Diabetologia (2005) 48: 1435–1438
DOI 10.1007/s00125-005-1833-0

EDITORIAL

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Type 1 diabetes in the young: the harvest of sorrow goes on

Published online: 14 July 2005

Elliott Joslin was 53 years old and had spent his career watching children dying of diabetes. In 1922 he watched in awe as insulin restored the moribund to life, and realised that 'a new race of diabetics has come upon the scene' [1]. He could only speculate as to how long they would survive. Eighty years later, hundreds of thousands of children are kept alive by insulin, and we too must keep asking what their future will hold. The pioneers of insulin therapy found that only one patient in two who started insulin before the age of 20 would see their 55th birthday [2]; mercifully, children on insulin now live very much longer. One important reason for this, as discussed by Peter Rossing in this issue of *Diabetologia* [3], is that the proportion destined to develop diabetic nephropathy continues to fall. For example, the cumulative incidence of persistent proteinuria in Danish children diagnosed from 1933 to 1942 was 40.6% after 25 years of diabetes, compared with 26.9% in those diagnosed from 1953 to 1962 [4]. More recently, a longitudinal study from Linköping in Sweden found that 30.3% of children diagnosed from 1961 to 1965 developed nephropathy within 25 years, as compared with 8.2% in the 1966–1970 cohort, with indications that subsequent cohorts are doing better still; the number needing laser treatment for retinopathy had also fallen [5]. This accords well with a Danish report that 31.1% of children and young adults diagnosed from 1965 to 1969 developed nephropathy within 20 years, as compared with 13.7% of those diagnosed from 1979 to 1984; here too there was a clear fall in the rate of proliferative retinopathy [6].

Encouraging though these results may seem, it is not yet time to break out the champagne. Surprisingly little is known about the long-term prognosis of childhood diabetes. There are few population-based studies, and the improved mortality in a widely cited study from Allegheny County in the USA [7] should be treated with some caution, given that three out of four African American children diagnosed from 1965 to 1969 failed to survive 30 years of diabetes. Provision of minimal standards may have had more to do with improved survival than the recent advances in management invoked by the authors. There are obvious difficulties in obtaining data that require decades of follow-up, and retrospective cohort studies from the Joslin Clinic in the USA and the Steno Diabetes Center in Denmark [8, 9] have provided most of our baseline information in this area. Of the more recent studies reviewed by Rossing [3], the landmark observation in Linköping was obtained in a clinic-based cohort of children in whom HbA_1c levels of 7.0% or less were achieved [10], equivalent—as he points out—to the intensively treated arm of the DCCT study [11]. His own studies, meanwhile, come from a tertiary referral centre and relate to patients who were, for the most part, diagnosed in adult life. These studies confirm that the prognosis of type 1 diabetes *can* be improved by better management, but—and despite the absurd complacency of some commentators—they provide no evidence at all that it actually *has* improved on a worldwide basis.

There are important issues relating to interpretation. The natural history of diabetic nephropathy can be described in terms of progression from subthreshold urinary albumin excretion to persistent microalbuminuria, followed by macroalbuminuria, end-stage renal failure and death. Different interventions at different stages—for example, improved glucose control in those with normal albumin excretion, and antihypertensive therapy in those with microalbuminuria—could result in the same outcome; namely, reduced progression to overt nephropathy. How much of the improvement is due to primary prevention by means of improved glycaemic control, rather than secondary prevention in those with microalbuminuria? And do these interventions provide a complete explanation? It is often assumed that any improvement must be the result of recent developments in techniques of diabetes management, and those who make this assumption should note that the cu-

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mulative incidence of diabetic nephropathy began to fall long before such measures were introduced [8, 9]. Even so, it is reasonable to believe that glucose control and blood pressure management have been a major influence. For example, there is no doubt that improved glucose control can transform the natural history of type 1 diabetes [11], but the fall in HbA_1c from 8.9 to 8.5% reported by the Danish study seems modest in relation to the simultaneous 60% reduction in the incidence of nephropathy [6]. Another study from the same centre found that 33.6% of a 1979–1984 inception cohort developed persistent microalbuminuria or proteinuria within 20 years of diabetes onset, implying that the reported delay in progression to nephropathy in this group is attributable to secondary prevention in those with incipient, but established, disease [12]. This raises the concern that the burden of nephropathy may have been postponed rather than prevented.

What are the wider implications of these findings? Glucose control remains the major modifiable primary risk factor for late complications, and the news here is far from reassuring. Nationwide surveys of children with type 1 diabetes in France and Scotland have shown an average HbA_1c of around 9.0% [13, 14], a level of control associated with a high risk of late complications. When glucose control was studied in 21 paediatric clinics in Europe, Japan and the USA in 1995, the overall mean HbA_1c was 8.62%. Three years later, and despite strenuous efforts, the mean HbA_1c remained at 8.67%, with a persistent 2.5% difference between the best- and worst-performing clinics —equivalent to a four-fold gradient in vascular risk [15]. This experience underscores what all clinicians know—that glucose control is mediated by complex psychosocial influences. Joslin once made the chilling remark that 'it is the uneducated, untrained, uncared for child in a family with limited resources who is lost' [16], and little has changed: the French study found a mean HbA_1c of 8.35% in children with good family support, whilst the corresponding figure in those with poor support was 10.03% [13]. It is not surprising that the authors of the multinational survey found their observations 'disquieting', and felt that they had 'revealed more questions than answers' [15].

Better news comes from a recent survey of 1,335 children treated in Western Australia from 1992 to 2002, which documented a reduction in average HbA_1c from 10.9 to 8.1% over the same period. Newer trends in management were reflected by a shift towards multiple-dose insulin therapy—96% were on two daily injections at the start as against 60% by the end—insulin analogues were increasingly used, and 8% of children ended on pump therapy. The incidence of severe hypoglycaemia rose sharply over the first 5 years, but levelled off thereafter, despite continued improvement in glucose control. Glycaemic control and risk of hypoglycaemia were unaffected by the number of daily injections or the use of insulin analogues, but the risk of severe hypoglycaemia increased with social disadvantage [17]. The unsurprising implications are that the total package of care is more important than manipulation of insulin therapy, and that well-supported children do better.

We should, therefore, take hope from the observation that the incidence of microvascular complications is falling, at least in some specialised centres, and from evidence that those in this age group can achieve and maintain better glucose control. On the other hand, it is clear that the risk of late complications remains unchanged in the majority of children. The paediatric diabetes community has mobilised itself to meet this challenge, but faces the problem that puberty is typically followed by a sharp rise in HbA_1c and that inadequate control, once established, tends to persist into later life. A follow-up study of teenagers with type 1 diabetes in the UK found that HbA_1c was unchanged (8.6% in men, 8.7% in women) after 11 years of follow-up, whilst the proportion with serious complications rose from 3 to 37% and psychiatric disorders increased from 16 to 28% [18]. The reasons for poor glucose control in adolescence range from the endocrine and physiological to the social, emotional and psychological; complicated by the natural inclination of young people to assert their autonomy in the face of parental and other constraints. Although clinical teams are understandably reluctant to impose further constraints upon a family struggling to cope with a newly diagnosed child, the need for near-normal glucose control must be emphasised right from the beginning, and there are sound physiological and psychological reasons for doing so [19]. More resources will be needed before current limitations can be overcome, and this may not be easy in a medical culture that is so much more adept at measuring cost than recognising value.

Although glucose control presents a major challenge, there is more to the management of children and young adults with type 1 diabetes than improved glucose control and prevention of microvascular complications. As Knut Dahl-Jørgensen and colleagues point out in their accompanying review [20], type 1 diabetes carries the same risk of premature arterial disease as familial hypercholesterolaemia, and cardiovascular disease has overtaken diabetic nephropathy as the leading cause of premature mortality in individuals over the age of 30 [21]. They describe post-mortem studies that identified fatty streaks in 100% of aortas and 50% of right coronary arteries in non-diabetic individuals who died between the age of 15 and 19 years [22], and thickening of the intima–media in the aorta and carotid arteries has been described in 11-year-old children with diabetes as compared with non-diabetic control subjects [23]. Arterial disease begins in childhood; therefore, as Dahl-Jørgensen argues, this is when treatment should begin. Lifestyle measures, such as smoking avoidance, must form the basis of any intervention, but we need to think the previously unthinkable in terms of much earlier intervention with statins and ACE inhibitors. Ambitious long-term trials will be needed to resolve these questions.

The most urgent need, as usual, is for more effective implementation of what is already known; but new approaches must also be tried. To take one example, there is preliminary evidence that ACE inhibitors have benefits that extend beyond their current indications for use in hypertension and microalbuminuria, and these must be explored [24]. New understanding of the biochemical basis of vas-

cular complications could lead to therapies that uncouple the link between hyperglycaemia and structural damage to the endothelium of blood vessels [25]. The disease itself is potentially preventable, and the first major intervention trials have already been completed. Stem cell technology could lead to a limitless supply of insulin-secreting cells for transplantation. But all this is still on the horizon. 'Planning blight' happens when the existing quality of life in a community suffers because of the future prospect of sweeping change, and 'future blight' must not be allowed to distract attention from the urgent needs of the present generation of children with diabetes.

The incidence of childhood-onset type 1 diabetes has risen steadily since the middle of the last century, with an average 3.5% year-on-year increment in Europe [26]. On present evidence, only a minority will achieve a level of glucose control that offers reasonable immunity from diabetic nephropathy and sight-threatening retinopathy. The individual and communal legacy of poor glucose control will remain with us for the next 30 years, even if an effective means of preventing new cases of the disease were to be introduced tomorrow [27]. Those who survive microvascular complications still face the prospect of accelerated arterial disease, and the studies needed to show us how to prevent this have yet to be launched. Advances in the practical management of diabetes are welcome and badly needed, but may only widen the gap between the best available care and that received by the average child. Results obtained in isolated centres of excellence must not be presented as if they represent overall progress; they are a call to action rather than a cause for complacency. The greatest need is for more effective implementation of what is already known.

In 1931 Joslin designed a medal (Fig. 1) to commemorate the children whose lives had been extended by insulin. The medal was modelled on a boy called George B who developed diabetes in 1920 at the age of 5, and he and his dog are pictured in a boat against the rising sun; the medal is engraved on the front with the words 'explorers of uncharted seas', and on the reverse with 'prolonging life span after the onset of diabetes—a scientific and moral victory' [28]. Three quarters of a century later, it is clear that the voyage is far from over, and that victory has yet to be won. Like Elliott Joslin, we have all watched too many children dying of diabetes. It is time to move on.

Fig. 1

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