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Institutional report - Transplantation

Diabetes as an outcome predictor after heart transplantation☆

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Abstract

We aimed to compare post-transplantation morbidity and survival among heart transplant recipients with and without diabetes mellitus. A retrospective review of 141 adult patients submitted to heart transplantation from November 2003 to June 2009 (with a minimum follow-up of one year) was undertaken. The patients were divided into two groups: those with (29%) and those without (71%) pre-transplantation diabetes. Those with diabetes were older (57.6±6.1 vs. 52.3±11.1 years; *P*=0.020) and had lower creatinine clearance (53.6±15.1 vs. 63.7±22.1; *P*=0.029). Nine patients died in hospital (6.4%; *P*=non-significant). No significant differences in lipid profiles (diabetes vs. no diabetes) existed before transplantation or at one year afterwards. Patients with diabetes showed a significant deterioration in their one-year lipid profile (158±43 vs.192±38 mg/dL; *P*=0.001), although one-year fasting diabetic was lower than before (178±80 vs. 138±45 mg/dL; *P*=0.016). During the first year, 17 (17%) patients previously free of diabetes developed new-onset diabetes. No significant differences were seen in rejection at one year (14% vs. 20%), infection (31% vs. 33%), new-onset renal dysfunction (8% vs. 14%) or mortality (17% vs. 7%). One-year survival was not significantly different (83% vs. 94%), but there was a significant decrease in the survival of individuals with diabetes at three years (73% vs. 91%; *P*=0.020). No significant difference was found in one-year survival or in terms of higher morbidity in the heart transplant patients with diabetes, but a longer follow-up showed a significant decrease in survival. Nonetheless, the patients with diabetes benefited significantly from transplantation and should not be excluded from it.

Keywords: Complications; Diabetes mellitus; Heart transplantation; Survival

1. Introduction

The prevalence of diabetes mellitus is increasing worldwide and is a significant risk factor for cardiovascular disease, which can manifest as coronary artery disease, heart failure, stroke and peripheral arterial disease, representing 65% of all the deaths in the diabetic population [1].

Transplantation is now the gold standard for the treatment of end-stage heart failure, and the number of patients with diabetes is increasing. Some studies have highlighted an increased risk of infection post-transplant, rejection, coronary artery disease, renal failure and mortality in diabetic recipients [2–4]. The International Society for Heart and Lung Transplantation (ISHLT) database shows an increase of 20–40% in late mortality among those with diabetes [5]. However, the results are sometimes contradictory, and some authors have found no differences in survival [3]. Recently, we reported no difference in survival at one year after transplantation [6].

On the other hand, immunosuppression aggravates pre-transplant diabetes and increases the post-transplant risk of new-onset diabetes [7]. Recent studies have shown that the incidence of new-onset diabetes after the first year of transplantation varies from 2% to 50% [6,8] and affects outcomes. Hence, some centres have been reluctant to offer transplantation to patients with insulin-dependent diabetes.

Here, we intended to determine the morbidity and survival among heart transplant recipients with and without diabetes at our centre to try to understand how diabetes mellitus might affect late outcome.

2. Methods

2.1. Study protocol

Between November 2003 and June 2009, 141 patients over 18 years of age underwent first heart transplantation. Patients with diabetes mellitus without severe secondary end-organ disease [retinopathy, neuropathy or nephropathy with creatinine clearance (CrCl) <40 ml/min under optimal medical therapy] [5], even with suboptimal glycaemic control, were included. The diagnosis of diabetes followed the American Diabetes Association criteria (fasting glucose ≥126 mg/dl or two occasional measurements >200 mg/dl and symptoms of hyperglycaemia) [9].

The surgical technique employed was total transplantation with bicaval anastomoses. All patients underwent immunosuppression induction with the anti-interleukin-2

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monoclonal receptor antibody (basiliximab) and maintenance therapy mainly with cyclosporin (89% of patients) or tacrolimus, in association with mycophenolate mofetil and prednisone. All 132 patients who were discharged from hospital (94%) were medicated with a statin dose-adjusted to their lipid profile, and were highly incentivised to adopt personalised dietary and physical activity programmes.

For the purpose of this analysis, performed from a prospectively organised database, the population was divided into two groups according to whether patients did or did not have pre-transplantation diabetes. All patients were followed by a dedicated group of surgeons and cardiologists, applying internationally accepted consultation and myocardial biopsy schedules. The follow-up was 100% complete and extended from 12 to 68 months.

The following complications were recorded: (1) mortality (cerebrovascular, cardiovascular, infection, rejection, postoperative haemorrhage, and other); (2) severe infection; (3) malignancies; (4) renal dysfunction (creatinine >2 mg/dl); and (5) acute rejection (grade ≥2R of the ISHLT classification of myocardial biopsy).

2.2. Statistical analysis

Continuous variables are presented as mean±standard deviation (S.D.). Comparison between the two groups was made using the Student's unpaired *t*-test or the Mann–Whitney test, depending on whether or not the variables had a normal distribution. Categorical variables are expressed in percentages and were analysed using the χ^2-test or Fischer's exact test. Survival was analysed by the Kaplan–Meier method and the log-rank test. Multivariate Cox regression analysis was used to test predetermined clinically important variables. A value of $P<0.05$ was considered statistically significant.

2.3. Baseline characteristics

The pre-transplantation demographic and general characteristics of the patients are shown in Table 1. Forty-one of the 141 patients (29%) had diabetes mellitus, of whom 80% were medicated using various insulin regimens. The patients with diabetes were older, but there were no statistically significant differences in the prevalence of cardiovascular risk factors or ischaemic heart failure between the two groups.

Table 2 shows the pre-transplant laboratory data. Diabetic patients more frequently presented a lower CrCl <60 ml/min (71% vs. 51% of those without diabetes) and significantly higher fasting plasma glucose levels. There were no significant differences in the lipid profile, uric acid or C-reactive protein level, or pre-transplantation haemodynamic data between the groups (Table 3).

There were also no significant differences in relation to the characteristics of the donors (32±11 years, body mass index 24.9±3 kg/m^2, and similar inotropic regimens). The mean time of myocardial ischaemia was 93.1±35.4 min, with no significant differences (96.5±38.0 for those with diabetes vs. 91.8±34.4 min for those without; P=0.99).

3. Results

3.1. New-onset diabetes

During the first year post-transplantation, 17 patients (17%) developed new-onset diabetes; these were kept in

Table 1. Demographic and general characteristics of the population

	Population (n=141)	Diabetic (n=41)	Non-diabetic (n=100)	P-value[a]
Male (%)	77	80	75	0.91
Age (years)±S.D.	53.6±10.6	57.6±6.1	52.3±11.1	**0.020**
Aetiology of heart failure (%)				
Dilated CM	56.7	48.8	60.0	0.62
Ischaemic DCM	34.0	43.9	30.0	0.36
Restrictive MC	8.5	7.3	9.0	0.97
Others	0.7	0	1.0	0.64
Cardiovascular risk factors (%)				
Hypertension	16.3	24.4	13.0	0.25
Dyslipidaemia	19.9	19.5	20.0	0.86
Smoking	24.8	14.6	29.0	0.22
Family history of coronary artery disease	12.1	9.8	13.0	0.85
Body mass index (kg/m^2)±S.D.	23.8±3.1	24.3±2.7	23.5±3.2	0.16
Carotid disease	19.1	26.8	16.0	0.33
Peripheral arterial disease	15.6	22.0	13.0	0.38
NYHA class (%)				
III	57.4	61.0	56.0	0.90
IV	42.6	39.0	44.0	0.86
UNOS status (%)				
IA	6.7	9.8	4.0	0.39
IB	17.0	17.1	17.0	0.82
II	76.6	73.2	78.0	0.93
Sinus rhythm (%)	51.8	53.7	51.0	0.99
Atrial fibrillation (%)	20.6	19.5	21.0	0.95
Pacemaker rhythm (%)	22.7	12.2	27.0	0.18

[a]Diabetic vs. non-diabetic patients. **Bold** type represents statistical significance $P<0.05$. CM, cardiomyopathy; DCM, dilated cardiomyopathy; MC, myocardiopathy; NYHA, New York Heart Association; S.D., standard deviation; UNOS, united network for organ sharing.

Table 2. Pre-transplantation laboratory data

	Population (*n*=141)	Diabetic (*n*=41)	Non diabetic (*n*=100)	*P*-value[a]
Fasting glucose (mg/dl)±S.D.	127±58	178±80	106±25	**0.001**
Creatinine clearance (mg/min)±S.D.	60.7±20.8	53.6±15.1	63.7±22.1	**0.029**
Total cholesterol (mg/dl)±S.D.	167±50	158±43	171±53	0.18
Low-density lipoprotein cholesterol (mg/dl)±S.D.	107±37.8	98±36.1	111±38.1	0.14
Triglycerides (mg/dl)±S.D.	111±52	115±60	109±49	0.78
Uricaemia (mg/dl)±S.D.	6.8±2.4	7.0±2.3	6.7±2.5	0.51
C-reactive protein±S.D.	1.3±1.9	1.2±1.8	1.3±1.9	0.12

[a]Diabetic vs. non-diabetic patients. **Bold** type represents statistical significance *P*<0.05. S.D., standard deviation.

the non-diabetic group. Pre-transplant fasting glucose impairment was observed in 26% of those who remained non-diabetic and in 53% (nine patients) of those who had developed new-onset diabetes by the one-year follow-up (*P*=0.22). Although not statistically significant, fasting glucose impairment appeared to be a determining factor in the new onset of diabetes.

There was no significant difference in the immunosuppressive regimen: 94% of those with diabetes received cyclosporin, compared with 90% of those without (*P*=0.96). All patients who developed new-onset diabetes were initially medicated with cyclosporin. However, at one year there was a tendency for non-diabetic patients to have been changed to tacrolimus more often than those with diabetes (10.4% vs. 2.8%; *P*=0.34).

3.2. Clinical course

There was a significant difference in the mean time of post-transplantation mechanical ventilation between patients with and without diabetes (23.6±47.2 h vs.16.9±16.6 h; *P*=0.017). There were nine hospital deaths (6.4%), as a result of hyperacute rejection, postoperative haemorrhage, cerebrovascular accidents and cardiovascular causes (two patients each) and one case of haemorrhagic pancreatitis, with no significant difference between those with and without diabetes (12.2% vs. 4.0%; *P*=0.20). The mean hospital stay was 16.3±14.9 days (median 13 days), also with no significant difference between the groups (15.9±9.7 for those with vs. 16.4±16.6 for those without diabetes; *P*=0.45).

With regards to the laboratory data (Table 4), there was no difference in the lipid profile between the two groups at one-year follow-up, but there was a significant deterioration in the diabetic group compared with the pre-transplant situation (total cholesterol 192 mg/dl vs. 158 mg/dl, *P*=0.001; low-density lipoprotein cholesterol 118 mg/dl vs. 98 mg/dl, *P*=0.015). There was a significant improvement in the control of fasting glucose level in patients with diabetes (glucose 178 mg/dl pre-transplant vs. 138 mg/dl at follow-up; *P*=0.016). At one year post-transplant, 17 patients without diabetes (17%) had developed new-onset diabetes (see below); hence 40% of the patients were diabetic, and 68% of these were on insulin regimens.

There were four additional deaths during the first year, for a total one-year mortality (including perioperative mortality) of 9.2%, with no significant difference between the groups (17% in those with diabetes vs. 6.0% in those without; *P*=0.13), as shown in Fig. 1. Three of the late deaths were caused by infection. The survival at one-year follow-up was not significantly different (Fig. 2a), but at three years there was a significant decrease in the survival of diabetic patients (73% vs. 91%; *P*=0.020) (Fig. 2b). At five years, the difference was not significant (69% vs. 84%; *P*=0.29), probably due to the small size of the sample (Fig. 2c). Table 5 shows the estimated survival (in days, ±S.D.) and 95% confidence interval (CI) for individuals with and without diabetes at one, three and five years. There was no further evolution of the metabolic and haemodynamic profiles from those observed at one year.

Seven variables were tested to determine their influence on survival at one and five years: pre-transplantation diabetes (*P*=non-significant), pre-transplantation fasting glucose ≥126 mg/dl (*P*=non-significant), CrCl <60 ml/min (*P*=0.007 at one year; *P*=0.012 at five years), recipient's age >50 years (*P*=non-significant), donor's age >45 years (*P*=non-significant), status IA (*P*=0.048 at one year; *P*=non-significant at five years) and total ischaemia time >90 min (*P*=non-significant). Using multivariate Cox regression analysis at one and five years, only CrCl <60 ml/min was a significant independent predictor of mortality, with a hazard

Table 3. Pre-transplantation haemodynamic data

	Population (*n*=141)	Diabetic (*n*=41)	Non-diabetic (*n*=100)	*P*-value[a]
LVEF (%)±S.D.	20.3±7.9	19.8±6.4	20.5±8.5	0.15
PSAP (mmHg)±S.D.	45.9±14.9	48.6±16.5	44.6±14.0	0.19
VO_2 max (ml/min/kg)±S.D.	114±3.0	12.1±2.9	13.0±3.0	0.15
PVR (Wood units)±S.D.	2.7±1.2	2.6±1.1	2.7±1.3	0.64
Transpulmonary gradient (mmHg)±S.D.	8.5±4.4	9.8±4.8	8.0±4.1	0.053

[a]Diabetic vs. non-diabetic patients. LVEF, left ventricular ejection fraction; PSAP, systolic pulmonary artery pressure; PVR, pulmonary vascular resistance; S.D., standard deviation.VO_2 max; maximal oxygen uptake.

T49 Table 4. Laboratory data at one-year follow-up

T50		Population (*n*=132)	Diabetic (*n*=36)	Non-diabetic (*n*=96)	*P*-value[a]
T51	Fasting glucose (mg/dl)±S.D.	114±37	138±45	104±28	**0.001**
T52	Total cholesterol (mg/dl)±S.D.	202±45	192±38	205±47	0.14
T53	Low-density lipoprotein cholesterol (mg/dl)±S.D.	128±40	118±29	132±43	0.17
T54	Triacylglycerol (mg/dl)±S.D.	169±81	175±69	166±86	0.25
T55	Uricaemia (mg/dl)±S.D.	7.0±2.0	6.8±1.9	7.1±2.1	0.72

T56 [a]Diabetic vs. non-diabetic patients. **Bold** type represents statistical significance $P<0.05$. S.D., standard deviation.

ratio of 9.7 (CI 95% 1.26–74.82) at one year and 9.0 (CI 95% 1.12–72.03) at five years.

Forty-three patients (33%) had infectious episodes requiring antimicrobial and/or antiviral therapy and close monitoring or hospitalisation [11 with diabetes (31%) vs. 32 without (33%); *P*=0.98].

Fifty-two patients (39%) showed a deterioration in renal function during the first year after transplantation, but none required dialysis during this period; 16 of these patients (12%) had previously had normal renal function (8.3% of those with vs. 14% of those without diabetes, with initial CrCl ≥60 ml/min; *P*=0.67). However, at the three-year follow-up, three patients with diabetes (4.9% of those alive) needed dialysis. None of the diabetic patients required dialysis. A total of 24 patients (18%) had had at least one episode of acute rejection ≥2R of the ISHLT classification (total number of episodes, 29), with no significant difference between groups (Fig. 1).

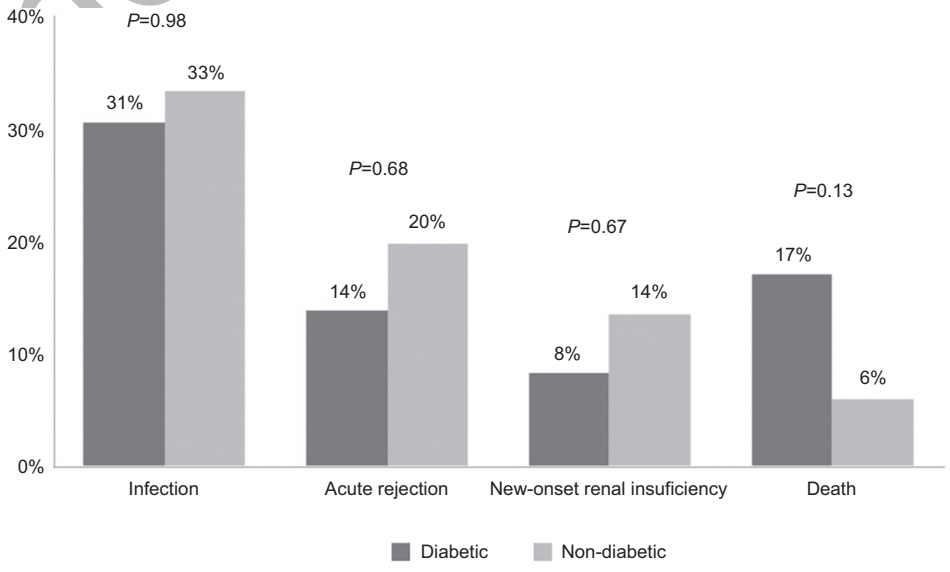
There were only three cases of post-transplant coronary artery disease (TCAD) at one-year follow-up, one in a patient with diabetes and two in patients without. One of these had developed new-onset diabetes. When comparing non-diabetic patients with patients with new-onset diabetes, there was no significant difference at the one-year follow-up (1.3% vs. 5.9%; *P*=0.34). No new cases of TCAD were detected up to the five-year follow-up.

At the five-year follow-up, there were 14 cases (11%) of neoplasia (19% in those with diabetes vs. 7.3% in those without; *P*=0.14). During the first year post-transplant, one non-diabetic patient developed a recurrent malignant neurological tumour (0.7% of the total transplanted population).

4. Discussion

Diabetes mellitus is generally seen as a risk factor for and a complication of heart transplantation and immunosuppressive therapy, being considered by some to be at least a relative contraindication to transplantation [10]. In our centre, the percentage of diabetic patients among heart transplant recipients (29%) was higher than in many published studies [3,4]. Nevertheless, the global survival at one-year follow-up (83%) was similar to that of patients without diabetes.

Neither fasting glucose impairment nor pre-transplantation diabetes were independent predictors of one-year mortality [6]. This is in accordance with some other authors' works, but differs from some studies with longer follow-up periods [2,11]. In fact, the three- and five-year mortalities observed in our study had already evolved to a lower survival in individuals with diabetes. We noticed no statistically significant differences in the incidences of infection, acute rejection or renal dysfunction during the first year, and this appeared to persist up to five years. In our centre, 23% of deaths at the one-year follow-up were due to infection, but there was no difference between patients with



F1 F2 Fig. 1. Mortality and morbidity during the first year post-transplantation.

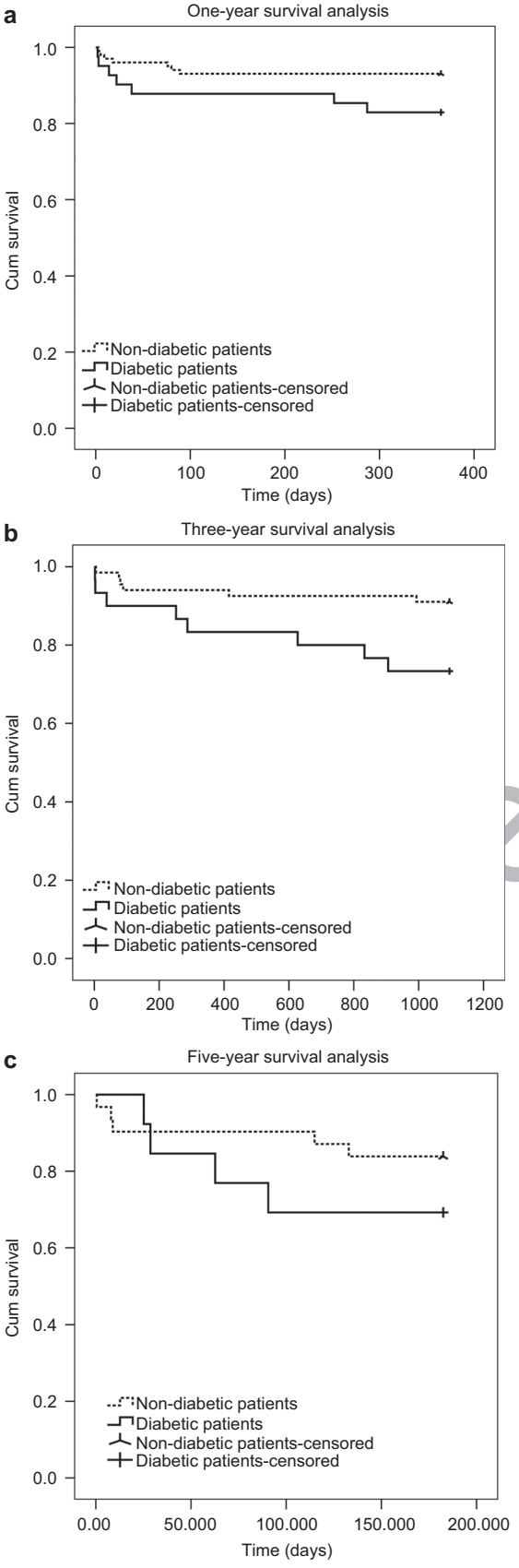


Fig. 2. (a) One-year survival of heart transplant recipients with (n=41) vs. without (n=100) diabetes (P=0.065). (b) Three-year survival of patients with (n=30) vs. without (n=67) diabetes (P=0.020). (c) Five-year survival of patients with (n=13) vs. without (n=31) diabetes (P=0.29).

Table 5. Estimate of survival (days±S.D.) of patients with and without diabetes and 95% confidence intervals (CI) at one, three and five years

	Condition	Estimate of survival time (days)±S.D.	95% CI	P-value[a]
One year	Diabetic	317.8±17.9	282.7–352.8	0.065
	Non-diabetic	342.5±78.3	326.3–358.7	
Three years	Diabetic	901.3±67.2	769.5–1033.0	**0.020**
	Non-diabetic	1021.7±31.2	960.4–1082.9	
Five years	Diabetic	1422.8±172.3	1085.1–1760.6	0.29
	Non-diabetic	1616.2±95.3	1429.5–1802.9	

[a]**Bold** type represents statistical significance P<0.05.

and without diabetes. The same was true for death due to cardiovascular causes (23%), acute rejection, haemorrhage and cardiovascular or cerebrovascular causes (15% each). By contrast, renal insufficiency (CrCl <60 ml/min) was confirmed as a significant predictor of one-year mortality (hazard ratio 9.7, 95% CI 1.26–74.82; P=0.029) and five-year mortality (hazard ratio 9.0, 95% CI 1.12–72.03; P=0.039).

The incidence of new-onset diabetes in our population was 17%, lower than that reported in other studies. It is known that immunosuppressors, especially the calcineurin inhibitors and steroids, play an important role in the development of diabetes. Tacrolimus is known to have a five-times higher diabetogenic effect than cyclosporin [4], and 18% of our non-diabetic patients who were changed to tacrolimus developed new-onset diabetes.

Our lower incidence of new-onset diabetes may also be explained by individualised therapeutic regimens and the aggressive metabolic control programme. It has previously been demonstrated that lipid-lowering agents, such as statins, raise the sensitivity to insulin and reduce the risk of new-onset diabetes after heart transplantation [12]. In addition, the use of drugs with known cardiovascular- and diabetes-protective properties, like angiotensin-converting enzyme inhibitors, which help to decrease insulin resistance [13,14], contributes to preventing new-onset diabetes and to delaying the metabolic effects of already present diabetes. However, oral glucose tolerance and haemoglobin A_{1c} level were not routinely tested at our centre, so the percentage of new-onset diabetes may be underestimated. Nevertheless, we observed a significant improvement in the control of fasting glucose levels in patients with diabetes at the one-year follow-up.

Finally, there was no difference between the lipid profiles of patients with and without diabetes, although we noticed a significant deterioration in the lipid profile of the diabetic group. Hence, we may say that having diabetes does not necessary raise the risk of complications associated with the lipid profile in the long-term. Additionally, 68% of diabetic patients were medicated with insulin regimens after heart transplantation, which makes it difficult to obtain long fasting periods; therefore, the assessment of lipid profile may be suboptimal in some patients.

This study has obvious shortcomings. The small size of our population and the short period of follow-up recommend caution in deriving conclusions and statistical significances. Larger series and longer follow-up studies are required to

better define the impact of diabetes mellitus in heart transplantation programmes.

5. Conclusion

In conclusion, no significant difference was seen in the prognosis of those with diabetes during the first year after heart transplantation, as long as patients maintained tight glucometabolic control. However, at three-year follow-up, survivals were significantly inferior among diabetic patients, although there were no significant differences in late morbidity. Preoperative fasting glucose impairment appears to raise the risk of development of new-onset diabetes after transplantation. Renal insufficiency was a predictor of one- and five-year mortality; hence, it is crucial to maintain a tight control and optimisation of renal function.

We believe that, overall, the results of heart transplantation in patients with diabetes mellitus are good, so this group should not be denied transplantation, although they require tighter glucometabolic control with individualised therapeutic regimens and lifestyle adjustments.

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Conference discussion

Dr. S. Daebritz (*Dusseldorf, Germany*): This interesting talk touches on the increasingly discussed issue of prioritising limited medical treatment for specific patients. According to the ISHLT Registry, about 20% of heart recipients are diabetic.

May I ask you for three comments: The mortality in follow-up is attributed to the comorbidity of diabetes potentiated by the side effects of immunosuppression. Did you coincidentally look at the time period the patients were insulin-dependent prior to transplantation, which the registries can't look at, just to see whether there is an impact of subclinical preexisting microvascular damage on outcome?

And second, did you have a specific regimen for the use of statins and control of the lipid profile and hypertension and weight in these patients?

And third, most importantly, did you apply a specific immunosuppressive protocol to these patients, particularly with regard to steroids? We had about more than 95% of patients steroid-free one year after transplantation, and this has proven to be beneficial, particularly for diabetic patients.

Dr Saraiva: Regarding the first question, some diabetics presented for transplant with a recent diagnosis of diabetes and so they were on insulin for a short time. So it's hard to say if they were on insulin for one year or just one month. We have some information on whether they were on insulin or oral antidiabetics, but we did not analyse that data.

About the second question, all the patients discharged from hospital were medicated initially with pravastatin, 20 mg, and then the statins were adjusted to the lipid profile of the patient. We insist on a rigorous diet and exercise program and medications, including statins, to control the lipid profile and to improve the glycaemic profile of diabetics.

As to the third question, the diabetic patients constitute a special therapeutic problem. So we adjust all the immunosuppressors individually. We try to avoid using tacrolimus initially in diabetic patients, because we know that it has a hyperglycaemic effect about five times greater than cyclosporine. We also try to reduce the steroids as soon as possible without compromising safety with regard to rejection.