Diabetes Mellitus

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Guidelines

a. We recommend that diabetes should not on its own preclude a patient from being considered for kidney transplantation (Ungraded).

b. We recommend that potential renal transplant candidates with diabetes are screened for cardiovascular disease (refer to "Cardiovascular Disease" guidelines for recommendations) (1A).

c. We suggest that renal transplant candidates with diabetes be considered for pre-emptive transplantation due to better patient and graft survival compared to transplantation after the commencement of dialysis. (2C)

d. We suggest that, following screening for cardiovascular disease, Type 1 diabetic transplant candidates should be considered for referral for simultaneous pancreas and kidney transplantation (SPK). (2B)

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

Diabetes is a multi-system disease, and some of the complications of diabetes can directly impact on the success of transplantation:

- **Consideration should be given to the possibility of diabetic enteropathy, which can reduce the oral absorption of immunosuppressive medications. Patients should be monitored carefully for immunosuppressive drug concentrations and for rejection.**
- **Consideration should be given to the urological implications of potential neuropathic bladder.**

IMPLEMENTATION AND AUDIT

Not warranted.

BACKGROUND

Diabetes mellitus is an increasingly common disease in Australia and New Zealand. It is an important cause of renal failure, and a common comorbidity among dialysis and transplant patients. It is associated with increased rates of cardiovascular disease and premature mortality. These factors make diabetes an important consideration in the assessment of patients for renal transplantation. The "Cardiovascular Disease" guidelines present recommendations and suggestions in relation to screening and testing for cardiovascular disease.

Suitability for transplantation is a difficult and sometimes imprecise concept. There are no studies to show us which patients will live longer after a transplant than on dialysis. Furthermore, the potential for an improved quality of life, means that there are patients who would "like a crack," even if the statistics are against their success. In Australia**,** the Transplantation Society of Australia and New Zealand (TSANZ) has suggested a benchmark for listing patients on the deceased donor transplant waiting list – an anticipated 80% chance of surviving at least 5 years after transplantation. This benchmark recognises that there are not enough kidneys available to offer transplantation to every patient who might be "suitable" for transplantation.

This guideline reviews the available data about the impact of diabetes mellitus on the outcomes of renal transplantation. The most frequently studied outcomes are patient and graft survival. This guideline will not specifically look at the cardiac assessment of these patients, which will be covered in another section. It will not specifically consider simultaneous pancreas with kidney transplantation.

SEARCH STRATEGY

Databases searched: Databases searched: MeSH terms and text words for kidney transplantation were combined with MeSH terms and text words for Type 1 Diabetes Mellitus, Type 2 Diabetes Mellitus, and then combined with MeSH terms and text words for prognosis, survival analysis, graft rejection, graft survival, mortality, incidence and diagnosis. The search was carried out in Medline (1950 – September Week 4, 2009). The Cochrane Renal Group Trials Register was also searched for trials not indexed in Medline.

Date of searches: 5 June 2011.

WHAT IS THE EVIDENCE?

There are no reliable studies, and little prospect of any studies that will accurately measure the benefit or otherwise of renal transplantation compared to remaining on dialysis, for diabetic patients. Prospective randomised trials are impractical, and retrospective analyses are potentially limited by the under-diagnosis of diabetes among wait-listed patients [1], and by differences between wait-listed patients who either do or do not receive transplants. [2]

An early analysis from the UNOS Registry [3] showed that for patients receiving a kidney alone transplant between 1991 and 1995, overall 5-year patient survival was 60%, but the figure was just 54% for diabetic recipients. A multivariable registry analysis of American diabetics transplanted between 1995 and 2002 showed that donor and recipient ages have increased with time, and that both are associated with poorer patient and graft outcomes [4].

There are numerous single centre, retrospective reviews of outcome data from renal transplants performed in diabetic patients. One such review from Malmo, Sweden [5] showed similar rates of cardiovascular and cerebrovascular death in their 189 diabetic renal transplant recipients, compared to non-diabetic recipients transplanted after 1988.

Kronson et al showed that at 5 years, transplanted type 2 diabetics had significantly lower patient and graft survival than either type 1 diabetics or non-diabetic patients over 50 years old [6].

A Kuwaiti study showed 10-year survival was significantly worse in diabetics (58%) compared to non-diabetics (86%), mainly as a result of cardiovascular disease and infections [7]. Ten-year death-censored graft survival was similar, 76% v 80%.

Orsenigo et al, showed that the 5-year patient survival was lower in diabetics who received a kidney only (60%), compared to non-diabetics (82%) or diabetics who received a SPK (82%) P =

0.02 [8]. There was less of a difference in death-censored graft survival at 5 years between non-diabetics (82%), diabetics after SPK (77%) and diabetics after kidney only (68%). In a multivariate analysis [9], the same unit showed that the survival of transplanted non-diabetics or diabetics who received a SPK, was significantly better than diabetics who received a kidney alone.

Two further retrospective analyses showed small differences in patient and graft survival favouring non-diabetics over diabetics [10, 11], but failed to demonstrate statistical significance other than for 10-year patient survival [11].

A number of retrospective case-control studies have been performed. These are generally small and despite an overall trend of lesser outcomes in diabetic patients across most of the studies, they generally lack the power to show significant differences in outcome. One such study of 78 type 1 diabetics with matched controls showed lower patient, graft and death-censored graft survival at 5 and 10 years for type 1 diabetics, but because of the small numbers, only the 10-year patient survival was significantly different [12].

A similarly small case-control study of 64 type 2 diabetics with matched controls, showed lower patient, graft and death-censored graft survival at 5 years for the type 2 diabetics, but only the graft survival reached statistical significance [13].

A case-control study of both type 1 and type 2 diabetics with controls showed lower patient and graft survival for type 1 and 2 patients, at either 1 or 3 years [14]. Age was a further independent predictor in this study.

A single centre case-control study of 46 type 2 diabetics transplanted between 1978 and 1997 showed that renal transplantation conferred a significant survival advantage compared with remaining on dialysis [15].

A further case-control study of 77 type 1 diabetics, compared to non-diabetic controls showed that diabetes carried an odds ratio of 4.38 for death, and of 4.47 for cardiovascular death [16].

A case control study of 78 type 1 diabetics matched with 78 non diabetic kidney transplant recipients, showed a significantly ($P<0.05$) lower 10 year patient survival of 86% in diabetics compared to 95% in the controls. Patient 5-year survival and graft survival at 5 and 10 years was not significantly different between diabetic recipients and the control group. [17]

A case-control series of 35 type 1, and 20 type 2 diabetics showed that the diabetics had more rejection ($P = 0.049$), more delayed graft function ($P = 0.03$), better patient survival ($P = 0.03$) and better graft survival ($P = 0.04$) [18].

A cohort study of 798 diabetic, renal transplant recipients in Vienna demonstrated that maximal glucose levels (but not HbA1c) was predictive of patient survival, but none of the studied parameters of glycemic control were predictive of death censored graft survival [19].

Unpublished data from ANZDATA for the recipients of first deceased donor renal transplants in Australia and New Zealand from 1998-2003, shows that for the recipients of first deceased donor renal transplants, 5-year patient and graft survival are reduced in diabetic recipients. See Table 1. Whereas the 5-year, unadjusted graft survival for all first deceased donor transplants was 80.0%, it was just 65.7% for type 2 diabetics. There was a trend towards graft survival being further modified by the presence or absence of vascular disease. For diabetics without vascular disease the 5-year graft survival was 69.2%, but for those with vascular disease, was just 60.5%.

Diabetes is a multi-system disease, and some of the complications of diabetes can directly impact on the success of transplantation. Diabetic gastroparesis can slow gastric emptying, and delay or reduce the absorption of immunosuppressive medication [19, 20]. This could potentially increase the risk of rejection in certain individuals. A small study of 49 diabetics [21] showed a rejection rate

of 16.3% versus 7.1% in non-diabetics (P = 0.11; ns). Furthermore, diabetes can lead to neuropathic changes affecting the bladder, with the potential for post-transplantation urological problems [22].

SUMMARY OF THE EVIDENCE

Numerous studies suggest that patients with either type 1 or type 2 diabetes have lower patient and graft survival than non-diabetic recipients. This reduction in graft survival is less pronounced if death-censored graft survival is considered. There is a higher rate of cardiovascular death in particular among diabetic renal transplant recipients, and this probably explains a significant part of the difference in outcomes.

It makes intuitive sense to screen diabetic transplant candidates carefully for evidence of cardiac or other vascular disease, either to inform peri-operative risk and management, to allow pre-emptive treatment, or to exclude on the basis of poor outcome (refer to "Cardiovascular Disease" guidelines),.

Diabetes is a multi-system disease, and some of the complications of diabetes can directly impact on the success of transplantation.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: No recommendation.

UK Renal Association: No recommendation.

Canadian Society of Nephrology: No recommendation.

European Best Practice Guidelines:

1. **I.5.3 Guideline N. Recurrence of Diabetes Mellitus:** Renal Transplantation should be considered as the treatment of choice for many patients with diabetes mellitus despite the almost inevitable histological recurrence a few years after renal transplantation. However, overt clinical nephropathy leading to late graft loss occurs in only a minority of patients. (Evidence Level B)

2. **I.5.5 Comorbid Conditions – Diabetes Mellitus:**
    - Kidney Transplantation should be considered as the first therapeutic choice for all suitable patients with end-stage renal disease (ESRD) due to diabetes mellitus, because kidney transplantation is able to significantly extend survival compared to dialysis. (Evidence Level B)
    - Diabetic ESRD patients should be considered for an early and pre-emptive transplantation of either a simultaneous pancreas-kidney transplantation (SPK), a living related donor graft, or an early cadaver graft early when residual glomerular filtration rate (GFR) decreases to <20 mls/min. (Evidence Level B)
    - Diabetes mellitus should be considered as a serious co-morbid condition affecting transplant success and patient morbidity/mortality, mainly because of increased cardiovascular and infectious risks. (Evidence Level B)
    - Therefore, a thorough evaluation of diabetic transplant candidates is recommended with particular attention to the cardiovascular risk. (Evidence Level C)

International Guidelines: No recommendation.

SUGGESTIONS FOR FUTURE RESEARCH

Analysis of the predictive value of pre-operative comorbidities and risk factors for renal transplant graft and patient survival in Australia. This should include the impact of diabetes, and the interaction of other comorbidities with diabetes.

CONFLICT OF INTEREST

Scott Campbell has no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by CARI.

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APPENDICES

Table 1. 5 Year Patient and Graft Survival from ANZDATA (95% Confidence Intervals in parentheses)

	Graft Survival	**Patient Survival**
All DD1 transplants	80.0% (78.2 – 81.6%)	88.4% (87.0 - 89.7%)
Non-Diabetic	81.4% (79.6 – 83.1%)	89.8% (88.3 – 91.1%
Type II Diabetes	65.7% (58.5 – 71.9%)	74.1% (67.2 – 79.7%)
Diabetes + any Vascular Disease	60.5%	69.1% (57.1 – 78.4%)
Diabetes but no Vascular Disease	69.2%	77.0% (67.5 – 84.0%)

Table 2. Characteristics of included studies

Study ID (author, year)	**N**	**Study Design**	**Setting**	**Participants**	**Outcomes**	**Results**	**Follow up (months)**	**Comments**
Hergesell and Zeier, 2003 [1]	377	Retrospective review	Single centre	377 patients on the waiting list, 9 with Type 1 diabetes and 37 with Type 2 diabetes.	How many diabetics are actually listed?	Only 20 of 37 with Type 2 diabetes were initially listed as such.		
Kyllonen and Salmela, 2004 [2]	405	Retrospective review	Single centre		Are transplanted patients the same as non-transplanted, wait-listed patients?	They are not the same, those not transplanted have more diabetic complications.		
Cecka, 1996 [3]		Retrospective review	UNOS database	1991-1995	1 and 5 year graft survival	1 year graft survival: All deceased donors = 84%		Old data

Study ID (author, year)	N	Study Design	Setting	Participants	Outcomes	Results	Follow up (months)	Comments
						Diabetics = 81% 5 year graft survival: All deceased donors = 60% Diabetics = 54%		
Waki, 2004 [4]	99933	Retrospective review	US database	Patients transplanted from 1995-2002. Type 1 = 11,251 Type 2 = 7,772 Non-diabetic = 80,910	Multi-variable analysis	Donor and recipient ages for Type 1 and Type 2 diabetic patients have increased over the years. These ages were associated with lower patient and graft outcomes in type 1 and Type 2 diabetics.		
Ekberg & Christensson, 1996 [5]	788	Retrospective review	Single centre in Malmo, Sweden	223 renal transplants into 189 diabetic patients.		Similar rates of cardiovascular and cerebrovascular deaths in both groups after 1988.		Old data.
Kronson et al, 2000 [6]		Retrospective review	Single centre, University of Minnesota	90 Type 2 diabetics.	5 year patient survival	5 year patient survival for Type 2 diabetics = 61% 5 year graft survival for Type 2 diabetics = 53% Graft survival was lower than Type 1 diabetics or non-diabetics who were over 50		
Nampoory et al, 2002 [7]	631	Retrospective review	Single centre in Kuwait	79 with pre-transplant diabetes 117 with post-	Patient survival and death-censored graft survival .	1 Year patient survival: Non-diabetics = 97% Diabetics = 84%		

Study ID (author, year)	N	Study Design	Setting	Participants	Outcomes	Results	Follow up (months)	Comments
				transplant diabetes (excluded from comparison) 435 non-diabetics		5 Year patient survival: Non-diabetics = 93% Diabetics = 65% 10 Year patient survival: Non-diabetics = 86% Diabetics = 58% 10 Year death-censored graft survival: Non-diabetics = 80% Diabetics = 76% P=ns		
Orsenigo et al, 2004 [8]	270	Retrospective review	Single centre	Renal transplants from 1985 – 2002. 161 SPK in diabetics, 43 kidneys alone in diabetics and 66 in non-diabetics.	5 year patient and graft survival	5 year patient survival: Non-diabetics = 88% After SPK = 82% After kidney = 60% P = 0.02 5 year graft survival: Non-diabetics = 82% After SPK = 77% After kidney = 68%		
Orsenigo et al, 2005 [9]	361	Retrospective review	Single centre	189 diabetics with SPK, 81 diabetics receiving a kidney only and 91 non-diabetics receiving a kidney only.	Multi-variable analysis	Survival was significantly better in non-diabetics (0.002), or diabetics receiving a SPK, compared to diabetics who received a kidney alone.		

Study ID (author, year)	N	Study Design	Setting	Participants	Outcomes	Results	Follow up (months)	Comments
Romming et al, 2006 [11]	498	Retrospective review	Single centre	68 transplants in 62 patients with diabetes. 498 transplants in 399 patients without diabetes.	Patient and graft survival at 1, 5 and 10 years.	1 Year patient survival: Non-diabetics = 91% Diabetics = 88% P = ns 5 Year patient survival: Non-diabetics = 73% Diabetics = 68% P = ns 10 Year patient survival: Non-diabetics = 52% Diabetics = 31% P < 0.05 1 Year graft survival: Non-diabetics = 72% Diabetics = 72% 5 Year graft survival: Non-diabetics = 52% Diabetics = 52% 10 Year graft survival: Non-diabetics = 33% Diabetics = 27%		
Revanur et al, 2001 [12]	939	Retrospective review	Single centre in Glasgow	First grafts in the cyclosporine era 1984-1999. 66 (7%) with renal failure due to Type 1 diabetes. 7 (0.8%) with renal	Patient survival	Mean survival was: PTDM = 10.3 yrs Type 1 = 8.4 yrs Type 2 = 3.7 yrs Non-diabetic = 12.8 yrs		Very few diabetics, so difficult to draw conclusions.

Study ID (author, year)	N	Study Design	Setting	Participants	Outcomes	Results	Follow up (months)	Comments
				failure due to Type 2 diabetes. 10 (1.1%) with co-existent diabetes. Also looked at PTDM				
Boucek et al, 2002 [13]	128	Retrospective case-control study	Single centre	64 Type 2 diabetics With 64 matched controls.	Patient, graft and death-censored graft survival.	1 Year patient survival: Non-diabetics = 84% Type 2 diabetics = 85% 5 Year patient survival: Non-diabetics = 74% Type 2 diabetics = 69% P = 0.43 1 Year graft survival: Non-diabetics = 73% Type 2 diabetics = 77% 5 Year graft survival: Non-diabetics = 61% Type 2 diabetics = 54% P = 0.19 1 Year death-censored graft survival: Non-diabetics = 82% Type 2 diabetics = 84% 5 Year death-censored graft survival: Non-diabetics = 77% Type 1 diabetics = 77% P = 0.52	Type 2 diabetics: 37 +/- 27 months Non-diabetics: 41 +/- 31 months	Too few patients.

Study ID (author, year)	N	Study Design	Setting	Participants	Outcomes	Results	Follow up (months)	Comments
Fernandez-Fresnedo, 2002 [14]	107	Retrospective case-control study	Single centre	31 with Type 1 diabetes. 25 with Type 2 diabetes. 51 age matched non—diabetics with nephrosclerosis.	1 and 3 year graft and patient survival.	1 Year patient survival: Non-diabetics = 88% Type 1 diabetics = 73% Type 2 diabetics = 69% 3 Year patient survival: Non-diabetics = 80% Type 1 diabetics = 69% Type 2 diabetics = 60% 1 Year graft survival: Non-diabetics = 76% Type 1 diabetics = 58% Type 2 diabetics = 50% 3 Year graft survival: Non-diabetics = 64% Type 1 diabetics = 50% Type 2 diabetics = 38% Age was a further independent predictor.		
Brunkhorst et al, 2003 [15]	92	Retrospective case-control study	Single centre	46 Type 1 diabetics transplanted between 1978 – 1997, with 46 matched controls who remained on haemodialysis.	Kaplan-Meier survival analysis.	Highly significant survival advantage with transplantation; p = 0.0001		
Luft et. al, 2004 [16]	154	Retrospective case-control		77 Type 1 diabetics with 77 matched	Risk of death. Risk of cardiovascular	Odds ratio for death = 4.38		

Study ID (author, year)	N	Study Design	Setting	Participants	Outcomes	Results	Follow up (months)	Comments
		study		non-diabetic controls	death.	Odds ratio for cardiovascular death = 4.47		
Kim et al, 2001[17]	156	Retrospective case-control study	Single centre	78 Type 1 diabetics with 78 matched non-diabetics.	Patient and death-censored graft survival at 5 and 10 years.	5 Year patient survival: Non-diabetics = 97% Type 1 diabetics = 86% 10 Year patient survival: Non-diabetics = 95% Type 1 diabetics = 74% P<0.05 5 Year graft survival: Non-diabetics = 80% Type 1 diabetics = 71% 10 Year graft survival: Non-diabetics = 72% Type 1 diabetics = 58% P=ns 5 Year death-censored graft survival: Non-diabetics = 81% Type 1 diabetics = 80% 10 Year death-censored graft survival: Non-diabetics = 73% Type 1 diabetics = 65% P=ns		Trends limited by small numbers.
Bittar et al, 2006 [10]	523	Retrospective review	Single centre	35 diabetics and 488 non-diabetics	Graft survival at 1, 3 and 5 years.	1 Year graft survival: Non-diabetic = 87.6%		

Study ID (author, year)	N	Study Design	Setting	Participants	Outcomes	Results	Follow up (months)	Comments
						Diabetic = 82.7% 3 Year graft survival: Non-diabetic = 79.0% Diabetic = 70.9% 5 Year graft survival: Non-diabetic = 72.5% Diabetic = 63.0%		
Einollahi et al, 2008 [18]	222	Retrospective case-control study	Single centre	111 diabetics and 111 random non-diabetic recipients. 36 had Type 1 diabetes, 20 had Type 2 diabetes and 55 had post-transplant diabetes.	Acute rejection, delayed graft function, patient and graft survival.	Diabetic patients had: More acute rejection; p = 0.049 More delayed graft function; p = 0.03 Worse patient survival; p = 0.03 Worse graft survival; p = 0.04		
Schiel et al, 2005 [21]	302	Retrospective review	Single centre	Patients transplanted since 1992. Type 1 diabetes; n=3 Type 2 diabetes; n=46	Acute rejection	8 Diabetics (16.3%) and 18 without diabetes (7.1%); p=0.11	3.3 +/- 1.5 years	