New Onset Diabetes Mellitus in Heart Transplant Recipients

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Introduction: New onset diabetes mellitus in patients with heart transplant is a known complication with importance in the long term survival.
Material and methods: We have studied the incidence of new onset diabetes in a group of 38 patients with heart transplant that are included database of Emergency Institute of Cardiovascular Diseases and Transplantation, Tîrgu Mureș, between 1999–2011.
Results: The incidence of new onset diabetes was of 24.32% in the 1st month of posttransplant evolution, 22.58% at 1 year of evolution, 18.18% at 3 years of evolution and 10% at 5 years of posttransplant evolution. We have studied these posttransplant complications in relation with the risk factors and the most important complications in the evolution of these patients.
Conclusions: New onset diabetes in heart transplant recipients is a serious complication with high incidence and with serious implications in their evolution, requiring an accurate screening of the recipients in the waiting list and a periodical posttransplant evaluation, an early detection and a prompt and efficient treatment.

Keywords: new onset diabetes mellitus, heart transplant, risk factors, complication, survival

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Introduction

Heart transplantation has today a survival rate of 80% at 5 years [1]. Considering the increased survival, complications as diabetes mellitus (DM), which have the potential to reduce the benefits of transplantation, are very important. For many years, new onset diabetes on solid organ transplant patient was a known complication, but its importance in the evolution of the patient required time to be properly assessed. Studies conducted in this area indicate an incidence of diabetes mellitus of 24% at 1 year and 32% at 5 years after heart transplant, similar to that encountered in kidney or liver transplantation [2].

At the present, the risk factors that lead to this complication are well established: pretransplant cardiac glucose intolerance, family history of diabetes, age over 40 years, race (black and hispanic), obesity – having as an indicator the body mass index (BMI), metabolic syndrome, immunosuppressive medication [3,4]. It is recommended that the diagnosis of the new onset diabetes after transplantation should be based on the definition of the World Health Organization (WHO): diabetes mellitus – patient who has the fasting plasma glucose value equal to or greater than 7.0 mmol/l or 126 mg%; IFG (impaired fasting glucose) – patients with plasma glucose between 6.1–6.9 mmol/l or 110–125 mg%; IGT (impaired glucose tolerance) – patients with plasma glucose below 7.0 mmol/l or 126 mg% [5].

We have studied the incidence of new onset diabetes mellitus in a group of patients with cardiac transplant and the risk factors that lead to this complication.

Material and methods

The study group is composed of 38 cardiac allograft recipient patients, aged between 12 and 57 years transplanted between 1999–2011 in the Emergency Institute of Cardiovascular Diseases and Transplantation Tîrgu Mureș. Table I contains the clinical characteristics of these patients.

Patients diagnosed with diabetes were not included in the cardiac transplant waiting list; pre-transplant screening included only the fasting plasma glucose (a jeune), we did not use the oral glucose tolerance test (OGGT). The diagnosis of diabetes mellitus was established according to the WHO definition. A temporary diagnosis of diabetes was established in patients with criteria for this diagnosis after the first week of posttransplant evolution. Diabetes cases that met the defined criteria one month after heart transplant were diagnosed as posttransplant diabetes mellitus with new onset.

Patients included in the study group have been on triple immunosuppressive therapy after heart transplantation: prednisone, with gradually reduced doses according to the time elapsed since transplant, cyclosprine (Sandimun Neoral) or tacrolimus (Prograf), and mycophenolate mofetil (Celcept). Dosing venous blood sample glucose, fasting collected and analyzed in the laboratory has been used as a test within 7 days. In the first 72 hours we also used as an indicator of glucose metabolism the glucose values collected during the day 4 values in total, of which only the morning value was fasting. Glucose values that were collected during the day, were considered above the exposure limit significance of carbohydrate metabolism deficit over 200 mg% [6].

Table II contains the values of fasting glucose in the day 7 post heart transplant, to the whole study group (under 110 mg%, between 110–125 mg%, over 125 mg%).

After the seventh day of evolution, patients with daily elevated fasting glucose levels were further evaluated by testing fasting and postprandial plasma glucose intermittently up to one month, and patients with normal blood glucose levels were tested twice a week for fasting plasma

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Table I. Characteristics of the study group

Characteristics	Study group	%
N (number of transplanted patients)	38	
Age (average age limits)	12–57 (38.5)	
Sex		
Male (n,%)	29	76.32
Female (n,%)	9	23.68%
Diagnosis		
Ischemic cardiomyopathy (n,%)	9	23.68%
Non-ischemic cardiomyopathy (n,%)	29	76.32%
Body mass index (BMI)		
Under 25	25	65.79%
Over 25	13	34.21%
Prednison treatment		
0 month (n,%)	2	5.26%
3 months (n,%)	9	18.42%
6 months (n,%)	13	57.89%
1 year (n,%)	14	18.42%
Ciclosporine treatment (n,%)	11	71.05%
Tacrolimus treatment (n,%)	27	28.95%
Cyclosporine-Tacrolimus conversion (n)	1	
Tacrolimus-Cyclosporine conversion (n)	1	
Acute rejection(n,%)	8	21.05%
Death (n,%)	9	23.68%

Table II. Fasting glucose on the 7th day posttransplant

Patient No.	<110 mg/ml	Patient No.	110–125 mg/ml	Patient No.	>125 mg/ml
2	104	1	119	4	140
3	69	5	115	7	223
6	94	10	121	9	190
8	90	12	116	11	259
13	102	15	116	14	135
16	91	38	110	17	273
19	77			18	133
22	104			20	144
23	101			21	137
29	100			24	140
31	96			25	136
33	67			26	152
34	108			27	173
36	94			28	157
				30	147
				32	144
				35	145
				37	147

glucose. Next, patients were tested in terms of fasting glucose monthly during the first 3 months posttransplant and then every third month during the first posttransplant year and the following years.

Table III includes patients with diabetes mellitus diagnosed at day 7, at 1, 3, 6, 12 months, at 3 and 5 years post heart transplant.

We followed these patients in relation to the risk factors mentioned in the literature for this development (family history of diabetes, age, weight, corticosteroids, cyclosporine and tacrolimus treatment). We also followed the evolution of these patients regarding the presence of acute rejection, coronary disease, arterial hypertension, peripheral arterial obstructive disease, renal failure, infections and death.

Results

Eighteen patients (47.37%) have been diagnosed with temporary diabetes mellitus at the end of the first week and 9 patients (24.32%) have been diagnosed with diabetes mellitus at one month after heart transplant.

At 3 months after heart transplant we established the diabetes mellitus diagnosis in 6 of the 34 transplanted patients (17.65%), at 6 months in 7 of 33 (21.21%), at 1

Table III. Diabetes mellitus at 7 and 30 days, 1, 3, 6 months, 1, 3, 5 years

Patient no.	7 days	DM at 7 days	1 month	DM at 30 days	3 months	DM at 3 months	6 months	DM at 6 months	1 year	DM at 1 year	3 years	DM at 3 years	5 years	DM at 5 years
4	140	YES	90											
5					90		60		688	YES	103	YES		DEATH
7	223	YES	101		90		82		125	YES	265	YES	170	YES
9	190	YES	81											
11	259	YES	153	YES	140	YES	175	YES	266	YES				
14	135	YES	82											
15	116		130	YES	87	YES	299	YES	88	YES	112	YES		
17	273	YES	86	YES	106	YES	75	YES	177	YES				
18	133	YES	71											
20	144	YES	152	YES	221	YES	168	YES	165	YES	150	YES		
21	137	YES	130	YES	107	YES	98	YES	86					
24	140	YES	109											
25	136	YES	126	YES										
26	152	YES	DEATH											
27	173	YES	103											
28	157	YES	119											
30	147	YES	86		122		154	YES	139					
32	144	YES	108											
33					83		89		150	YES				
35	145	YES	187	YES	336	YES	200	YES						
37	147	YES	175	YES										
38	110		148	YES										

Table IV. Diabetes mellitus patients with the risk factors

Patient no.	Age >40	BMI >25	Family history	Prednison	C/T	DM 1 m	DM 3 m	DM 6 m	DM 1 year	DM 3 years	DM 5 years
5		X	X	1 year	T				X	X	
7		X	X	1 year	T				X	X	X
11	X			1 year	T	X	X	X	X		
15	X		X	6 m	T	X	X	X	X	X	
17				6 m	C	X	X	X	X		
20	X	X		1 year	T	X	X	X	X	X	
21	X		X	1 year	C	X	X	X			
25				1 year	T	X					
30	X	X		6 m	T			X			
33				1 year	T				X		
35		X		6 m	T	X	X	X			
37	X	X		3 m	T	X					
38	X			3 m	T	X					
26	152	YES	DEATH								
27	173	YES	103								
28	157	YES	119								
30	147	YES	86		122		154	YES	139		
32	144	YES	108								
33					83		89		150	YES	
35	145	YES	187	YES	336	YES	200	YES			
37	147	YES	175	YES							
38	110		148	YES							

m = month, C = Ciclosporine, T = Tacrolimus, DM = Diabetes Mellitus

year in 7 of 31 (22.58%), at 3 years in 4 of 22 (18.18%) of the patients that have an evolution of 3 years with heart transplant and at 5 years in 1 of the 10 patients who survived 5 years after heart transplant (10%).

Under the age of 40 there were 20 patients — 6 with diabetes (30%) and over the 40 there were 18 patients — 7 with diabetes (38.89%).

Our study revealed an incidence of 28 % (7 of 25) in the group with BMI under 25 and 46.15% (6 of 13) in the group with BMI over 25.

The incidence of diabetes in our posttransplant patients was 22.22% after 3 months of treatment (2 of 9), 23.08% (3 of 13) after 6 months of treatment and 57.14% (8 of14) after 12 months of corticosteroid treatment, showing a positive correlation between the incidence of diabetes and the length of corticosteroid treatment.

The percentage of patients with new onset diabetes was 18.18% (2 of 11) of those who received cyclosporine and 40.74% (11 of 27) of those on tacrolimus.

Table IV presents the recipients of heart transplant with posttransplant diabetes, who presented major risk factors for this development.

Table V presents the complications in the evolution of transplanted patients.

Table V. Complications in diabetes mellitus/non diabetes mellitus patients

Complication	DM posttransplant patients (n=13)	Non DM posttransplant (n=25)
Acute rejection	3 (23.07%)	5 (20.00%)
Coronary disease	2 (15.38%)	1 (4.00%)
Arterial hypertension	5 (38.46%)	4 (16.00%)
Peripheral arterial disease	0 (0.00%)	2 (8.00%)
Renal failure	3 (23.07%)	4 (16.00%)
Infections	5 (38.46%)	11 (44.00%)
Deaths	2 (15.38%)	6 (24.00%)

Discussions

It appears that the resulting values in our study regarding the incidence of new onset diabetes in post-heart transplant pacients are superimposable to those mentioned in the literature for 1 year follow-up posttransplant. Our study group was too small to properly assess 5-year data, and our results are different from those in the literature.

Considering the significant incidence of metabolic diseases, diabetes is currently a serious problem for solid organ transplant recipients, including heart transplant, with an increasing incidence, as long as post-transplant survival is increasing.

Family history of diabetes in first degree relatives is considered an important risk factor in the development of diabetes in heart transplant patients, according to literature data. In our situation, this risk factor was not superimposable with the results of these data, probably because the only way of screening was the history of transplant recipient on first degree relatives and not their actual screening, as is the case of the studies on this subject.

The second major risk factor in the development of diabetes in heart transplant patients is the age of the transplant recipient. Our study confirms the results of similar studies that recipients over 40 years of age have a significantly higher incidence of posttransplant new onset diabetes, than those under the age of 40.

Obesity is another significant risk factor incriminated in the etiology of diabetes in heart transplant patients. We

found that a BMI over 25 is an important independent risk factor in the occurrence of posttransplant new onset diabetes. Existing studies in this area indicate an incidence of new onset diabetes of 20.3% in patients with a BMI below 25 and 49.2% in patients with a BMI over 25 [8].

Immunosuppressive therapy with corticosteroids is considered most likely to trigger new onset diabetes mellitus after solid organ transplant. Any reduction in the dose of corticosteroid therapy must be properly balanced against the possible development of cardiac allograft rejection. The use of calcineurin inhibitors (CNIs) — cyclosporine and tacrolimus — as immunosuppressive therapy is associated with an increased risk of onset of posttransplant diabetes. There is evidence that tacrolimus is more diabetogenic than cyclosporine, particularly in patients with increased cumulative risk for this development. Calcineurin inhibitors treatment waiver is not recommended, due to an increased risk of allograft rejection.

The incidence of acute rejection is not favored by diabetes mellitus. Allograft vasculopathy is the main cause of allograft dysfunction and the main factor limiting long-term survival in heart recipient patiens. This complication is considered to be influenced by diabetes through their metabolic disturbances.

Arterial hypertension and chronic peripheral arterial disease are frequent complications in heart transplant patients with new onset diabetes. Renal failure is also favored by diabetes in heart transplant recipients.

Infections in posttransplant patients are very important complications, representing a high risk in situations of new onset diabetes.

The short-term (1 year) and long-term (5–10 years) survival rates were similiar in both posttransplant diabetes and non-diabetes recipients in the majority of studies. In our study, we analyzed this indicator at 1 years post-transplant: 6 of 7 (85.71%) patients with diabetes mellitus survived compared to 23 of 24 (95.83%) patients without diabetes.

Conclusions

New onset diabetes mellitus in heart transplant recipients is a serious complication of solid organ transplantation. Its high incidence, as well as the complications that result, require a fair and rigorous screening for risk factors in recipients on waiting lists, an early and accurate diagnosis and an early and effective treatment, in order to accomplish a positive impact in the evolution of heart transplant patients.

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