

Complications of diabetes: progress, but significant challenges ahead

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The prevalence of type-2 diabetes (T2D) is growing rapidly worldwide and societal costs associated with T2D are immense (1). In many countries, diabetes is now a major cause of cardiovascular disease, renal failure, blindness and lower limb amputation, and a significant proportion of healthcare expenditure is undertaken in the management of diabetes and its attendant complications. It is estimated that at the time of diagnosis, around half of people with T2D may have a complication related to diabetes (2). Cardiovascular disease accounts for much of the premature mortality seen in people with T2D. With growing prevalence and increasing costs of treatments, diabetes is set to add further pressure on healthcare systems worldwide, particularly amongst countries at the forefront of economic development.

In recent years, the management of diabetes has benefitted greatly from a number of large scale randomised controlled trials (RCTs) of interventions to determine how to reduce complications. These suggest that intensive risk factor management targeting blood pressure, cholesterol and glucose control, along with regular screening for complications, can have a significant impact on reducing complications. In the Steno-2 study, 12 years of sustained reduction of blood pressure (systolic 130 *vs.* 145 mmHg), cholesterol (3.5 *vs.* 5.0 mmol/L) and a modest reduction in glycaemic control (HbA1c reduction of 0.5%) led to around 50% risk reductions in cardiovascular and all cause mortality and 80% reductions in stroke and renal replacement therapy (3). Angiotensin converting enzyme (ACE) inhibitors and statins are cheap and have proven efficacy in reducing cardiovascular disease in people with T2D, and should probably be prescribed in all people with T2D over the age of 40 years unless contra-indicated (4,5).

Evidence around use of aspirin for primary prevention in patients with diabetes is less certain (6), but smoking cessation must be strongly encouraged in all people with T2D who smoke.

The paramount importance of optimal blood glucose control in patients with type-1 diabetes (T1D) cannot be underestimated. The results of the Diabetes Control and Complications Trial (DCCT) (7), and its long term follow up (8), showed that tight blood glucose control in people with T1D reduced microvascular and macrovascular complications significantly. There is, however increasing debate around the value of very tight glucose control in patients with T2D. The seminal United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that improved glucose control for a period of around 10 years from diagnosis of T2D could provide significant protection from microvascular disease, but had little impact on the development of cardiovascular complications (9). Ten years follow up of the UKPDS cohort showed relative risk reductions in all cause mortality and myocardial infarction, suggesting a “legacy effect” of tight glucose control early in the diabetes journey (10). More recent data from randomised controlled trials of patients with longer duration of diabetes (around 10 years from diagnosis) suggest that there is little benefit in very tight glucose control later in the disease, and possible evidence of harm (11-13).

Taken together, current evidence suggests that early tight glucose control from diagnosis, may provide some benefit in reduction of complications, but after around 10 years from diagnosis, attempts to tighten glycaemic control may lead to adverse outcomes. Whilst we must avoid therapeutic nihilism when managing blood glucose in people with long

standing diabetes, a pragmatic approach will benefit patients in reducing symptoms and recent American and European guidelines suggest individualising targets for glycaemic control (14). A number of factors may be considered when deciding who might benefit from tight glucose control, such as age, duration of diabetes, medical co-morbidities, motivation, capacity for self care, and social support. Furthermore, individualised patient management plans should be reviewed at least annually and should include screening for complications of diabetes, with feet, eye and kidney checks being mandatory.

Although we have evidence that there is much that may be done to reduce diabetes complications, is there evidence that we are implementing such therapy to reduce these complications? In the April issue of the *New England Journal of Medicine*, Edward W. Gregg and colleagues try to shed some light on this (15). They report on changes in the prevalence of diabetes related complications in the U.S. over the two decades spanning 1990–2010. This detailed study used data from four large databases to compare incidences of lower extremity amputation, end stage renal failure, myocardial infarction, stroke and death from hyperglycaemic crises between 1990 and 2010, with an age standardised U.S. population in the year 2000. The databases used were the National Health Interview Survey—a questionnaire based survey of 57,000 patients per year, the National Hospital Discharge Survey—a discharge summary survey of over 200 short stay hospital in all 50 states, the U.S. Renal Data System (USRDS)—a registry of end stage renal disease for patients on Medicare and Medicaid Services, and the U.S. National Vital Statistics System—a registry of all U.S. deaths. The methodological criteria for determining presence of complications appears to have been robust and careful statistical analysis was undertaken.

The results are fascinating. Between 1990 and 2010, the number of adults with a diagnosis of diabetes tripled from 6.5 to 20.7 million subjects, in the context of a 27% increase in the U.S. population. The good news is that rates of all five complications surveyed reduced substantially over this period. Acute myocardial infarction declined by 67.8% (95% confidence intervals 59.3–76.2%), stroke by 52.7% (40.9–64.4%), amputation by 51.4% (34.5–68.2%), end stage renal failure by 28.3% (21.6–34.6%), and deaths from hyperglycaemic crises by 64.4% (60.9–68%). The bad news is, however, that the absolute number of cases of stroke, amputation and end stage renal disease actually increased by 59,703, 22,703 and 32,434 cases respectively. Acute myocardial infarction bucked this trend, declining by 4,379 cases as did

hyperglycaemic crises deaths, declining by 529 cases. In subgroup analysis, the steepest declines in diabetes related complications were seen amongst people 75 years or older, although declines were seen in all age strata. The decreases in cardiovascular complications seen over these two decades surpassed that of decreases in cardiovascular disease in non-diabetic patients.

This robust analysis of a nationally representative sample of subjects with diabetes suggests that clinicians in the U.S. are using the evidence from RCTs to treat patients with established diabetes to reduce the rate of complications in these high risk patients, and furthermore suggests that the complications of diabetes can and are indeed being prevented. The reduction in cardiovascular complications is particularly gratifying, as these are what kill diabetic patients, and U.S. clinicians should take great heart from these results, which suggest that their interventions are having a real impact. The authors suggest that the improving rates of complications may be presumed to be due to improvements in clinical care, performance of health systems and health promotion in people with diabetes and through working within a multidisciplinary team environment. Enhanced systems and networks of care for patients, including education, risk factor intervention and complications screening are likely to have contributed most to the improvements seen. Improvements in the management of ischaemic heart disease and peripheral vascular disease by way of re-vascularisation therapies may have also had an impact as will societal trends in smoking and reduction in use of trans-fats. The authors speculate that the lower reduction in rates of end stage renal disease is the result of people surviving longer from cardiovascular disease, and developing end stage renal disease as a result of older age.

In this regard, by its own admission, this study has assessed only the quantifiable and more easily accessible outcomes of the impact of diabetes on health. What it has been unable to neither assess nor quantify is the quality of life experienced by patients with diabetes and whether the improvement of care in diabetes over the past two decades has truly resulted in the adding of life to years. One major complication of diabetes, that of eye health including diabetic retinopathy, cataracts and blindness has not been assessed due to the difficulty in gathering this data. Nor is there an assessment of the complications of diabetic neuropathy and its various syndromes, for example chronic pain syndrome or limb weakness. Furthermore, diabetes is associated with a number of mental health disorders

including depression and schizophrenia (16). In one recent analysis of the WHO World Health Survey of 2002 of over 231,000 individuals from 47 countries, the authors showed that diabetes is associated with a twofold increased prevalence of depressive symptoms in most regions of the globe which represents a significant disease burden. One final impact of diabetes is its social cost, for example, that to the wider economy by way of the loss to the labour force through early retirement and in sickness benefit payments. Furthermore, elderly patients and those with severe complications may also require intensive nursing and residential support whether this is to administer medications, in their activities of daily living or in dealing with diabetic foot and skin complications such as chronic ulceration.

As such, whilst this study provides evidence of the impact of medical interventions based on RCTs, the worrying data from this survey is the dramatic rise in diabetes prevalence that has occurred over these two decades and which is predicted to grow over the coming decade. Thus, whilst rates of complications may be decreasing, the actual number of complications and demand for diabetes services is growing. A threefold rise in prevalence is of grave concern, and whilst the U.S. health system appears to be coping with this rise in diabetes prevalence, other less well developed health systems may not be able to cope with this dramatic rise. Without appropriately structured care and employing targeted interventions based on appropriate risk stratification, the costs of diabetes and its complications could threaten to engulf health systems, both in well developed and developing health economies.

It is with this in mind, that worldwide, we need to grapple with the thorny issue of diabetes prevention (17). Prevention is likely to be a lot cheaper than treatment of diabetes and its complications. The health benefits of weight reduction and improving physical activity levels will not just be realized in diabetes prevention, but also in the prevention of cardiovascular disease, cancer and mental illness. The health and financial benefits are not likely to be seen immediately, but will accrue over many years. Whilst the data from the U.S. shows that diabetes complications can be reduced, without a change in our diabetogenic environment and a reduction in prevalence of diabetes, diabetes complications are likely to be a major health issue in decades to come.

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