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Diabetes

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GUIDELINES

No recommendations possible based on Level I or II evidence

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

- **The prevalence of diabetes in the dialysis population is increasing and the presence of this comorbidity has a significant adverse impact on patient survival.**
- **Sepsis and poor glycaemic control appear to contribute to increased morbidity and mortality. Efforts should be made to achieve good glucose control (HbA1C < 7.3%) as well as identify high-risk patients who may benefit from more aggressive interventions.* The belief that earlier dialysis in diabetics may improve morbidity and mortality has not been substantiated in a prospective study.**

IMPLEMENTATION AND AUDIT

No recommendation.

BACKGROUND

The incidence of diabetes mellitus in incident dialysis patients in the USA is 44.3% (USRDS 2008 report, 2006 data).[1] This proportion is similar in Australia (44.0%) and New Zealand (46.0%).[2]

Diabetes mellitus types I and II have been shown to be independent comorbid conditions associated with higher mortality.[2] However, in patients with diabetes mellitus, only age at initiation of dialysis was demonstrated to be an independent factor in predicting survival in the earlier clinical experience.[3] These results may have been related in part to the selection of patients with diabetes mellitus who had relatively uncomplicated medical comorbidity. In later analyses,[4] it was demonstrated that in addition to age, the presence of heart disease, chronic obstructive pulmonary disease and peripheral vascular disease (PVD) significantly contributed to the increased mortality of diabetic patients who started therapy at the Regional Kidney Disease Program (RKDP) in the USA between 1976 and 1992. In addition, the level of functional activity, as measured by the Karnofsky score, also had a significant impact on survival within the first 3 months of starting haemodialysis in both diabetic and non-diabetic patients.

*The target HbA1C differs to that outlined in the 'Prevention and/or management of CKD in type 2 diabetes' guidelines because the patient population from which the evidence is drawn is different (i.e. dialysis vs pre-dialysis patients).

SEARCH STRATEGY

Databases searched: MeSH terms and text words for type 1 and type 2 diabetes mellitus were combined with MeSH terms and text words for renal replacement therapy and dialysis. The search was carried out in Medline (1950–March, Week 3, 2008). The Cochrane Renal Group Trials Register was also searched for trials not indexed in Medline.
Date of search/es: 2 April 2008.

WHAT IS THE EVIDENCE?

A prospective study was conducted by Villar *et al.*[5] in order to examine the epidemiology and long-term survival of patients with incident end-stage kidney disease (ESKD) by diabetes status in Australia and New Zealand. The ANZDATA Registry was used to identify patients ≥16 years of age who began dialysis from 1 April 1991 to 31 December 2005. Data collection consisted of information on patient demographics, comorbidites and multiple other parameters (Table 1).

This study included 1284 patients with type 1 diabetes (4.5%), 8560 patients with type 2 diabetes (30.0%) and 18 704 non-diabetic patients (65.5%). Rates of coronary artery, peripheral vascular and cerebrovascular disease were higher in diabetic than in non-diabetic patients (Table 1) ($P < 0.0001$). Multivariate survival analysis showed the risk for death after the first dialysis treatment was 64.0% (HR 1.64 (1.47–1.84) greater in type 1 diabetic ($P < 0.0001$) and 13.0% (HR 1.13 (1.06–1.20) higher in type 2 diabetic ($P < 0.0001$) patients *versus* non-diabetic patients. Sex was not associated with survival in type 1 diabetics or in non-diabetics; however, older (≥60 years) type 2 diabetic women had a worse outcome than older type 2 diabetic men, and this difference did not appear to be explained by different comorbid conditions.

In type 1 diabetic patients, survival did not alter over time (adjusted HR 0.94 (0.83–1.07) per 5-year period, $P = 0.36$ but it improved significantly by 9.0% per 5-year period in type 2 diabetics (0.91 (0.87–0.95), $P < 0.0001$) and by 5% in non-diabetic patients (0.95 (0.92–0.98), $P = 0.001$).

In the DOPPS, a prospective observational study of haemodialysis practices and clinical outcomes among patients treated at randomly selected dialysis facilities in France, Germany, Italy, Japan, Spain, UK and the USA (2004), diabetes was associated with a significantly higher relative risk of mortality (RR = 1.55, $P < 0.001$).[6] Similarly, from the USRDS database, the 5-year survival in diabetic haemodialysis patients is 20% compared with 50% in non-diabetic patients.[7] The percentage of all deaths attributed to cardiovascular disease (CVD) in diabetic haemodialysis patients varies from 23% to 54%. In countries with traditionally lower rates of cardiovascular death in the general population (East Asian and Mediterranean countries), diabetic haemodialysis patients tend to have better survival than such patients in countries with significantly higher cardiovascular mortality (USA and certain Western European countries).

A large observational study of incident and prevalent haemodialysis patients from Canada showed similar findings.[8] Two cohorts of patients, those with diabetes and those without, were created between 1994 and 2000 and followed until 2001. Diabetic patients had significantly higher comorbidities and not surprisingly, once on dialysis, diabetic patients had lower rates of survival than non-diabetics (3-year survival 55% *vs* 68%, $P < 0.0001$). This finding was consistent with that reported by the Canadian Organ Replacement Register, which reported a 3-year survival of 52% for diabetics and 65% for non-diabetics.[9]

A retrospective analysis of 756 Spanish peritoneal dialysis patients was published in 2002.[10] This group analysed comorbidity and mortality in type 1 diabetics, type 2 diabetics and non-diabetic patients. Different comorbidity factors such as age and the presence of CVD at the initiation of peritoneal dialysis were analysed as well as the incidence of peritonitis, need for hospitalization and among other factors, mortality rate. The number of comorbid conditions when starting the treatment (comorbidity index) and the peritonitis incidence was higher for type 2 diabetics and death during the first year of treatment was higher for type 1 diabetics. The actuarial survival curves showed a higher mortality for type 2 diabetics with no differences between non-diabetics and type 1 diabetics after adjustment for age. The mortality odds ratio was 1.78 for type 2 diabetics and 1.13 for type 1 diabetics, differences that were not significant after age at >70 years and CVD were added to the variables analysed. This study thus highlighted that while cardiovascular comorbidity was responsible for the higher mortality found in the first year in type 1 diabetics compared with non-diabetics, both age and CVD were responsible for the higher mortality and complications faced by the type 2 diabetics.

Infection is another leading cause of death in diabetic patients receiving haemodialysis, and septicaemia has been reported to be responsible for 75% of deaths related to infections.[11] The infected dialysis access or infected foot, impaired cellular immunity and humoral immunity and nutritional deficiency may play major roles.

Very few studies have examined the association of glycaemic control (HbA1C) and clinical outcomes in the dialysis population.[12] Four of these studies[12–14,16] had small sample sizes of less than 150 subjects and four were performed in exclusively Asian populations.[12,13,16,17] The three largest studies[15,17,18] have conflicting results. Williams *et al.*[15] performed a primary data analysis of glycaemic control and survival on 23 504 diabetic dialysis patients in the USA. Five per cent of the population had type 1 diabetes and patients were followed for 12 months. No difference in survival was observed across the different HbA1C strata with survival rates ranging from 80% to 85%.

In contrast to this, the two larger studies outlined below did show an association. Hayashino *et al.*[17] in the Japan DOPP study analysed data from 1569 patients with diabetes and 3342 patients without diabetes on haemodialysis. Patients without diabetes had a smaller body mass index and more years since the initiation of haemodialysis than those with diabetes, as well as less cardiovascular comorbid conditions. A Cox proportional hazards model was used to investigate the association between presence or absence of diabetes, glycaemic control (HbA1C quintiles) and mortality risk. Among patients on haemodialysis, patients with diabetes had a higher mortality risk than those without (HR 1.37, 95% CI: 1.08–1.74). The multivariate-adjusted HR for mortality was not increased in the bottom to fourth quintiles of HbA1C (HbA1C 5.0–5.5% to 6.2–7.2%), but was significantly increased to 2.36 (95% CI: 1.02–5.47) in the fifth quintile (HbA1C ≥7.3%). This effect did not appear to be influenced by baseline comorbidity status.

The largest study to date is the one by Kalantar-Zadeh *et al.*[18] This study analysed the data of 82 933 maintenance haemodialysis patients in the DaVita outpatient clinics in the USA over a 3-year period. HbA1C values were divided into seven categories, i.e. <5%, ≥10% and 1% increments in between. Unadjusted survival analyses showed paradoxically lower death hazard ratios with higher HbA1C values. When the model was adjusted however, for potential confounders such as demographics, comorbidities, anaemia, dialysis vintage and dose, higher HbA1C values were incrementally associated with higher death risks.[17] The adjusted all-cause mortality and cardiovascular HRs compared with HbA1C in the 5–6% range were 1.41 (95% CI: 1.25–1.60) for HbA1C values ≥10% and 1.73 (95% CI: 1.44–2.08) ($P < 0.001$).

SUMMARY OF THE EVIDENCE

All of these studies have limitations and whether glycaemic control affects survival in diabetic ESKD patients remains unclear. More prospective controlled studies are needed to verify the true relationships between different methods of diabetes management and outcome in dialysis patients.

WHAT DO THE OTHER GUIDELINES SAY?

UK Renal Association:
Guideline 3.5 – CKD: Preparation for dialysis
'Nephrology Units should provide or facilitate the optimal management of patients with established renal failure who opt for non-dialytic treatment.'
Kidney Disease Outcomes Quality Initiative:
Guideline 1. Initiation of Dialysis
CPG for Hemodialysis Adequacy
1.3 Timing of therapy: 'When patients reach stage 5 CKD (estimated GFR <15 mL/min/1.73 m^2), nephrologists should evaluate the benefits, risks, and disadvantages of beginning kidney replacement therapy. Particular clinical considerations and certain characteristic complications of kidney failure may prompt initiation of therapy before stage 5. (B)'
Canadian Society of Nephrology: No recommendation.
European Best Practice Guidelines: No recommendation.
International Guidelines: No recommendation.

SUGGESTIONS FOR FUTURE RESEARCH

Whether glycaemic control affects survival in diabetic ESKD patients remains unclear. More prospective controlled studies are needed to verify the true relationships between different methods of diabetes management and outcome in dialysis patients.

CONFLICT OF INTEREST

Eugenie Pedagogos 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 Baseline characteristics and renal replacement therapy (RRT) in type 1 diabetic, type 2 diabetic and non-diabetic patients

	Type 1 diabetic	Type 2 diabetic	Non-diabetic	*P**
n	1284 (4.5)	8560 (30.0)	18 704 (65.5)	
Male	733 (57.1)	4943 (57.7)	10 934 (58.5)	0.002
Age at first RRT (years)	43.1 ± 11.3	61.2 ± 11.2	56.5 ± 17.0	<0.0001
Racial origin				<0.0001†
Caucasoid	1136 (88.5)	4493 (52.5)	15 882 (84.9)	
Australian Aboriginal	31 (2.4)	1444 (16.9)	562 (3.0)	
Maori/Pacific Islander	71 (5.5)	1784 (20.8)	930 (5.0)	
Other people	46 (3.6)	839 (9.8)	1 327 (7.1)	
Primary renal disease				<0.0001†
Diabetes	1205 (93.8)	6345 (74.1)	0 (0)	
Renal vascular disease	15 (1.2)	572 (6.7)	3 114 (16.6)	
Glomerular nephropathy and related disease	36 (2.8)	775 (9.1)	7 699 (41.2)	
Polycystic	2 (0.1)	89 (1.0)	1 842 (9.8)	
Other	26 (2.1)	779 (9.1)	6 049 (32.4)	
Biopsy-proven nephropathy	162 (12.6)	1421 (16.6)	7 032 (37.6)	
Comorbid conditions at first RRT				<0.0001
Chronic lung disease	84 (6.5)	1490 (17.5)	2 728 (14.6)	
Coronary artery disease	135 (33.9)	4802 (56.1)	5 550 (29.7)	<0.0001
Peripheral vascular disease	555 (43.2)	3624 (43.2)	2 989 (16.0)	<0.0001
Cerebrovascular disease	153 (11.9)	1692 (19.8)	2 134 (11.4)	<0.0001
BMI (kg/m^2)	25.0 ± 4.7	28.6 ± 6.4	25.2 ± 5.3	<0.0001
<18	29 (2.3)	128 (1.5)	844 (4.5)	<0.0001
18–24	727 (56.6)	2574 (30.1)	9 633 (51.5)	
25–29	368 (28.7)	2878 (33.6)	5 495 (29.4)	
≥30	160 (12.5)	2980 (34.8)	2 832 (15.1)	
Cigarette smoking				
Never	676 (52.7)	3725 (43.5)	9 135 (48.8)	<0.0001†
Former	384 (29.9)	3720 (43.5)	7 131 (38.1)	
Current	224 (17.5)	1115 (13.0)	2 438 (13.1)	
Serum creatinine at first RRT (μmol/L)‡	686 ± 263	735 ± 306	795 ± 339	<0.0001
eGFR at first RRT (mL/min)‡§	8.5 ± 3.8	7.5 ± 4.0	7.0 ± 3.6	<0.0001
90-day RRT modality				<0.0001†
Haemodialysis	531 (41.3)	4971 (58.1)	10 860 (58.1)	
Peritoneal dialysis	639 (49.8)	3554 (41.5)	6 992 (37.4)	
Renal transplantation	114 (8.9)	35 (0.4)	852 (4.5)	
Details of RTx				
n	1257¶	6551¶	10 860¶	
Waiting list registration	522 (41.5)	724 (11.1)	5 069 (36.7)	<0.0001
Pre-emptive renal transplantation	85 (6.8)††	18 (0.3)	502 (3.6)	<0.0001
Living donor renal transplantation	89 (7.1)‡‡	111 (1.3)	2 024 (14.6)	<0.0001
Cadaveric renal transplantation	436 (34.7)§§	340 (5.2)	3 638 (26.3)	<0.0001
Median times to RTx (months)	18.3 (16.7–20.9)	48.8 (45.7–55.9)	26.0 (24.9–26.9)	<0.0001

Data are *n* (%), mean ± SE, or medium (95%) CI. *Comparisons across the three groups. †Comparisons in categorical variables (racial origin, primary renal disease, BMI categories, cigarette smoking status, 90-day RRT modality). ‡Analysis restricted to patients who started RRT after 1 April 1998: *n* = 17 809; type 1 diabetic, *n* = 694; type 2 diabetic, *n* = 6176; non-diabetic, *n* = 10 939; for conversion to milligrams per deciliter divide by 88.4. §Estimated by the simplified Modification Diet in Renal Disease formula (12). ¶Analyses restricted to patients aged <70 years. ††Including 15 living donor renal transplantations, 5 single cadaveric renal transplantations, and 65 simultaneous kidney-pancreas transplantations. ‡‡Including 15 pre-emptive renal transplantations. §§Including 159 single renal transplantations and 277 simultaneous kidney-pancreas transplantations. BMI, body mass index; eGFR, estimated glomerular filtration rate.

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