

LONG-TERM RESULTS OF RENAL TRANSPLANTATION IN 104 IRANIAN PATIENTS TRANSPLANTED ABROAD

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SUMMARY

The renal transplantation program in Iran had substantially been lagged behind in comparison to hemodialysis until 1985. Between 1979-1984, due to lack of the facilities, over 400 Iranian patients went abroad and underwent renal transplantation there. In order to evaluate the outcome of these transplants, all medical records of a nephrology clinic between the years 1978-1990 were reviewed and the records of 104 patients who had renal transplantation abroad were selected for this study. Out of these, 78 patients were transplanted from living related, 23 from cadaveric, and, 3 from living unrelated donors. Seventy-two percent of the transplants were carried out in England. The duration of follow-up since the date of transplantation, ranged from 3.5-14.8 years. The patient and graft survival rates in recipients of living related kidneys were significantly longer, but 23 cadaveric transplants (performed before cyclosporine) had inferior results. The most common cause of death was coronary artery disease. Four cases of malignancies were seen at an average time period of 70 months posttransplant. Coronary artery disease, septicemia, pneumonia, and

hypertension were more common in the recipients of cadaveric kidneys, and urinary tract infection in recipients of living related allografts.

KEY WORDS: *Coronary artery disease; Malignancy; Renal transplantation*

INTRODUCTION

The first renal transplantation was carried out in Shiraz in 1968 when small hemodialysis units were appearing in few university hospitals in Tehran. In 1976, an end stage renal disease office was established in the Ministry of Health to cover the dialysis expenses and to expand dialysis facilities throughout the country. The annual acceptance of new dialysis patients increased steadily, but the renal transplantation program of the country substantially lagged behind in comparison to hemodialysis until 1985. During 1976-1984, over 3150 dialysis patients were registered and referred to dialysis units, but only about 100 renal transplants were performed. Due to inadequate renal transplantation programs in the country, over 400 dialysis patients went abroad and underwent renal transplantation over there (1). Most of these patients returned home after transplantation and were followed up at nephrology clinics.

The purpose of this study is to evaluate the long-term results of these transplants being carried out abroad. As previously stated, since 1985, the renal transplantation programs of the country have been fostered by authorities of the

Ministry of Health, and over 1200 renal transplants have been carried out during 1985-1990 (2-4).

PATIENTS AND METHODS

All medical records of a nephrology clinic during 1978-1990 (over 21000 records) were reviewed and only the records of 104 patients who had renal transplantation abroad were selected for the study. Among them, 63 patients were male and 41 were female. The age of recipients at the time of transplantation ranged from 16-62 years. The duration of follow-up since the date of transplantation ranged from 3.5-14.8 years. All 104 patients were divided into three groups according to the type of their kidney donors. Group 1 consisted of 78 patients who had received renal grafts from their living related donors. The transplantations were carried out in: England (67), Germany (4), U.S.A. (3), Israel (2) (before February, 1979), Italy (1), and Austria (1).

In Group 2, there were 23 patients who were transplanted from cadaveric kidneys. The transplantations were performed in England (8), U.S.A. (7), France (5), Spain (2), and South

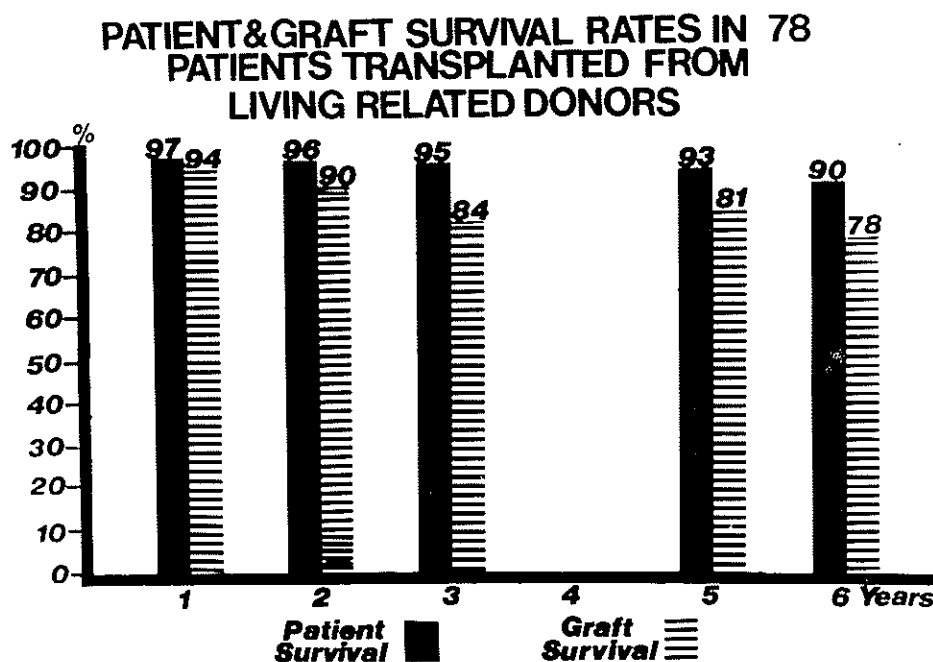


Figure 1. Patient and graft survival rates in 78 patients transplanted from living related donors.

Africa (1) (before February, 1979).

Group 3 consisted of just 3 patients from south-east (Baluchistan), who had travelled to India and had bought kidneys from unrelated live donors.

In 93 (89%) recipients, immunosuppression therapy was azathioprine and prednisolone. Only for eleven patients cyclosporine was used. The patients' records were also reviewed for causes of death and graft failure. The major long-term morbidity factors such as: coronary artery disease, malignancy, hypertension, cataract operation, steroid induced diabetes,

septicemia, urinary tract infection, avascular necrosis as well as the number and outcome of pregnancies were also studied.

RESULTS

The outcome of renal transplantation in 78 patients who received allografts from their alive relatives has been shown in Figure 1. The patient survival rates were 97%, 96%, 95%, 93%; 90%, and, graft survival rates were 94%, 90%, 84%, 81%, 78% within 1, 2, 3, 5, and 6 years respectively. The results of transplantation in 23 recipients of cadaveric kidneys have been

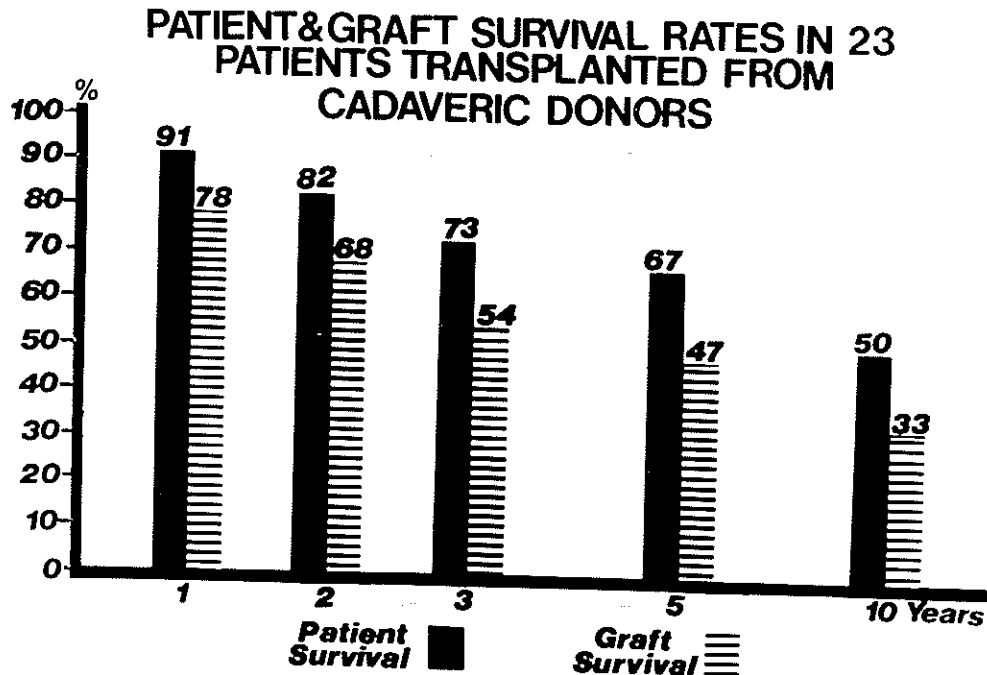


Figure 2. Patient and graft survival rates in 23 patients transplanted from cadaveric kidneys

shown in Figure 2. In this group, the patient survival rates were 91%, 82%, 73%, 67%, 50%; and, graft survival rates were 78%, 68%, 54%, 47%, 33% within 1, 2, 3, 5, and 10 years respectively.

Group 3 consisted of only 3 patients who had bought kidneys from unrelated live donors in India.

One patient rejected the graft 18 months posttransplantation and is now on chronic hemodialysis; two other recipients have

functional kidneys 46 and 47 months posttransplantation.

The patient mortality and graft failure were as follows: of the 104 grafts, 30 were lost subsequently; eight patients died despite having functional allografts; their death was due to myocardial infarction in 3, lymphoma in 2, sepsis in 1, tuberculosis meningitis in 1, and CVA (Cerebrovascular Accident) in 1. The twenty-two other patients lost their grafts because of chronic rejection. Five of the 22

patients with failed grafts died subsequently, two of myocardial infarction and three of septicemia (all five were recipients of cadaveric kidneys). Of the 17 alive patients, 5 had retransplants (1 from cadaveric and 4 from living relatives), and 12 patients continue to be dialysed.

Among 104 allograft recipients, at least 10 patients developed coronary artery disease (5 of the 7 patients who had acute myocardial infarction died, and 3 other recipients revealed typical angina pectoris). Nine of these 10 patients were male (age 30 to 56 years) and 5 of them had long smoking histories. Coronary artery disease was more common in recipients of cadaveric kidneys (22%; 5 of 23) as compared to recipients of living related allografts (6%; 5 of 78). Nine of these 10 patients had rejection episodes, requiring higher cumulative prednisone doses. Four cases of malignancies were seen at an average time period of 70 months post transplant.

PATIENT 1: A 38-year-old female who had been transplanted from her HLA identical sister in 1981 revealed abnormal Pap Smear four years posttransplant. A Wide Cone Biopsy was performed at that time and the carcinoma of cervix was confirmed. She has been followed up carefully in the last five years, but no recurrence of malignancy has been observed.

PATIENT 2: A 37-year-old male who had received a cadaveric renal transplant referred with obstructive jaundice and septicemia 43

months posttransplant. Laparotomy revealed non-Hodgkin's lymphoma and he died of septicemia.

PATIENT 3: A 40-years-old male who had received a living related renal transplant was admitted with severe weight loss about six years posttransplant. Work-up disclosed malignant lymphoma, and he died with septicemia several weeks afterwards.

PATIENT 4: A 34-year-old male transplanted from his haploidentical sister fifteen years ago. About ten years posttransplant, he developed chronic rejection and revealed Kaposi's sarcoma in his foot. Azathioprine and prednisone were reduced, Kaposi's sarcoma remitted significantly, but required chronic dialysis. After two years of dialysis treatment, he was retransplanted in 1988. In the last three years, he has been on cyclosporine, azathioprine, and prednisolone with careful follow-up. His Kaposi's sarcoma has not yet been relapsed.

The records of 101 recipients (Group 1 and 2) were also studied for prevalence of ten major morbidity factors and the results have been shown in Table 1. Coronary artery disease, septicemia, pneumonia, and hypertension were more common in the recipients of cadaveric kidneys, and urinary tract infection in the recipients of living related allografts.

Pregnancies occurred only in women who had received living related kidneys (12 patients, 26 pregnancies). There were seven spontaneous

abortions, one therapeutic abortion, eight premature deliveries, and ten pregnancies ended in full-term deliveries; 3 of 8 premature babies died (42% fetal death rate). No congenital abnormalities were observed.

DISCUSSION

Since 1985, renal transplantation programs of Iran have been fostered by the authorities of the Ministry of Health, and in the last five years, over 1200 transplants have been performed. As cadaveric kidney donation has not been possible, unrelated live donors with true voluntarism of consent have been accepted to solve the problem of patients who have no living related

donors (5). As a result, no more Iranian patients now are travelling abroad to receive a renal transplantation.

Seventy-five of 104 (72%) transplants have been performed in England. Renal transplantation abroad has been a luxurious treatment and not every patient has been able to afford it. Every Iranian patient who was going to England for a living related donor transplantation had to pay at least £ 12000 of his own fund to the hospital in London before the operation to be performed. For patients who had no living related donors, obtaining a cadaveric kidney in abroad has been difficult and much more costly.

Major morbidity factors	Relative N=78	Cadaveric N=23	Total N=101
1) Coronary artery disease	5 (6%)	5 (22%)	10 (10%)
2) Malignancy	3 (4%)	1 (4%)	4 (4%)
3) Septicemia	1 (1%)	5 (22%)	6 (6%)
4) Hypertension	24 (31%)	10 (43%)	34 (34%)
5) Steroid-induced diabetes	4 (5%)	1 (4%)	5 (5%)
6) Pneumonia	1 (1%)	3 (13%)	4 (4%)
7) Urinary tract infection	18 (23%)	3 (13%)	21 (21%)
8) Cataract operation	1 (1%)	1 (4%)	2 (2%)
9) Cerebrovascular accident	1 (1%)	---	1 (1%)
10) Avascular necrosis	---	1 (4%)	1 (1%)

Table 1. Prevalence of ten major morbidity factors in 101 renal transplant recipients (Groups 1 & 2)

In this study, only transplantations from living related donors had a significantly longer patient and graft survival rates. But 23 cadaveric transplants (performed before cyclosporine) had inferior outcome. Many morbidity factors have been also more common in cadaveric kidney recipients.

Coronary artery disease was the most common cause of death (38%; 5 of 13). Five of seven patients with posttransplant acute myocardial infarction died, and three patients had typical angina pectoris. The actual prevalence of ischemic heart disease is expected to be much higher than 10% (10 of 104). First of all, in similar studies ischemic heart disease was defined by the presence of myocardial infarction or more than 70% coronary occlusive disease

determined by coronary angiography or by the use of thallium stress testing (6). In this study, the whole determination of disease had to be based on myocardial infarction or typical chest pain only. Secondly, we still discourage our dialysis patients with coronary artery disease or insulin dependent diabetes to undergo renal transplantation. None of these 104 patients had pretransplant symptomatic coronary artery disease or insulin dependent diabetes.

Risk factors for posttransplant ischemic heart disease has been shown in Table 2. Not surprisingly, the list of risk factors is headed by pretransplant ischemic heart disease and followed by insulin dependent diabetes (7). Braun *et al* studied 100 patients with insulin

Variables	Relatives risk
Pretransplant ischemic heart disease	5.41
Insulin dependent diabetes	3.39
Male	2.02
Rejection (cumulative prednisolone doses)	1.35
Smoking	1.10
Age at transplant	1.05
Hematocrit	1.05

Table 2. Risk factors for posttransplant ischemic heart disease

dependent diabetes and end-stage renal disease; 25 had more than 70% coronary occlusive disease, and 75 had less than 70% occlusive

disease prior to transplantation (8). After renal transplantation, 13 of 25 and 8 of 75 had a new acute myocardial infarction at an average time

of 21 and 35 months respectively.

Patients who develop ischemic heart disease after renal transplantation, when compared with those without coronary disease, are predominantly male, have more rejection episodes or higher cumulative prednisolone doses, have long smoking histories, are older and hypertensive, have higher hematocrit, cholesterol and triglyceride levels.

Successful renal transplantation, thus, does not reduce and in fact appears to accelerate the rate of atherosclerosis. The possible role of prednisolone in this accelerated atherosclerosis is suggested by the cumulative higher doses in a study of 36 patients with SLE by BH, Bulkley, *et al* who showed that only 1 of 17 patients treated for six months developed greater than 50% coronary narrowing, compared with 8 of 19 patients treated for an average of 38 months (9). In patients with rheumatoid arthritis who received steroids, peripheral arteriosclerosis with medial necrosis and calcification was seen three times as frequently as in controls (10).

In this presentation, coronary artery disease was more common in recipients of cadaveric kidneys as compared to recipients of living related allografts (22% vs. 6%), most likely due to frequent rejection episodes and higher cumulative prednisolone doses in recipients of cadaveric allografts.

Malignancies were seen in four patients at an average time period of 70 months

posttransplant. Increased susceptibility to malignancies remains a serious transplant concern. The Cincinnati Transplant Tumor Registry reported that a total of 3054 malignancies occurred at an average of 64 months following predominantly renal transplantation in 2837 patients treated primarily with prednisolone and azathioprine. In contrast, the 366 patients whose treatment featured cyclosporine developed 373 malignancies at a much shorter average time after transplantation, 25 months (11). The relative risk following renal transplantation is 28-49 fold for non-Hodgkin's lymphoma, up to 400-500 fold for Kaposi's sarcoma, and 14 fold for carcinoma of cervix.

Sepsis, pneumonia, and hypertension were more common in recipients of cadaveric kidneys, most probably due to frequent rejection episodes, poor graft functions, and higher levels of immunosuppression.

Urinary tract infection was seen in 21 of allograft recipients. An interesting case was a 35-year-old male who had a renal transplant from his HLA identical sister. His allograft functioned for a period of twelve years. During this period, he had over fifteen recurrent urinary infections with *salmonella typhi*. Evaluation of bladder for schistosomiasis was negative. *salmonella* urinary infection disappeared soon after patient lost his graft; immunosuppressions were discontinued, and he started on chronic

hemodialysis.

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