ORIGINAL ARTICLE

Impact of Diabetes Mellitus on Heart Transplant Patients

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Introduction and objectives. At present, there is some controversy about the impact of diabetes mellitus on heart transplant patients. The effect of the disease on mortality and on other complications, such as infection or rejection, is unclear. The objective of this study was to investigate these factors in our heart transplant patients.

Methods. We studied 365 consecutive patients who underwent heart transplantation between November 1987 and May 2003. We divided them in 3 groups according to whether they had pretransplantation diabetes (Group 1), de novo diabetes (Group 2), or no diabetes (Group 3). Baseline variables and the development of complications were recorded, and findings were analyzed using Student *t* test, χ^2 test, and Kaplan-Meier survival analysis.

Results. There was no difference in the 1-year or 5-year survival rate between the groups (*P*=.24 and *P*=.32, respectively). Patients with pretransplantation and de novo diabetes were older (54.6 years vs 54.9 years vs 50.6 years, *P*=.04), had a higher prevalence of hypertension (48% vs 36% vs 23%, *P*=.001), and had more frequently been treated with tacrolimus (10% vs 12% vs 4%, *P*=.04) or steroids (92% vs 86% vs 70%, *P*=.001). The incidence of rejection during follow-up was greater in these 2 groups (64% vs 70% vs 45%, *P*=.001).

Conclusions. Neither pretransplantation diabetes nor de novo diabetes had a negative impact on survival in our heart transplant patients. The disease's presence was associated with treatment with steroids and tacrolimus. In these patients it would be preferable to individualize immunosuppressive therapy.

Key words: *Diabetes mellitus. Transplantation. Survival. Complications.*

Impacto de la diabetes mellitus en el paciente con trasplante cardiaco

Introducción y objetivos. Actualmente, el impacto de la diabetes mellitus en los pacientes con trasplante cardiaco es controvertido y su efecto sobre la mortalidad y otras complicaciones, como las infecciones y los rechazos, no está completamente aclarado. El objetivo de este estudio es analizar estos efectos en nuestra población de pacientes trasplantados.

Métodos. Se ha estudiado a una población de 365 pacientes consecutivos con trasplante cardiaco desde noviembre de 1987 hasta mayo de 2003, dividiéndolos en 3 grupos en función de la presencia de diabetes pretrasplante (grupo 1), diabetes de novo (grupo 2) y no diabéticos (grupo 3). Se analizaron variables tanto basales como de complicaciones evolutivas, y los resultados se compararon mediante test t de Student, test χ^2 y método de Kaplan-Meier para la supervivencia.

Resultados. No apreciamos diferencias entre grupos en la supervivencia al año (p = 0,24) ni a 5 años (p = 0,32). Los pacientes de los grupos con diabetes mellitus pretrasplante y de novo tenían mayor edad (54,6 frente a 54,9 frente a 50,6 años; p = 0,04), mayor prevalencia de hipertensión arterial (el 48, el 36 y el 23%; p = 0,001) y mayor porcentaje de tratamiento con tacrolimus (el 10, el 12 y el 4%; p = 0,04) y esteroides (el 92, el 86 y el 70%; p = 0,001). Evolutivamente, estos 2 grupos presentan mayor incidencia de rechazo (el 64, el 70 y el 45%; p = 0,001).

Conclusiones. La diabetes previa al trasplante o de novo no tuvo impacto negativo sobre la supervivencia de nuestros pacientes trasplantados. Su presencia se asocia al tratamiento con esteroides y tacrolimus. En estos pacientes sería deseable realizar un ajuste individualizado de la inmunodepresión.

Palabras clave: *Diabetes mellitus. Trasplante. Supervivencia. Complicaciones.*

INTRODUCTION

Diabetes mellitus (DM) is a systemic disease with a high prevalence around the world. Some 176 million people were estimated to have DM in 2000, and its

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ABBREVIATIONS

DM: diabetes mellitus.
HT: heart transplant.
AGF: acute graft failure.
GVD: graft vessel disease.

prevalence is expected to increase over the coming years.[1] Cardiovascular disease in patients with DM can become evident in different ways, such as coronary artery disease, heart failure, stroke, or peripheral arterial disease,[2] and it is the cause of death in 65% of DM patients.[3] Patients with DM also have a greater susceptibility to infection.

Patients who have undergone transplantation have a high incidence of new onset DM. The accumulative incidence of DM after transplantation is around 30% 5 years after surgery.[4,5] Clinical trials suggest that kidney transplant patients who develop de novo DM, apart from the complications derived from both macroangiopathy and microangiopathy that are seen in the general population, have a greater incidence of graft complications[6] and a worse survival.[7-9] The development of de novo DM has also been shown to be an independent risk factor for death in the liver transplant patient.[10] Two studies undertaken in kidney transplant recipients suggest that the greater incidence of infections, and consequently the higher risk for sepsis in transplant patients with DM, may contribute to the increase in mortality.[11,12] However, the impact of DM in the heart transplant (HT) patient is less well established. Whilst some studies have shown that HT patients with DM do not necessarily have a higher risk for infection or rejection,[13,14] other studies suggest the opposite.[15] The aim of this study was analyze in our HT patients the impact of DM, either present prior to transplantation or of new onset after transplantation, on mortality and other complications requiring hospital admission.

PATIENTS AND METHODS

We studied 365 consecutive HT patients who underwent transplantation between November 1987 and May 2003. Pediatric patients and those who received a combined heart and lung transplant or a retransplantation were excluded from the study. The diagnostic criteria for DM were the need for treatment, either with oral antidiabetic agents or insulin, for at least four weeks.[16]

The patients were divided into 3 groups: those who had DM prior to transplantation (n=50, Group 1), those who developed DM after transplantation (n=65, Group 2), and those who did not develop DM (n=250, Group 3). Variables analyzed included those associated with the donor, the immunosuppressive therapy given and the post-transplant course of the patient, in an attempt to detect differences between the 3 groups both at baseline and after transplantation.

Post-transplant complications were considered to be those requiring hospital admission. Amongst these, acute graft failure (AGF) was considered to be present when: *a)* severe ventricular dysfunction was noted at surgery with prolonged surgery time prior to sternal closure, *b)* high doses of various inotropic drugs were required during the first 24 hours after transplantation, or *c)* hemodynamic worsening occurred with ventricular dysfunction detected by echocardiography during the immediate post-operative period. The presence of acute rejection was documented either by endomyocardial biopsy (histologic grade greater than 2), or clinically from the presence of symptoms and signs of frank heart failure which responded to specific treatment, or by echocardiographic findings (previously non-existing left or right ventricular dysfunction). Graft vessel disease (GVD) was not systematically searched for, but rather it was suspected from clinical criteria related with heart failure in the absence of acute rejection, chest pain suggestive of angina, and arrhythmia, and diagnosed by coronary angiography with intravascular ultrasound. Kidney failure was defined as the presence of sustained serum creatine concentrations >1.5 mg/dL during the follow-up. The other complications (neurologic, bone, and digestive complications, infections and the need for dialysis) were recorded as such when the diagnosis was established either clinically or by complementary studies.

The univariate statistical analysis was undertaken using the Student *t* test for numerical variables and the χ^2 test for categorical variables. Survival was analyzed from Kaplan-Meier curves and the log-rank test. The calculations were performed with SPSS 9.0®.

RESULTS

The baseline characteristics of the HT patients showed that those who had DM prior to transplantation, as well as those who developed DM after transplantation, were older and had a greater prevalence of hypertension. The group of patients who developed de novo DM included a lower percentage of NYHA Functional Class IV patients prior to transplantation than the group with prior DM and the control group. These patients with de novo DM also included a lower proportion requiring an urgent operation. Concerning immunosuppressive therapy, both groups of DM patients had a higher proportion of patients being treated with tacrolimus and steroids than the control group patients (Table 1).

The mean overall survival was 2793±153 days for the group without DM (median, 4117 days; SD, 941),

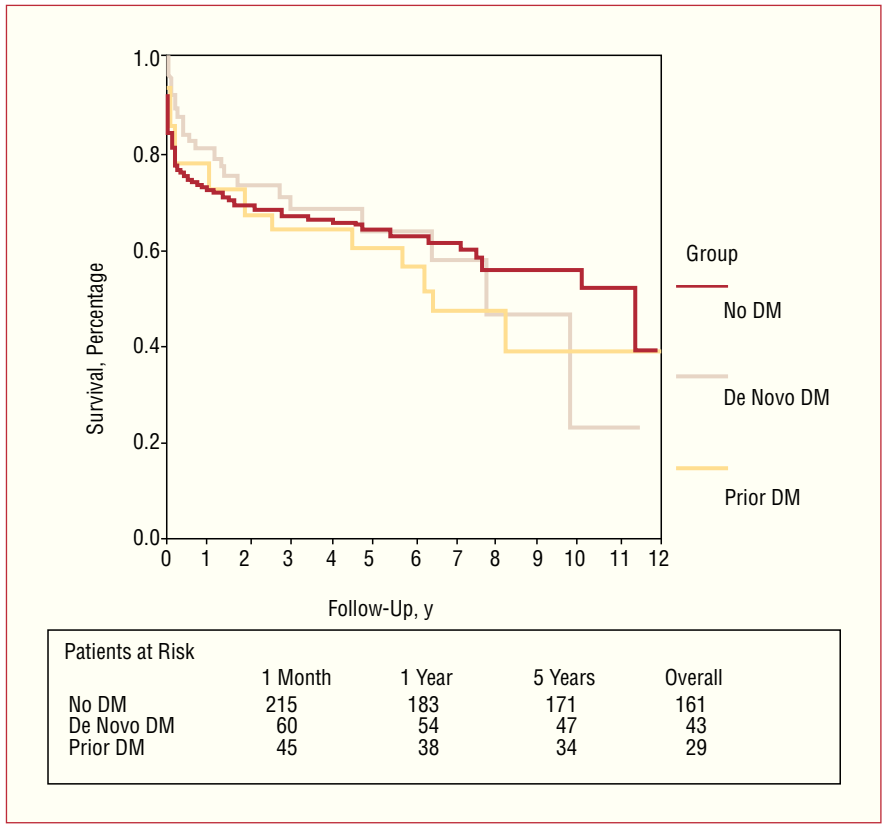

Figure. Overall Kaplan-Meier survival analysis (*P*=.78). DM indicates diabetes mellitus

2467±277 days for the group with de novo DM (median, 2815 days; SD, 448) and 2384±296 days (median, 2330 days; SD, 490) for the group with previous DM. No significant differences were noted between the groups (*P*=.78) (Figure). One-year survival and 5-year survival after transplantation in the patients with DM (both prior and de novo), were not significantly different (*P*=.24 and *P*=.32) as compared with the control group.

Analysis of the variables related with the follow-up of the 3 groups showed that both the patients with prior DM and those with de novo DM had a higher incidence of episodes of acute rejection. The remaining variables (infections and other complications leading to hospital admission) showed no significant differences between groups (Table 2).

DISCUSSION

Diabetes mellitus has been considered a relative contraindication for inclusion of patients on the HT waiting list, owing to the possibility of having more infections and worsening due to immunosuppression therapy with steroids.[17] However, new immunosuppressive drugs are currently available whose combination permits us to reduce the dose of steroids in these patients and achieve a better

TABLE 1. **Baseline Characteristics of the Study Groups***

	Prior DM (N=50)	De Novo DM (N=65)	No De Novo DM (N=250)	*P*
Age, y	55	55	51	.04
BMI	27	27	26	.06
Male	86%	89%	88%	.8
Smoker	34%	40%	37%	.8
Dyslipidemia	24%	35%	39%	.1
NYHA Class IV	62%	37%	55%	.01
Kidney failure	16%	7.7%	6.4%	.07
Hypertension	48%	37%	24%	.001
Etiology				
Ischemic	46.0%	46.2%	50.4%	
Dilated	40.0%	41.5%	38.8%	.9
Valvular	12.0%	10.8%	8.4%	
Other	2.0%	1.5%	1.6%	
Prior CVS	18%	20%	25%	.3
Urgent transplant	18.0%	9.2%	26.4%	.009
Immunosuppression				
CsA	84.0%	86.2%	82.4%	.7
AZA	46.0%	47.7%	43.6%	.8
MMF	36.0%	46.2%	35.6%	.28
TAC	10%	12.3%	4%	.042
STE	92.0%	86.2%	70.0%	.0001

*BMI indicates body mass index; CVS, cardiovascular surgery. CsA, cyclosporin; AZA, azathioprine; MMF, mycophenolate mofetil; TAC, tacrolimus; STE, steroids.

TABLE 2. **Evolutionary Factors in the Study Groups***

	Prior DM (N=50)	De Novo DM (N=65)	No De Novo DM (N=250)	*P*
Mean time	2384± 296 days	2467± 277 days	2793± 153 days	
AGF	18%	21%	26%	.37
Rejections				
None	36.0%	29.2%	55.6%	
One	34.0%	30.8%	22.0%	.001
Two or more	30.0%	40.0%	22.4%	
Infection				
None	56.0%	55.4%	64.0%	
One	28.0%	23.1%	22.4%	.4
Two or more	16.0%	21.5%	13.6%	
GVD	4.0%	3.1%	4.4%	.8
Neurological complications	16.0%	9.2%	8.8%	.2
Bone complications	8.0%	10.8%	8.8%	.8
Digestive C.	20.0%	17.2%	16.0%	.7
Kidney failure	42.0%	50.8%	56.0%	.1
Need dialysis	4.0%	0%	2.4%	.3
Mortality				
1 month	10%	8%	14%	.06
1 year	24%	17%	27%	.24
5 years	32%	28%	32%	.32
Overall	42%	34%	36%	.78

*AGF indicates acute graft failure; GVD, graft vessel disease; C, complications.

metabolic control. The aim of this study was to determine whether differences exist between HT patients with prior DM, those who develop DM after transplantation, and patients who do not develop DM, both in terms of survival and of complications requiring hospital admission during post-transplant follow-up.

The results of the analysis of the baseline characteristics of the study population showed that the patients with pre-transplant DM and the patients with de novo DM (Groups 1 and 2) were older and had a greater prevalence of hypertension, which is in agreement with the presenting characteristics for DM in the general population. However, unlike in other series, we found no differences between the three groups with respect to the body mass index, dyslipidemia, smoking, and the presence of kidney failure (serum creatinine >1.5 mg/dL).[4,11] Again, as elsewhere, we detected no differences between the groups relating to the inclusion diagnosis,[15] or the presence of previous heart surgery. However, we did find a lower percentage of Group 1 and Group 2 patients who were included urgently on the transplant waiting list. This finding may be due to the fact that patient selection criteria for an urgent transplant tend to be much more strict, in order to try to reduce the potential risks, given the greater likelihood of complications.

Regarding immunosuppressive therapy, we noticed a greater frequency for the use of tacrolimus among the patients with de novo DM as compared with the patients without diabetes, which is in line with other studies reporting that tacrolimus is up to five times more diabetogenic.[4] Nevertheless, tacrolimus was used more frequently in the patients with previous DM, which might be explained by conversion to this drug due to the greater incidence of rejection with cyclosporin. Steroid therapy was more common in patients from both Groups 1 and 2, which might be because of the greater presence of rejection in these groups and may have contributed to the Group 2 patients becoming diabetic.

The results seen concerning survival showed no significant differences between the 3 groups, either in the overall analysis or after one year or 5 years. This is in agreement with some, such as Marelli,[15] but not with others, for instance Czerny.[18-20] The patients with diabetes showed no greater incidence of AGF. Rejection was significantly more common in Groups 1 and 2 than the non-diabetic patients. However, no differences were detected in the infection rates between the 3 study groups. This is unlike the results of other series,[13-15] and may perhaps be due to a more adjusted immunosuppressive regimen in our patients in an attempt to achieve better metabolic control.

The incidence of GVD was similar in the 3 groups, as it was in the study by Czerny.[18] However, it should be mentioned that GVD was not studied systematically, but just by clinical orientation, and the true incidence of this disease may have been underestimated in our study, as demonstrated in other studies that have carried out a systematic search for the disease.[15,21] With respect to other complications requiring hospital admission, we found no differences between the groups concerning the rates of neurologic, digestive, or bone complications. Nor did we detect any differences for the rates of kidney failure (defined as a serum creatinine >1.5 mg/dL), although the need for dialysis was more frequent in the group of patients who had DM before heart transplantation. This might have been due to the greater length of time the kidneys of the patients in this group had been exposed to the deleterious effects of diabetes.

It should be noted that this study has a series of limitations. Firstly, although it would have been more desirable to use the current diagnostic criteria for DM,[22] we, like others who have studied this particular topic, have had to follow the criteria relating to the need for treatment for at least four weeks. Likewise, we were unable to stratify the patients with diabetes according to whether they were insulin-dependent or not, since the characteristics of these patients often make it necessary to alternate the type of glycemia-lowering treatment depending on the dose of the immunosuppressive treatment and the presence of

certain events, such as rejection. Another limitation of this study concerns the evaluation of the rates of GVD, which, as mentioned earlier, was not searched for systematically. Concerning the study design, it should be noted that we are unable to determine which of the patients who died early in the control group would have developed de novo DM, which could reflect a worse prognosis for the patients without DM. However, we believe that this effect was minimized by comparing the results with a group of patients with DM before transplantation.

CONCLUSIONS

The follow-up undertaken in our series of heart transplant patients showed that the presence of diabetes mellitus prior to transplantation or de novo DM after transplantation had no negative impact on survival. The presence of DM was associated with greater use of steroid therapy (probably associated with a higher rate of rejection during the follow-up) and tacrolimus. These patients would benefit from individual adjustment of their immunosuppression therapy in order to reduce the incidence of rejection without increasing the rate of other complications. Accordingly, the withdrawal, or at least the early reduction, of the steroids would be useful, since although steroid therapy may increase the rejection rate it does not increase mortality. A greater use of immunosuppressive therapy with other less diabetogenic drugs would also be of benefit. Further studies with a longer follow-up are desirable in order to better define the impact of diabetes mellitus in heart transplant patients.

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