

Is there really good news about pandemic diabetic nephropathy?*,†

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Defined in the dictionary as an adjective, the word pandemic, meaning: ‘occurring over a wide geographic area and affecting an exceptionally high proportion of the population,’ like epidemic, has evolved to its current usage as a noun [1]. In 2005, growth in number of individuals in the United States treated for end-stage renal disease (ESRD) was analysed using data generated by the United States Renal Data system (USRDS), sustaining the conclusion that most of the expansion ‘was due to a three-fold increase in risk of ESRD in people with diabetes and therefore, qualifies as an epidemic (Figure 1) [2].’ Examination of the epidemic growth curve of diabetes [3] pointed to diabetes mellitus as the leading cause of ESRD (i.e. kidney failure requiring dialysis or transplantation) in the United States, accounting for 44% of new cases of treated ESRD in 2002 [4]. As depicted in Figure 2, the incidence count of new ESRD patients between 1984 and 2002 whose renal failure was associated with diabetes has continuously increased each year over the preceding year.

More than 53 million Europeans, 8.4% of adults, have diagnosed diabetes with a predicted increase to 9.8% of adults by 2025. Industrialized nations devote about 10% of their healthcare budgets to diabetes care, an estimate that must rise, due to continuing growth of diabetic persons, of about 7 million a year globally. Appreciating that reluctance to accept diabetic persons for ESRD treatment is fading, the financial impact

imposed by treating the myriad comorbidities of diabetes must continuously expand. Developing nations, for the present, have avoided including diabetes in the roster of acceptable causes for treating ESRD.

Experts in the epidemiology of diabetes have sounded a frightening alarm, typified by the remarks of Dr Martin Silink, President-elect, International Diabetes Federation, in July 2006: ‘Diabetes is one of the biggest health catastrophes the world has ever seen. The diabetes epidemic will overwhelm health care resources everywhere if governments do not wake up now and take action [5].’ Echoing this plea for action, Dr Richard Insel, Executive Vice President of Research for the Juvenile Diabetes Research Foundation proclaimed in late July 2006: ‘The toll in human lives and medical costs will continue unabated unless we address this crisis on a global scale. Diabetes knows no geographical borders and affects people around the world. We must, therefore, work together to find a cure for both types of diabetes [6].’

However, first sensed in 2005, examination of trends in ESRD attributed to diabetes mellitus (ESRD–DM) in the United States suggests a downturn in incidence and even a decline. The Center for Disease Control and Prevention (CDC)-analysed 1990–2002 data from the USRDS and the National Health Interview Survey (NHIS) [7], summarizing findings in a most encouraging report [8]. As redrawn in Figure 3, it is clear that although the number of new cases of ESRD increased overall, the incidence rate of ESRD among persons with diabetes is clearly decreasing. Using all persons known to have diabetes as denominator, with incidence of newly diagnosed ESRD as numerator, the curves demonstrate a remarkable downward slope in incidence from a peak of 305/100 000 in 1996 to 232 in 2002 ($P < 0.01$). As commented in the CDC report, ‘Although the number of new cases of ESRD in persons with diabetes increased overall, the incidence of ESRD–DM among persons with diabetes is not increasing among blacks, Hispanics, men and persons aged 65–4 years, and is declining among persons aged <65 years, women, and whites [6].’

While it appears that the tide in ESRD due to diabetes is turning, it is far too early to celebrate a victory for renoprotection, a collection of poorly

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†USRDS Disclaimer: Data reported herein were supplied by the United States Renal Data System (USRDS). Interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as official policy or interpretation of the US government.

ESRD INCIDENCE 2004*

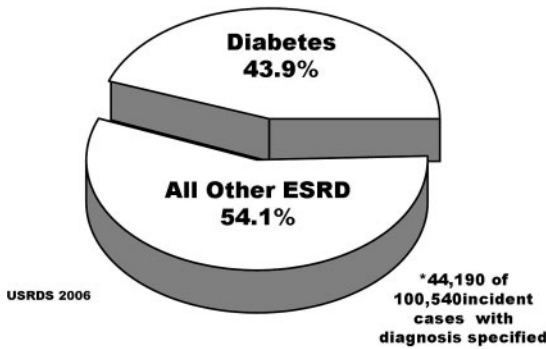


Fig. 1. Pie chart depicting incident patients with ESRD as reported by the USRDS in 2005 with the dominant disorder being DM.

ESRD INCIDENCE RATE:USA PER MILLION : 1998-2003

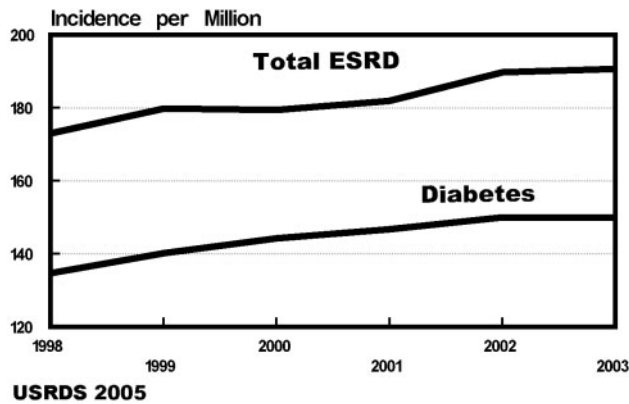


Fig. 2. As reported by the USRDS, the incident rate per million population for both ESRD and the proportion of ESRD patients with diabetes shows flattening curves signalling levelling-off in the pandemic of ESRD driven mainly by progressive increases of ESRD in persons with diabetes.

understood complex regimens. Diabetic persons risk ESRD because of variables including familial and genetic factors, duration of diabetes and level of hyperglycaemia, hypertension and hyperlipidaemia [9]. No evidence-based explanation for this important epidemiological change has yet been reported.

Should this positive trend continue, it may be predicted that as the total US population continues to increase, the number of diabetic persons will also increase but the proportion (rate) of diabetic individuals who will develop ESRD is falling and, by trend analysis, should continue to decrease. Why this encouraging transformation is taking place provokes speculation that must be addressed by clinical trials.

At present, incorporating renoprotection into a standard of care for diabetes as outlined by Miyata and de Zepsele [10] is attractive:

- (i) Normalize elevated blood pressure and/or treat microalbuminuria with an angiotensin-converting

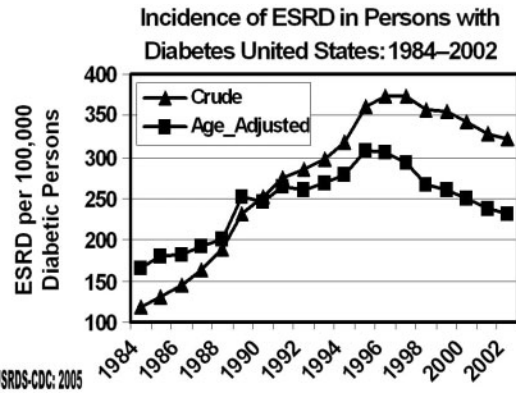


Fig. 3. A key inference indicating a favourable trend in the pandemic of diabetes is evident as both crude and age-adjusted incident rates of new onset ESRD per 100 000 persons with diabetes declining outcomes in incidence starting in 1995. This observation was first noted in the Centers for Disease Control and Prevention (CDC)'s Weekly Morbidity and Mortality Report in November 2005 [8]. From this finding, the subsidence of the pandemic of ESRD in persons with diabetes is inferred.

enzyme inhibitor or receptor blocker (ACEi/ARB) [11]. Normalizing a hypertensive blood pressure is a bedrock component of all regimens for contemporary renal care in diabetic and non-diabetic persons. The American Diabetes Association Clinical Practice recommendations for 2006 were devised based on all clinical trials to date, sustaining inclusion of an ACEi and/or ARB as first line medications in a renoprotective regimen [12]. Combination treatment with both an ACEi and an ARB appears to be developing into the present standard of care [13].

- (ii) Normalize hyperglycaemia in all stages of diabetes [14]. The American Diabetes Association proposes a target glycosylated haemoglobin level (HbA1c) of <7%, an attainable and cost-effective standard health care system [15]. Unequivocal findings in multiple trials sustain the conclusion that intensive metabolic control slows progression of micro- and macro-vasculopathy and must be incorporated as a central tenet of treatment strategy.
- (iii) Correct dyslipidaemia. Elevated LDL cholesterol and hypertriglyceridaemia are risk factors separate from proteinuria (microalbuminuria). Adults with diabetes should be tested 'at least annually and more often to achieve goals' of an LDL <100 mg/dl with triglycerides <150 mg/dl using statins and other lipid-lowering agents as necessary [16].
- (iv) Stop cigarette smoking, reduce excess weight, exercise in an overall program [17] of life style modification [18]. Whether altered life style deserves credit for delaying ESRD in diabetes cannot be substantiated. In fact, studies of adherence indicate that the goals of smoking cessation, weight reduction 'healthy' eating are objectives more extolled than attained. On the

other hand, none of these measures bears a negative consequence if adopted.

Epidemiology is more a descriptive than a hard science. Good news is less likely than bad news to stimulate broad dissemination. Consider the foreboding during the past 2 years over a possible devastating pandemic of H5N1 avian influenza [19]. Caution in reading the favourable change in diabetes progression is still appropriate. What appears to be a favourable, albeit of major medical, economic and social impact, change in course in the epidemic curve for ESRD in diabetes may yet be a 'statistical fluke.'

It is nevertheless difficult to suppress the good feeling that renoprotective regimens really work. Sometimes, rational medical advice is followed: As reported in the *Washington Post* on 9 March 2006: 'Americans smoked fewer cigarettes last year than at any time since 1951... a 4.2 percent decline in 2005 alone [20].' Furthermore, optimists among care givers for diabetic persons eagerly anticipate the promise of curing diabetes by molecular intervention, stem cell or islet cell infusion xenogeneic pancreas-kidney solid organ transplantation. Until these magic interventions are in hand, growing evidence that arduous renoprotective regimens, as described earlier, are effective, proffers support in the struggle to pre-empt a terrible end to a terrible disease, raising the probability that those with diabetes today will maximize their tomorrows.

(See related article by Jager and van Dijk. Has the rise in the incidence of renal replacement therapy in developed countries come to an end? *Nephrol Dial Transplant* 2007; 22: 678-680.)

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