

Incidences, treatments, outcomes, and gender effect on survival in end-stage renal disease patients by diabetic status in Australia and New Zealand (1991-2005)

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Abstract

Objective: We aim to update the epidemiology of type 1 (T1DM) and type 2 diabetes (T2DM) patients among the incident end-stage renal disease (ESRD) population in Australia and New Zealand (ANZ), and to determine if outcome is worse for diabetic women, as described in the general population.

Research Designs and Methods: All resident adults of ANZ who began renal replacement therapy (RRT) from 01/04/1991 to 31/12/2005 were included using data from the ANZDATA Registry. Incidence rates, RRT, and survival were analysed. Risk factors for death were assessed using Cox regression.

Results: The study included 1284 T1DM (4.5%), 8560 T2DM (30.0%), and 18704 non-diabetic (noDM) (65.5%) patients. Incidence rate of ESRD with T2DM increased markedly over time (+10.2% annually, $p < 0.0001$). In patients < 70 years, rates of renal transplantation in T1DM, T2DM, and noDM patients were 41.8%, 6.5% ($p < 0.0001$ vs. other patients), and 40.9% ($p = 0.56$ vs. T1DM patients) respectively. Compared with noDM, adjusted hazard ratio (HR) for death was 1.64 ($p < 0.0001$) in T1DM, and 1.13 ($p < 0.0001$) in T2DM. Survival rates per five-year periods improved by 6% in T1DM ($p = 0.36$), by 9% in T2DM ($p < 0.0001$), and by 5% in noDM ($p = 0.001$). In ≥ 60 year-old T2DM patients, adjusted HR for death in women versus men was 1.19 ($p = 0.0003$).

Conclusions: Incidence of ESRD with T2DM increased markedly. Despite high access to renal transplant, T1DM patients had a poor prognosis after starting RRT. Survival improved significantly in T2DM patients during study period. Elderly T2DM women had a worse prognosis compared to elderly T2DM men.

Abbreviations

ANZ: Australia and New Zealand

ANZDATA: Australia and New Zealand Dialysis and Transplant Registry

BMI: body mass index

eGFR: estimated glomerular filtration rate

ESRD: end-stage renal disease

HR: hazard ratio

MDRD: modification of diet in renal disease

noDM: without history of diabetes mellitus

pmp: per million populations

RRT: renal replacement therapy

RTx: renal transplantation

T1DM: type 1 diabetes mellitus

T2DM: type 2 diabetes mellitus

Diabetes is associated with high mortality in the general population [1, 2]. Worse prognosis has also been reported in diabetic women compared to diabetic men [3-4]. ESRD in patients with type 2 diabetes mellitus (T2DM) has dramatically increased worldwide during the last decades and diabetes is associated with worse survival among dialysis population [5-7].

Nevertheless, a study in Denmark showed that survival rate of ESRD patients with T2DM has improved during the 1990-2005 period [8]. Available studies on ESRD patients with type 1 diabetes mellitus (T1DM) and T2DM have shortcomings because analyses were limited to patients with diabetic nephropathy [6-7], did not differentiate the two types of diabetes [9], were short-term [10], or were based on single-centre experiences [11].

The aim of the present study is to examine the epidemiology and long-term survival of incident ESRD patients by diabetic status (T1DM, T2DM and no diabetes) in Australia and New Zealand (ANZ) and to determine if outcomes were different between genders among patients with diabetes.

Research Design and Methods:

We performed a prospective study including all patients ≥ 16 years who began chronic renal replacement therapy (RRT) in ANZ from 01/04/1991 to 31/12/2005. We used data from the Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry [5]. Patients were followed until death or 31/12/2005. Data collection consisted of information on patient demographic characteristics, cause of ESRD, comorbidities at RRT start (presence of T1DM, T2DM, coronary artery disease, peripheral vascular disease, cerebrovascular disease, chronic lung disease, body mass index (BMI), and smoking status), estimated glomerular filtration rate (eGFR) at first RRT, details of RRT modality and of renal transplantation (RTx), date and cause of death. BMI (ratio of weight to the square of height at commencement of RRT) was analysed in categories: underweight, < 18 kg/m², normal weight, 18 to 24.9 kg/m², overweight, 25 to 29.9 kg/m², and obese, ≥ 30 kg/m². Smoking status at start of RRT was

categorised as never, former, or current smoker. Glomerular filtration rate was estimated by the simplified Modification of Diet in Renal Disease (MDRD) formula [12] in patients who began RRT after 01/04/1998 because data on serum creatinine before first RRT was collected after this date.

When appropriate, univariate comparisons were performed using χ^2 test or Fisher's exact test for categorical variables, Student's t-test for continuous variables between two groups and ANOVA for continuous variables across the three groups by diabetic status.

We calculated age and gender standardised ESRD incidence rates by diabetic status among ANZ populations using direct standardisation. For 1991, incidence was projected for the entire year. Data on ANZ populations were provided by the Australian Bureau of Statistics and Statistics New Zealand. The reference populations were the 1991-2005 Australian and New Zealand populations ≥ 16 years. Calculation of average annual changes in incidence and comparisons between subgroups were performed by Poisson regression and we checked for overdispersion.

Times to RTx or to death were examined with Kaplan-Meier models and Cox regression for multivariate analyses. RTx outcomes were examined in patients younger than 70 years. Cox models to analyse variations in access to RTx by diabetic status per five-year periods (1991-1995, 1996-2000, and 2001-2005) were adjusted for age, gender, primary renal disease, comorbidities at first RRT, BMI categories, smoking status, and were stratified on racial origin, state where RRT was started (seven states in Australia; one in New Zealand), and initial RRT modality.

Causes of death were classified into sudden death, cardiovascular, infection, malignancy, and other causes. In survival analyses, death from any cause was the end-point. In multivariate survival analysis, diabetic status (T1DM, T2DM, or noDM) was the variable of interest. We also examined the evolution of all-cause and cause-specific mortality over 1991-2005 by using period of first RRT (1991-1995, 1996-2000, and 2001-2005) as parameter of interest. Models were adjusted

for age, gender (except in analyses of patient subgroups by diabetic status), primary renal disease, comorbidities at first RRT, BMI categories, and smoking status. eGFR at RRT start was modelled as a fractional polynomial function (analyses restricted to patients who started RRT from 01/04/1998). Cox regression was stratified on racial origin group, year of first RRT (1991-2005) with the exception of analysis by period of first RRT, state where RRT was started, initial RRT modality, and RTx during study period. We checked for interactions between variables by including multiplicative terms in Cox regression. In cases of where significant interactions were found, we performed stratified survival analysis as described above. Validity of the Cox proportional hazard assumption was checked by tests based on Shoenfeld's residuals. All statistical analyses were performed with S-PLUS 6.0 Software Professional Release 2 (© 1988-2001 Insightful Corp).

Results:

Baseline patient characteristics

T1DM patients were the youngest and T2DM patients the oldest ($p < 0.0001$, Table 1). Rates of cardiovascular diseases were higher in diabetic than in non-diabetic patients ($p < 0.0001$). T2DM patients had higher average BMI ($p < 0.0001$). The proportion of current smoker was higher in T1DM patients ($p < 0.0001$).

Proportions of T1DM and T2DM in Caucoid, in Australian Aboriginal, and in Maori / Pacific Islander patients were 5.3% and 20.9%; 1.5% and 70.9%; and 2.6% and 64.1% respectively ($p < 0.0001$). Gender ratio (male/female) in these groups were 1.5, 0.76, and 1.25 respectively ($p < 0.0001$). Average ages at first RRT were 58.8 ± 16 , 49.9 ± 11.9 , and 53.0 ± 12.9 years respectively ($p < 0.0001$).

ESRD incidence rates by diabetic status

Standardised incidence rates of ESRD with associated T1DM remained stable over time at about 5 per million populations (pmp). Average annual change was -0.3% per year [-1.6% to +0.9%], without significant

difference between countries, genders and age (Figure 1).

Standardised incidence rates of ESRD with associated T2DM rose from 10.6 pmp in 1991 to 48.8 pmp in 2005 in Australia. In New Zealand, they varied between 23.9 pmp in 1991 and 68.7 pmp in 2002. Across countries, average annual change was +10.2% per year [+9.6% to +10.8%]. For incidence of ESRD at age < 60 years with associated T2DM, the increase was +8.7% [+7.7% to +9.7%] in Australia and +5.3% [+3.9% to +6.8%] in New Zealand. For ESRD at age ≥ 60 years with associated T2DM, the increase was +11.7% [+10.8% to +12.6%] and +11.5% [+9.7% to +13.4%] respectively ($p < 0.001$ in comparison with patients < 60 years of the same country).

Standardised incidence rates of ESRD without diabetes increased significantly (+1.5% [+1.1% to +1.8%] in Australia and +2.9% [+2.1% to +3.8%] in New Zealand).

RRT modalities on the 90th day and access to renal transplantation

T1DM patients were more likely to be treated by peritoneal dialysis than T2DM and noDM patients ($p < 0.0001$) (Table 1). T2DM patients were less likely to receive RTx ($p < 0.0001$). Over time, rates of RTx were stable in T1DM patients (adjusted hazard ratio (HR):1.02 [0.91-1.15] per 5-year period, $p = 0.72$), and in noDM patients (1.00 [0.96 – 1.03], $p = 0.84$). Adjusted rates of RTx decreased in T2DM patients (0.78 [0.68-0.90], $p = 0.0005$), without difference between genders.

Crude survival and causes of death

Unadjusted median survival from first RRT in T1DM, T2DM and noDM patients were 72.5 [66.3 – 82.1], 40.1 [38.8-41.3], and 80.2 months [77.7-83.0] respectively. Median survivals from birth were 55.7 [54.4-56.7], 70.5 [70.2-70.9], and 74.7 years [74.5 – 74.9] respectively (Figure 2).

Among T1DM patients, 627 (48.8%) died during study period. Proportions of sudden death, cardiovascular, infection, malignancy, and other cause as cause of death were in men and in women 27.2%, 40.4%, 11.3%, 3.3%, 17.8%, and 18.7%, 34.8%, 19.5%, 2.0%, 25.0% respectively ($p = 0.01$). Among T2DM

patients, 4997 (58.4%) died. Proportions were 17.9%, 42.2%, 14.7%, 4.6%, 20.6%, and 15.7%, 41.0%, 15.9%, 3.7%, 23.7% respectively ($p=0.01$). Among noDM patients, 8393 (44.9%) died. Proportions were 14.9%, 35.7%, 13.4%, 11.5%, 24.5%, and 12.2%, 35.4%, 15.4%, 8.7%, 28.3% respectively ($p<0.0001$). Causes of death were significantly different between patient groups, by diabetic status ($p<0.0001$).

Over time, there was a decrease in adjusted rates of cardiovascular death (adjusted HR: 0.96 [0.92-0.99] per 5-year period, $p = 0.04$), infectious death (0.89 [0.83-0.95], $p=0.003$), and sudden death (0.88 [0.83-0.94], $p<0.0001$), while rates of malignancy death increased (1.19 [1.08-1.30], $p=0.0002$). These trends were similar in the three patient groups.

Multivariate survival analysis in the whole cohort

Multivariate survival analysis showed that the risk for death after first RRT was 64 % higher in T1DM ($p<0.0001$) and 13% higher in T2DM ($p<0.0001$) than in noDM patients (Table 2).

Multivariate survival analysis by diabetic status

There was a significant interaction between gender and diabetic status ($p=0.0004$). Female gender was significantly associated with higher risk for death in T2DM patients (adjusted HR for death in women versus men: 1.08 [1.015-1.16], $p=0.02$). Gender was not associated with survival in T1DM (1.12 [0.87-1.46], $p=0.38$) and in noDM patients (0.95 [0.91-1.005], $p=0.07$).

In T2DM, there was a significant interaction between gender and age ($p<0.0001$). Adjusted HR for death in women versus men was 0.93 [0.83-1.04] ($p=0.20$) in T2DM patients <60 years ($n=3762$) and 1.19 [1.08-1.30] ($p=0.0003$) in T2DM patients ≥ 60 years ($n=4798$). This last adjusted HR was similar for cardiovascular and non-cardiovascular causes of death.

No other significant interactions were found with race, cause of ESRD (diabetic nephropathy versus other causes of ESRD), and BMI. Results were unchanged when

follow-up were censored at time of transplant and/or RRT modality switches, and when analyses were adjusted for eGFR.

In T1DM patients, survival did not change over time (adjusted HR: 0.94 [0.83-1.07] per 5-year period, $p=0.36$), while it significantly improved by 9% per 5-year period in T2DM patients (0.91 [0.87-0.95], $p<0.0001$), and by 5% in noDM patients (0.95 [0.92-0.98], $p=0.001$).

Conclusions:

This study in ANZ showed a large increase in the incidence rate of ESRD with associated T2DM from 1991 to 2005, especially marked in T2DM patients ≥ 60 years (+11.5% per year). The incidence of ESRD with associated T1DM remained stable. After adjustment for age, gender and risk factors for death, T1DM had a greater effect on survival in ESRD patients than T2DM when compared with noDM patients. In each patient group, the proportions of cardiovascular, infectious and sudden death decreased over study period, while rates of malignancy death increased. Female gender was associated with worse outcome than male gender in T2DM patients ≥ 60 years. This difference did not appear to be explained by the different comorbid conditions, age, races, causes of ESRD, BMI at first RRT, or RRT modalities.

The strength of this analysis is that T1DM and T2DM are separately reported in a prospective and population-based study. Previous analyses may have been biased because they only included patients with diabetic nephropathy and because nephropathy may have been misclassified if it is not biopsy-proven.

Despite an increase of about +3% per year in the incidence of childhood T1DM in ANZ during the last decades [13-14], incidence of RRT with associated T1DM remained stable between 1991 and 2005. The difference in trends between general and ESRD populations may indicate improvements in care of T1DM patients, due to treatment with angiotensin converting enzyme inhibitors and aggressive glycemic control available since 1980 [15]. High transplant rates, including simultaneous kidney-pancreas transplant, remained stable over time. The higher risk for

death in T1DM than in T2DM patients was not explained by risk factors in the multivariate analyses. This difference should be accounted for by differences in diabetes duration and severity or glycemic control. These data were not available for analysis and this result should be interpreted with this limitation in mind.

In T2DM, the overall 10.2% annual increase in ANZ is consistent with studies in Europe and USA over comparable periods [6-7]. The increase was higher in patients ≥ 60 years than in younger patients. Possible explanations for this rise are the increasing incidence and prevalence of overweight, obesity [16] and T2DM in the general population [17], improved life expectancy in T2DM patients with earlier stage of kidney disease due in part to better management of cardiovascular diseases [18], and greater access to RRT [5-7].

These results highlighted the specific epidemiology of diabetes and ESRD in the Australasian population. Two-thirds of Australian Aboriginal and Maori / Pacific Islander ESRD patients had T2DM at RRT start, which was significantly different from the Caucasoid population (about 20% with T2DM at RRT start). Incidence and prevalence of T2DM and hypertension is high in Aboriginal population [19]. This higher incidence of ESRD with associated T2DM may be explained in part by genetic susceptibility and higher rates of kidney disease progression than in Caucasoid population [19].

After first RRT, overall survival was short in T2DM patients, with median survival time less than 3.5 years, similar to reports from Europe [8, 11] and US [9, 12]. Less than 10% of T2DM patients received RTx, as in France [20] and USA [21]. Adjusted rates of RTx declined over study period among T2DM patients, but remained stable in the other two groups. Survival rates improved with a decrease in cardiovascular death. We hypothesize that improvements in dialysis management and in cardiovascular treatments may explain this improvement over time.

Moreover, female gender was significantly associated with death in T2DM patients ≥ 60 years. Interactions between female gender,

diabetes mellitus and excess mortality in the ESRD population compared to the general population have also been noted in France [22].

Several dialysis-specific explanations can be proposed, such as gender difference in the effects of dialysis dose [23] and importance of glycemic control [12] on ESRD diabetic patient survival.

Although it remains controversial [24], worse prognosis has also been reported in women compared to men in the non-ESRD diabetic population [3-4]. In diabetics without chronic kidney disease, most studies have found that this difference was not accounted for by traditional risk factors [25]. Higher risk for death in women may be related to interactions between cardiovascular risk factors and menopause [26], a stronger inverse association between coronary disease and cholesterol level in women, differences in coagulation and in patterns of obesity, and hyperinsulinemia [2-4, 25-26].

In conclusion, this study confirms that incidences, treatments and survivals are different between ESRD patients with T1DM and T2DM. Future studies of diabetic ESRD patients should differentiate between these two groups to provide interpretable results. ESRD remains a dreadful complication in patients with T1DM and great effort on kidney disease prevention in these young patients is needed. A marked increase in the incidence rate of ESRD with associated T2DM was seen over study period. The study emphasises the burden of ESRD with associated T2DM in Australian Aboriginal and in Maori / Pacific Islander populations. Prevention of renal impairment [27], nephroprotection in patients with overt nephropathy, early referral to nephrologists [28] and access to RTx [29] may improve the prognosis of T2DM patients. This study also highlights the poorer prognosis in elderly T2DM women compared with elderly T2DM men. This deserves further explanatory studies.

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Table 1: Baseline characteristics and renal replacement therapy in T1DM, T2DM, and noDM patients.

	T1DM n=1284, 4.5%	T2DM n=8560, 30.0%	noDM n=18704, 65.5%	p ^a
Male (n, %)	733 (57.1%)	4943 (57.7%)	10934 (58.5%)	0.002
Age at first RRT in year (mean ± se)	43.1 ± 11.3	61.2 ± 11.2	56.5 ± 17.0	<0.0001
Racial origin (n, %)				<0.0001 ^b
Caucasoid	1136 (88.5%)	4493 (52.5%)	15882 (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%)	1327 (7.1%)	
Primary renal disease (n, %)				<0.0001 ^b
Diabetes	1205 (93.8%)	6345 (74.1%)	0 (0%)	
Renal vascular disease	15 (1.2%)	572 (6.7%)	3114 (16.6%)	
GN and related disease	36 (2.8%)	775 (9.1%)	7699 (41.2%)	
Polycystic	2 (0.1%)	89 (1.0%)	1842 (9.8%)	
Other	26 (2.1%)	779 (9.1%)	6049 (32.4%)	
Biopsy-proven nephropathy	162 (12.6%)	1421 (16.6%)	7032 (37.6%)	<0.0001
Comorbid conditions at first RRT				
Chronic lung disease	84 (6.5%)	1496 (17.5%)	2728 (14.6%)	<0.0001
Coronary artery disease	435 (33.9%)	4802 (56.1%)	5550 (29.7%)	<0.0001
Peripheral vascular disease	555 (43.2%)	3694 (43.2%)	2989 (16.0%)	<0.0001
Cerebrovascular disease	153 (11.9%)	1692 (19.8%)	2134 (11.4%)	<0.0001
BMI (mean, se)	25.0 ± 4.7	28.6 ± 6.4	25.2 ± 5.3	<0.0001
BMI < 18	29 (2.3%)	128 (1.5%)	844 (4.5%)	<0.0001 ^b
BMI 18 – 24	727 (56.6%)	2574 (30.1%)	9633 (51.5%)	
BMI 25 – 29	368 (28.7%)	2878 (33.6%)	5495 (29.4%)	
BMI ≥= 30	160 (12.5%)	2980 (34.8%)	2832 (15.1%)	
Cigarette smoking : never	676 (52.6%)	3725 (43.5%)	9135 (48.8%)	<0.0001 ^b
Cigarette smoking : former	384 (29.9%)	3720 (43.5%)	7131 (38.1%)	
Cigarette smoking : current	224 (17.5%)	1115 (13.0%)	2438 (13.1%)	
Serum creatinine at first RRT (µmol/L, se) [†]	686 ± 263	735 ± 306	795 ± 339	<0.0001
eGFR at first RRT (mL/min, se) ^{†,‡}	8.5 ± 3.8	7.5 ± 4.0	7.0 ± 3.6	<0.0001
90-day RRT modality (n, %)				<0.0001 ^b
Haemodialysis	531 (41.3%)	4971 (58.1%)	10860 (58.1%)	
Peritoneal dialysis	639 (49.8%)	3554 (41.5%)	6992 (37.4%)	
Renal transplantation	114 (8.9%)	35 (0.4%)	852 (4.5%)	
Details of RTx *	n=1257*	n=6551*	n=10860*	
Waiting list registration	522 (41.5%)	724 (11.1%)	5069 (36.7%)	<0.0001
Preemptive renal transplantation	85 (6.8%) ^c	18 (0.3%)	502 (3.6%)	<0.0001
Living donor renal transplantation	89 (7.1%) ^d	111 (1.3%)	2024 (14.6%)	<0.0001
Cadaveric renal transplantation	436 (34.7%) ^c	340 (5.2%)	3638 (26.3%)	<0.0001
Median times to RTx (months, 95%CI)	18.3 [16.7-20.9]	48.8 [45.7-55.9]	26.0 [24.9-26.9]	<0.0001

n: number. %: percentage. se: standard error. RRT: renal replacement therapy. BMI: body mass index. eGFR: estimated glomerular filtration rate. RTx: renal transplantation.

[†]: analysis restricted to patients who started RRT after April 1, 1998, n=17809; T1DM, n=694; T2DM, n=6176; noDM, n=10939; for conversion to mg/dL divide by 88.4.

[‡]: estimated by the simplified MDRD formula [12].

*: analyses restricted to patients younger than 70 years.

a: comparisons across the three groups.

b: comparisons in categorical variables (racial origin, primary renal disease, BMI categories, cigarette smoking status, 90-day RRT modality).

c: including 15 living donor renal transplantations, 5 single cadaveric renal transplantations, and 65 simultaneous kidney-pancreas transplantations.

d: including 15 preemptive renal transplantations.

e: including 159 single renal transplantations, and 277 simultaneous kidney-pancreas transplantations.

Table 2: adjusted hazard ratio of death of any cause in the whole cohort, n=28548, patients not censored at renal replacement modality switches or renal transplantation.

	Hazard ratio	95% CI	p
Patients without diabetes*	1		
Patients with type 1 diabetes	1.64	1.47 – 1.84	<0.0001
Patients with type 2 diabetes	1.13	1.06 – 1.20	<0.0001
Male versus Female	1.0	0.96 – 1.04	0.89
Age at first RRT (+ 1 year)	1.024	1.022 – 1.026	<0.0001
Diabetes	1.21	1.12 – 1.31	<0.0001
Renal vascular disease	1.10	1.04 – 1.17	0.002
GN and related disease*	1		
Polycystic	0.76	0.69 – 0.83	<0.0001
Myeloma, light chain deposit, and amyloid	3.0	2.72 – 3.32	<0.0001
Renal cancer	1.67	1.4 – 2.0	<0.0001
Other	1.07	1.02 – 1.13	0.01
Lung disease	1.24	1.18 – 1.29	<0.0001
Coronaropathy	1.22	1.17 – 1.27	<0.0001
Peripheral vascular disease	1.21	1.15 – 1.26	<0.0001
Cerebrovascular disease	1.16	1.11 – 1.22	<0.0001
BMI < 18	1.33	1.21 – 1.45	<0.0001
BMI 18 – 24*	1		
BMI 25 – 29	0.89	0.86 – 0.93	<0.0001
BMI >= 30	0.91	0.87 – 0.96	0.0005
Cigarette smoking : never*	1		
Cigarette smoking : former	0.99	0.95 – 1.03	0.72
Cigarette smoking : current	1.10	1.04 – 1.17	0.001

Results were unchanged when patients were censored at time of transplant and/or RRT modality switches, when analyses were adjusted for eGFR, or when analyses were performed only in patients starting RRT with hemodialysis or in patients starting with peritoneal dialysis.

*: reference group in categorical variables.

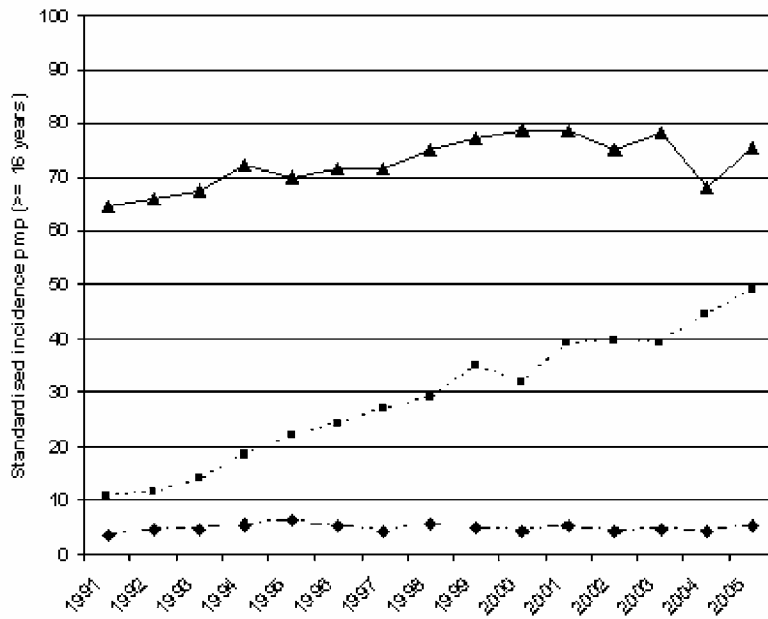
Figure legends

Figure 1: age and gender standardised ESRD incidence per million population (≥ 16 years) by diabetic status among general population in Australia (top, n=23417) and in New Zealand (bottom, n=5131).

Figure 2: survival curve for national cohorts after birth by diabetic status, computed for mortality rates for the period 1991-2005.

Figure 1

Australia



New Zealand

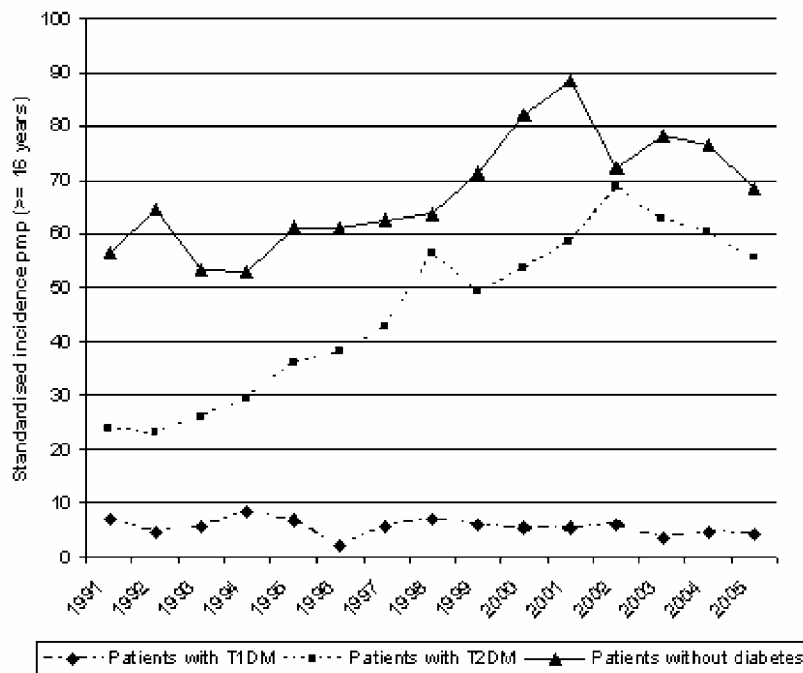


Figure 2

