

HEART TRANSPLANTATION IN PATIENTS WITH TYPE II DIABETES MELLITUS

ABSTRACT

Introduction: The risk of infections and failure of other organs can complicate the evolution of the diabetic patient who receives a heart transplant. The experience of a group of diabetic patients who received a heart transplant is presented.

Objective: To analyze the evolution, complications, and survival of diabetic patients receiving heart transplants.

Material and methods: Diabetic patients receiving heart transplants between October 1, 2010, and April 30, 2020, were selected. We analyzed age, sex, time of evolution with diabetes and treatment received, additional risk factors, presence of exacerbation of these complications, rejection reactions, post-transplant diabetes, infections, survival, and mortality and its causes.

Results: During the period analyzed, 181 heart transplants were performed; of these, 29 (16.02%) were performed in patients with diabetes mellitus. The predominant sex was male, and the indication for transplantation was ischemic cardiomyopathy; the time of evolution of diabetes was 10.2 years, and most patients were receiving treatment with oral hypoglycemic agents. As a cause of mortality, infections were predominant in the early and late postoperative stages, graft failure was predominant in the perioperative period, and graft vasculopathy was the cause of death after one year after transplantation. The highest number of deaths occurred in men (83.3%). The mean follow-up was 5.4 ± 2.95 years (range: 1-9 years).

Conclusion: When comparing the results with other series, we conclude that diabetic patients with end-stage heart failure can receive a heart transplant if there is strict metabolic control.

Keywords: *diabetes mellitus, heart transplantation, heart failure, graft vasculopathy, hypoglycemic agents, post-transplant diabetes.*

Authors:

Guillermo Careaga-Reyna¹,
Hugo Jesús Zetina-Tun², Efraín
Arizmendi-Urbe³

¹Medical Area, Medical Care Unit,
Mexican Institute of Social Security,
Mexico.

²Heart Transplant Clinic, High
Specialty Medical Unit, Hospital
General Dr. Gaudencio González
Garza, Centro Médico Nacional La
Raza, Instituto Mexicano del Seguro
Social, Mexico.

³Medical Care Unit, Mexican
Institute of Social Security, Mexico.

Corresponding author:

Guillermo Careaga-Reyna
gcareaga3@gmail.com

INTRODUCTION

Diabetes mellitus is one of the most prevalent chronic metabolic disorders; the International Diabetes Federation predicts that by 2025, there will be 300 million diabetics worldwide¹⁻⁴.

In diabetic patients, cardiovascular pathology causes 65% of mortality and can present as ischemic heart disease, heart failure, cerebrovascular disease, and peripheral arterial disease^{1,2}. In addition, people with diabetes are more susceptible to infections^{5,6}.

Most complications and 80% of deaths from atherosclerotic disease result from endothelial and vascular smooth muscle abnormalities, platelet dysfunction, vasoconstriction, and proliferative response at sites of injury.

The role that diabetes plays in heart transplant patients has not yet been uniformly defined^{1,2}. There are case series in which no significant differences are observed in the mortality of diabetic and non-diabetic heart transplant patients^{6,8}. However, it is known that heart transplant patients who present the three metabolic risk factors (systemic arterial hypertension, diabetes mellitus, and obesity) have a 63% increase in mortality. The results of heart transplantation as a treatment for end-stage heart failure in diabetic patients are shown here.

MATERIAL AND METHODS

The casuistry was taken from the High Specialty Medical Unit of the Mexican Social Security Institute, which, at the time of the review, had the most significant experience in heart transplantation in Mexico. Adult patients with type II diabetes mellitus with end-stage heart failure accepted and treated by heart transplantation between October 1, 2010, and April 30, 2020, were selected.

Age, sex, time of evolution of diabetes and its treatment, additional risk factors (systemic arterial hypertension, obesity, renal failure, retinopathy, peripheral vasculopathy), and, in the perioperative period, the presence or exacerbation of these complications and the presence of rejection reaction, post-transplant diabetes, infections, survival, and mortality and their causes were analyzed.

The preoperative evaluation considered the degree of target organ involvement. It included diabetic patients with retinopathy present (without legal blindness or previous ophthalmologic surgery), creatinemia of 2.0-2.5 mg/dL or proteinuria of 300-1000 mg/d, ankle-brachial index equal to 1 in any of the pelvic extremities, without pelvic limb amputation, and peripheral neuropathy or gastroparesis. Diabetic patients with heart failure and blindness or previous ophthalmologic surgery, creatinemia >2.5 mg/dL,

proteinuria 1 g/d, history of toe or pelvic limb amputation, and symptomatic orthostasis were not included in the transplant program.

RESULTS

Between October 1, 2010, and April 30, 2020, 181 heart transplants were performed, of which 29 (16.02%) were performed in patients with diabetes mellitus. In this group, the male sex predominated and, as the etiology of terminal heart failure, ischemic cardiomyopathy. Although the range of time of evolution of the disease is vast, the average was 10.2 years; the great majority of patients were receiving treatment with oral hypoglycemic agents (*Table 1*).

Tables 2 and 3 present the causes of mortality and the period in which they occurred. It is possible to observe the predominance of infections that appeared early and late in the postoperative period. In contrast, graft failure was predominant in the perioperative period, and graft vasculopathy was the cause of death after one year after transplantation. The highest number of deaths occurred in men (83.3%).

The mean time the deaths occurred was 659.2 days \pm 941.03, equivalent to 1.8 \pm 2.57 years (range: 1-2719 days).

In the group of patients who continue to be followed up at 5.4 \pm 2.95 years (range: 1-9 years), no significant difference was observed in the age at which they received heart transplantation, which was 53.6 \pm 7.15 years (range: 43-62 years), and 66.6% were male. In addition to the immunosuppression scheme, for diabetes control, one of them only takes diet (11.1%), four receive oral hypoglycemic agents (44.4%), and the remaining four, insulin glargine (44.4%).

DISCUSSION

Although diabetic patients with heart transplants have a shorter survival than non-diabetic patients, with a late mortality that varies between 20 and 40%, and, in addition, this group of patients is more susceptible to renal failure and post-transplant infections, when stratified, the diabetic patient with less severe disease has a survival comparable to the non-diabetic patient with heart transplant^{5,6,10,11}. In this same aspect, Megna et al. studied a group of 952 heart transplant patients between 2010 and 2018, of whom 28.78% were diabetic. When they separated them into two groups with and without adequate metabolic control, they did not observe significant differences in chronic vasculopathy, non-fatal major cardiac events, transplant rejection, need for dialysis, or infection at one year of follow-up. However, they did observe higher mortality at

Demographic data	Number and percentage (%) of patients
Males	22 (75.86)
Women	7 (24.13)
Age (years)	52,75 ± 7,05 (rango 40-65)
Ischemic cardiomyopathy	24 (82.75)
Dilated cardiomyopathy	5 (17.25)
Time of evolution of diabetes (years)	10,27 ± 5.92 (rango: 1-21)
Pretransplant treatment of diabetes	
Diet	1 (3.44)
Oral hypoglycemic agents	22 (75.8)
Insulin	6 (20.7)
Blood group	
O+	13 (44.8)
A+	12 (42.4)
B+	3 (10.3)
AB+	1 (3.4)

TABLE 1. Demographic characteristics of the patients, time of evolution, and preoperative treatment received.

Etiology	Number and percentage (%) of patients
Post cardiorespiratory encephalopathy	2 (10.52)
Pulmonary sepsis	7 (38.8)
Abdominal sepsis	2 (10.52)
Primary graft dysfunction	2 (10.52)
Chronic graft vasculopathy	4 (21.04)
COVID-19	1 (5.25)

TABLE 2. Causes of mortality in diabetic patients with heart transplantation.

Time after transplant (days)	Number and percentage (%) of patients
<30	4 (22.2)
30-90	3 (15.78)
90-180	0
180-365	2 (10.52)
>365	9 (47.36)

TABLE 3. Periods in which deaths occurred after heart transplantation in diabetic patients.

one year in the group with poor metabolic control¹¹. This evolution in survival may be influenced by the fact that it has been observed that, in healthy hearts transplanted into diabetic patients, there is an early and progressive deposition of lipids in the myocardiocytes. This was shown by Marfella et al. in a study in which they found a significant difference in deposition ($p = 0.019$) when comparing three groups of patients: i) healthy patients (without lipid deposition), ii) diabetic patients treated with metformin, and iii) untreated diabetic patients who presented significant lipid deposition¹².

Evidence indicates that the diabetic patient with end-stage heart failure who has reasonable metabolic control may have a prognosis of recovery after heart transplantation equivalent to that of the patient with heart failure without diabetes, so the possibility of offering transplantation to diabetic patients should not be ruled out after careful selection^{8,13}. On the other hand, perhaps patients with complicated diabetes should be included in the lists of high-risk patients, destination therapy, or other treatment options^{9,10,13} since it has been observed that diabetic patients who receive support with ventricular support systems in the pre-transplant stage have a better evolution. Therefore, it would be a good option to leave mechanical circulatory support as destination therapy and not as a bridge to transplantation¹⁴.

When comparing the results of our study, there is a lower percentage of diabetic patients in our series (16.02% versus 28.78%), 30-day mortality similar to that of other series (22.2% versus 28.6%), and mortality due to sepsis higher than in other series (50% versus 17.2%)^{9,14}; therefore, these results could not be attributed to diabetes alone given the lower prevalence of the disease in our series. Undoubtedly, other perioperative and mid-term factors (surgery time, hemorrhage, duration of ventilatory support, and home care) have an influence.

On the other hand, the appearance of post-transplant diabetes has been observed in an average of 37% of patients (48% at six months, 36% at one year, 26% at two years, and 17% at three years). This condition implies a higher frequency of infections (80% versus 61%; $p = 0.036$) and lower survival at two years (16% versus 35%, $p = 0.046$), with a greater possibility of acute cellular rejection¹⁵.

Based on these findings, we conclude that it is feasible to perform heart transplantation in patients with diabetes mellitus after a comprehensive evaluation and very clear selection criteria, accompanied by strict metabolic control before and after transplantation. It is also necessary to keep in

mind other treatment options for heart failure in this type of patient⁹.

Declarations

The authors declare no conflict of interest.

REFERENCES

1. Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. *JAMA*. 2002 May 15;287(19):2570-81. doi: 10.1001/jama.287.19.2570. PMID: 12020339.
2. Mitka M. Rethinking treatment for patients with diabetes and cardiovascular disease. *JAMA*. 2002 May 15;287(19):2488-91. PMID: 12020317.
3. Howard BV, Rodriguez BL, Bennett PH, Harris MI, Hamman R, Kuller LH, Pearson TA, Wylie-Rosett J. Prevention Conference VI: Diabetes and Cardiovascular disease: Writing Group I: epidemiology. *Circulation*. 2002 May 7;105(18): e132-7. doi: 10.1161/01.cir.0000013953.41667.09. PMID: 11994263.
4. Poptsov VN, Zolotova EN. Heart transplantation in diabetic recipients. *Russian Journal of Transplantology and Artificial Organs*. 2018;20(1):120-126.
5. Saraiva J, Sola E, Prieto D, Antunes MJ. Diabetes as an outcome predictor after heart transplantation. *Interactive CardioVascular and Thoracic Surgery* 2011; 13: 499-504
6. Moro JA, Martínez-Dolz L, Almenar L, Martínez-Ortiz L, Chamorro C, García C, Arnau MA, Rueda J, Zorio E, Salvador A. Impacto de la diabetes mellitus en el paciente con trasplante cardiaco [Impact of diabetes mellitus on heart transplant recipients]. *Rev Esp Cardiol*. 2006 Oct;59(10):1033-7. Spanish. doi: 10.1157/13093980. PMID: 17125713.
7. Novitzky D. Comparación entre la cirugía de revascularización miocárdica y el implante de stent en el paciente diabético con enfermedad aterosclerótica. *Rev Arg Cardiol* 2009; 77 (4): 294-297.
8. Morgan JA, Ranjit John R, Weinberg AD, Colletti NJ, Mancini DM, Edwards NM. Heart transplantation in diabetic recipients: A decade review of 161 patients at Columbia Presbyterian. *J Thorac Cardiovasc Surg* 2004;127: 1486-1492.
9. Kilic A, Conte JV, Shah AS, Yuh DD. Orthotopic heart transplantation in patients with metabolic risk factors. *Ann Thorac Surg*. 2012 Mar;93(3):718-24. doi: 10.1016/j.athoracsur.2011.11.054. Epub 2012 Feb 2. PMID: 22305053.
10. Mehra MR, Kobashigawa J, Starling R, et al. Listing criteria for heart transplantation: International Society for Heart and Lung Transplantation guidelines for the care of cardiac transplant candidates—2006. *J Heart Lung Transplant* 2006; 25:1024–1042.
11. Megna D, Emerson D, Cole R, Levine R, Chikwe J, F. Esmailian F, et al. Orthotopic heart transplantation in the diabetic patient, are we still worried? A review of 952 consecutive patients. *Megna D y cols. J Heart Lung Transplant*. 2020; 39 (4S): S252.
12. Marfella R, Amarelli C, Cacciatore F, Balestrieri ML, Mansueto G, D'Onofrio N, et al. Lipid accumulation in hearts transplanted from nondiabetic donors to diabetic recipients. *J Am Coll Cardiol* 2020; 75 (11): 1249 – 1262
13. Russo M, Chenn JM, Hong KN, 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.
14. Weidner G, Hemmersbach M, Smits JMA, Kubiak T, Schulz U, Gummert J, et al. Prognosis of patients listed for a heart transplant during the pretransplant period: ¿does diabetes matter? *Diabetes Care* 2013; 36: e45-e46.
15. Alvarez CK, Nnani D, Patel SR, Goldstein D, Saeed O, Sims D, et al. Post-transplant diabetes mellitus and the risk of acute rejection in heart transplant. *J Heart Lung Transplant* 2020; 39 (4S): S244.