

Delayed hypersensitivity skin tests and subsequent renal transplant outcome

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Summary

Background Some studies in the literature have supported, while others have denied, the relationship between results of delayed hypersensitivity skin tests (DHST), renal allograft and patient survival rates. Several factors contribute to the unreliability of these studies. For example, most of these studies were performed in the precyclosporine era, furthermore, other variables which influence renal allografts and patient survival rates were not controlled in those studies.

Objective The purpose of this study was to investigate the relationship between results of DHST performed in the pretransplant period with the subsequent renal transplant outcome in the cyclosporine era.

Methods The study included 103 first cadaveric renal transplant recipients. DHST were performed during pretransplant evaluation by intradermal injections of a battery of recall antigens. Based on skin-test results, the patients were assigned to two groups — those with a positive skin test (STP+) and those with a negative (anergic) skin test. These two groups were compared with each other regarding allograft survival, patient survival, and other variables known to influence survival rates.

Results The mean age, sex and racial distribution, degree of HLA matches between recipients and donors, number of acute rejection episodes, and number of patients with acute tubular necrosis were similar between the two groups. Renal allograft survival rates in the anergic group at 6 months, 1 year, 2 years, and 3 years were 97%, 90%, 84%, and 57%, respectively. The survival rate for renal allografts in the STP+ group for the same time points was 90%, 86%, 80%, and 72%, respectively. Patient survival rates for the anergic group at 6 months, 1 year, 2 years, and 3 years were 95%, 94%, 89%, and 85%, respectively, while those for the STP+ group were 98%, 98%, 98%, and 97% respectively. Differences between the STP+ and anergic groups, with regard to patient and allograft survival rates, were not significant.

Conclusion We conclude that DHST is not helpful in predicting outcome of patient or renal allograft survival rates over a 3-year time period.

Keywords: delayed hypersensitivity skin tests (DHST), renal allograft survival, patient survival, transplantation, kidney

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Introduction

Delayed hypersensitivity skin tests (DHST) to a battery of recall antigens are performed as bedside screening tests to evaluate a patient's cell-mediated immune

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response *in vivo* [1]. In the context of renal transplantation this may be relevant for two reasons. First, the most common cause of renal allograft failure are immunological rejection episodes. The cell-mediated immune responses are a major component leading to allograft injury in many rejection episodes. It is, therefore, likely that impaired cell-mediated immunity judged by unresponsiveness to DHST (anergy) in the pretransplant period may be associated with fewer rejections and better renal allograft survival rates. Secondly, cell-mediated immunity is an important arm of host defences against various bacterial, viral, fungal, protozoal, and other parasitic infections. It has been reported that the lack of responsiveness (anergy) to DHST may be associated with higher risk of morbidity and mortality resulting from infections [2–5].

Some studies in the literature have supported [2,3,5,6], while others [4,7] have denied, the relationship between results of DHST and renal allograft survival rates. There were several reasons for performing this study. First, the results of previous studies have been conflicting. Secondly, all the previous studies were performed in the precyclosporine era and, finally, other variables which influence renal allograft and patient survival rates were not controlled in the previous studies.

Materials and methods

This study included 103 first cadaveric renal transplants performed between February 1985 and December 1991 at the University Hospital/LSU Renal Transplant Service in New Orleans, Louisiana, USA. The study was approved by the LSU Medical Center Institutional Review Board. During pretransplant evaluation, DHST was performed by the standard method on either the right or left forearm [8]. The antigens used were a purified protein derivative of tuberculin (PPD), *Candida albicans*, tetanus toxoid, mumps and trichophyton. Tests were read at 48 and 72 h. A complete absence of induration at the test site and reactions with induration of less than 5 mm were considered negative. Patients were considered 'anergic' if responses to all antigens were negative, and positive if the response to at least one antigen was positive (>5 mm induration).

Patients were divided into two groups — the 'anergic' group and the 'skin-test positive' (STP+) group. Patients ranged in age between 24 and 59 years. All living donor transplants and cadaveric retransplants were excluded. The histocompatibility testing carried out in the pretransplant period revealed that none of the patients in either group were matched on five or six HLA A, B, C, or DR antigens with the donor. Both groups received a similar immunosuppressive therapy with prednisone,

azathioprine, and Cyclosporine A. Acute rejection episodes were treated with intravenous methylprednisolone and, when refractory, with OKT3 monoclonal antibody. Acute tubular necrosis (ATN) post-transplant was defined as the need for dialysis in the first 2 weeks after transplantation. The frequency of post-transplant ATN, a major variable which influences renal allograft survival, was similar between the two groups. The ATN rate in the anergic group was 10/37 (27%), while it was 16/59 (27%) in the STP+ group.

Logistic regression analysis was used to compare the differences between the two groups with regard to both patient and renal allograft cumulative survival at 6 months, 1 year, 2 years, and 3 years or more follow-up periods. The dependent variables were absence or need for dialysis and death due to sepsis by the end of each follow-up period; independent variables were anergy (DHST) and the following covariates: age, race, sex, total number of HLA A, B, and DR matches, number of acute rejections, and presence of ATN. Allograft survival curves for the two groups were drawn using actuarial methods.

Results

Table 1 indicates the distributions of the covariates in the two groups. None of these differences were significant. Renal allograft cumulative survival rates in both groups are shown in Table 2. There were four occurrences of graft loss due to causes other than rejection, namely primary non-function and recurrent disease. These graft failures are not included in Table 2. Statistical analysis using logistic regression showed that, after allowing for significant covariates, the response to DHST does not significantly affect graft survival. The odds ratio of graft survival up to 36 months in the STP+ group vs that of the anergic group was 1.15 with 80% confidence limits

Table 1. Distribution of covariates in the anergic and STP+ groups

Covariates	Anergic	STP+
Age (years) mean $\pm$ STD	39.7 $\pm$ 13.9	39.00 $\pm$ 12.2
Sex (% males)	56	68
Race (% white)	51	47
HLA matches (number)		
mean $\pm$ STD	1.69 $\pm$ 1.22	1.79 $\pm$ 1.22
Acute rejections		
(number) mean $\pm$ STD	0.77 $\pm$ 0.81	0.51 $\pm$ 0.70
ATN (% with ATN)	27	27

Table 2. Renal allograft cumulative survival rates*

Type of patient	6 months	1 year	2 years	3 years
Anergic	36/37† 97%	26/29 90%	16/19 84%	8/14 57%
Skin-test positive (STP+)	57/63 90%	51/59 86%	35/44 80%	28/39 72%

* Only graft failure due to rejection is included in Table 1.

† The numerator indicates the number of patients who had functioning renal allografts up to each time point. The denominator indicates the number of patients available for follow up at the different timepoints, including all previous failures.

(0.349 and 3.812). Figure 1 depicts survival rates for these groups based on actuarial analysis.

The patient cumulative survival rates in both groups are shown in Table 3. Eleven patients (five from the anergic group and six from the STP+ group) died of cardiac causes, cerebrovascular disease, or massive gastrointestinal bleeding. Those deaths are not included in Table 3.

Three patients, two from the anergic group and one from the STP+ group, died of infections. Those infections included gram negative bacterial septicaemia, cerebral aspergillosis, and disseminated tuberculosis. The patient who died due to tuberculosis had a positive PPD skin test and received chemoprophylaxis with Isoniazid for 1 year before transplantation. Differences in patient survival rates between the two groups were not statistically significant at any of the four time points used. The only significant covariates were ATN and the number of acute rejections. These two covariates were highly correlated specifically for renal allograft survival.

The renal allograft cumulative survival rates in patients with ATN ($n = 24$) were 80% at 6 months, 52% at 1 year, and 36% at 2 years. In contrast, in the patients without ATN, renal allograft survival rates for the same periods were 97%, 86%, and 61%, respectively. Thus, ATN was a significant predictor of graft survival, ($P < 0.01$) at each of the four time points used. The

proportion of patients with ATN was the same (27%) in both groups.

Discussion

In the United States, the current 1 year cadaveric allograft survival is 79.6% [9]. Although this represents significant improvement from that of the past, there are still many problems. For example, about 20% of cadaveric transplanted kidneys lose function within a year. Furthermore, long-term graft survival rates over a period of 10 years are 25–57% [10]. The identification of variables which influence graft survival is important because strategies to modify them might influence survival rates. One such variable, cell-mediated immunity responder status of the transplant recipient may be important because that mechanism contributes to rejections, a main cause of graft loss. Delayed hypersensitivity skin test (DHST) to a battery of recall antigens is a simple bedside screening technique and is used to measure cell-mediated immunity. There are conflicting reports in the literature regarding DHST results in the pretransplant period and renal allograft survival rates. For example, in one study [5], a 10–20% higher renal allograft survival was reported in the anergic ($n = 32$) vs the STP+ group ($n = 30$). However, in other studies [3,4] no significant difference in renal allograft survival and the result of

Table 3. Patient cumulative survival rates*

Type of patient	6 months	1 year	2 years	3 years
Anergic	36/38† 95%	29/31 94%	18/20 89%	11/13 85%
Skin-test positive (STP+)	63/64 98%	59/60 98%	46/47 98%	34/35 97%

* Only death due to sepsis is included in Table 2.

† The numerator indicates the number of patients alive up to each time point. The denominator indicates the number of patients available for follow-up at the different time points, including previous deaths.

DHST to recall antigens was observed. The major pitfall in these studies was that the two groups were not matched for some of the known variables, such as the degree of HLA-A, B, and DR matching between recipients and donors, development of post-transplant ATN, living vs cadaveric donor transplants, and first kidney transplant or retransplants, which influence graft survival rates.

Since living related donor transplants have better short- and long-term survival compared with cadaveric transplants [9], the present study excluded living related donor transplants to keep the two study populations homogenous with regard to donor source. Likewise, outcomes for repeat transplants are worse than first transplants [9] and, therefore, repeat transplants were also excluded from the study. Furthermore, the presence of post-transplant ATN and/or the number of acute rejections is a significant risk factor adversely affecting renal allograft survival. The proportion of patients with or without ATN and acute rejections in both of our groups was, however, similar. In addition, both groups were also similar for the degree of HLA, A B, C, and DR antigen matches.

Finally, all of the previous studies were performed in the precyclosporine era. Therefore, a time comparison of the present study with those in the past cannot be performed.

The results of our study, with regard to renal allograft survival, do not show any significant difference between anergic and STP+ patients over a follow-up period of up to 3 years. Perhaps the current immunosuppressive therapy, including cyclosporine A and OKT3 monoclonal antibody, might have blunted the difference between these two types of patients.

As far as patient survival is concerned, there are many more studies suggesting higher morbidity and mortality from sepsis in transplant and non-transplant patients among anergic patients compared with those who are STP+ [2–4,6]. Those results are in agreement with the notion that cell-mediated immunity is an important host defense mechanism against certain infections. The present study, however, failed to demonstrate any significant difference in patient survival between those two groups. There are at least two possible explanations for this. First, in the face of serious infections, most

transplant centers, including ours, consider reduction or even cessation of immunosuppressive therapy. Secondly, the prophylaxis for and the treatment of infections with newer antibiotics and antiviral agents is far more aggressive than in the past.

We conclude that DHST is not helpful in predicting the 3-year outcome of patient or renal allograft survival rates.

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