 %; log rank $p = 0.01$). The importance of this study lies in the notion that CAV and diabetes are major confounders of mortality and morbidity after HTx and therefore every effort should be made to reduce their burden (18). Therefore, metformin appears to be a very potent drug with a positive effect on the most common diseases that limit the long-term survival of patients after HTx, that is CAV, malignancies, and DM. Currently, there are no definite guidelines regarding DM patient management after HTx with newly developed malignancies. It´s a multidisciplinary problem that requires collaboration between a transplant specialist, an oncologist, and a DM specialist (19). The transplant specialist must perform a thorough screening for the most common malignancies and consider switching their patients to mTOR inhibitors if a malignancy develops. The DM specialist should consider treating with metformin, if such a treatment is not contraindicated. In DM patients after HTx, the oncologist should pay an attention to managing co-morbidities, take into account the patient's fragile immunity and possible toxicity of oncological treatment, but also comply with the prescribed dose of chemotherapy with an emphasis on supportive care. There are several limitations in our study. Firstly, it was conducted at a single centre and has a retrospective design. Secondly, although quite a high number of patients was enrolled in our study, there were relatively few patients in the metformin group.

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