Diabetes-Related Mortality

A pediatrician's view

Individuals with newly diagnosed type 1 diabetes or members of their families invariably ask questions about the morbidity and mortality associated with this new disorder they must contend with. Some younger children are frightened that the "di" in diabetes means that they will die soon. Teens often use as an excuse for their noncompliance the view that they are going to die young and that nothing they do will alter that course.

What are the facts? And, are they already out-of-date, given recent improvements in diabetes care? Feudtner (1) called type 1 diabetes " a disease in motion," citing its "transmutation" from a uniformly lethal condition in the preinsulin era to its present status as a serious chronic disorder based on its long-term morbidity and mortality.

Diabetes-related mortality should be separated in two: deaths occurring early in the course, invariably associated with diabetic ketoacidosis (DKA) or hypoglycemia, and those resulting from long-term micro- and macrovascular complications. The article in this issue of *Diabetes Care* by Nishimura et al. (2) reports long-term mortality in nearly 1,000 type 1 diabetic patients diagnosed before age 18 years in Allegheny County, Pennsylvania, between 1965 and 1979. They found a significant improvement in survival in the more recently diagnosed individuals and concluded that this improvement likely stems from better glycemic and blood pressure control resulting from the availability of blood glucose monitoring, HbA_{1c} assays, and newer antihypertensive agents.

In life table analyses provided by Nishimura et al. (2) the cumulative survival was 98% at 10 years and 79.6% at 30 years. Recently, Matsushima et al. (3) published mortality data on diabetic subjects <24 years of age from around the world. Adjusting their data based on the frequency of type 1 diabetes in different populations, they found a 10-fold variation in mortality, with the lowest levels in Canada and Western Europe, and the highest in Japan, Eastern Europe, and Russia. Of note was the close relationship between incidence-adjusted mortality and the incidence of type 1 diabetes, as well as with infant mortality and life expectancy at birth. These data suggest that early diabetes mortality relates to both overall standards of health care and diabetes-specific care.

Prevention of early mortality depends on a thorough understanding of its causes. Scibilia et al. (4) reported 55 deaths in a cohort of children from the Children's Hospital of Pittsburgh diagnosed between 1950 and 1980: DKA accounted for 17 (85%) of the 20 deaths at disease onset and 18 (54%) of those occurring 2 months to 11 years after diagnosis. No deaths were attributed to hypoglycemia. In contrast, Sartor and Dahlquist (5) reported 33 deaths in 4,919 children with type 1 diabetes in Sweden: only 7 deaths (21%) were DKA-related, with 9 (27%) "deaths-in-bed," some presumed to be a result of hypoglycemia. More recently, Edge et al. (6) from the U.K. reported 116 deaths in diabetic subjects <20 years of age, of which 83 were diabetes-related. Of these, DKA was implicated in 69 deaths (83%) and hypoglycemia in 7 (8%), giving a standardized mortality ratio of 2.3 for young people with diabetes.

Most deaths associated with DKA result from the development of cerebral edema. In a multicenter study of 6,977 hospitalizations for DKA in the U.S., Glaser et al. (7) documented 61 (0.8%) episodes of cerebral edema. Of these 61 children, 13 (21%) died and another 13 had serious neurological sequelae. Two more children died during the episode of DKA but not from cerebral edema. Thus, the overall mortality rate from DKA was 0.21%, similar to the 0.25% rate previously reported from pediatric institutions in the U.S. (8).

The contribution of hypoglycemia to early diabetes mortality is much less well documented. The report by Edge et al. (6) suggests that hypoglycemia-associated deaths are about one-tenth as common as those related to DKA. Nevertheless, with increasingly intensive attempts to achieve excellent metabolic control to prevent the onset or to slow the progression of complications, hypoglycemia is more frequent. In the adolescent cohort in the Diabetes Control and Complications Trial, not only was tight control more difficult to achieve than in the adult cohort, but severe hypoglycemia occurred more frequently (9). Furthermore, severe hypoglycemia is even more common in the youngest children with diabetes, which may account in part for the highest standardized mortality rate in the 1–4 year age-group reported by Edge et al. (5,10). Clearly, hypoglycemia is the rate-limiting step in the achievement of excellent control; more frequent blood glucose monitoring, insulin analogs, continuous insulin infusion pumps, and sensor technology may all contribute to a reduction in severe hypoglycemia over the next few years.

Because most early diabetes-related deaths are attributable to DKA or hypoglycemia, prevention of these conditions should lower mortality. There are only three causes of DKA: at disease onset, as a result of intercurrent illness, and following insulin omission. All are potentially preventable. Vanelli et al. (11) from Parma, Italy, were able to prevent most episodes of DKA at diabetes onset using an educational approach that targeted both school personnel and physicians. Experience shows that DKA during intercurrent illness can be prevented using patient guidelines and 24-h hotlines (12). Finally, recurrent DKA inevitably results from insulin omission (13). Ensuring insulin injection in these individuals, mostly teens, will significantly decrease the incidence of DKA.

While making every effort to reduce this early mortality, pediatric diabetes health care professionals must not overlook the substantial threat that faces our patients over the next 20 years. The risk of death due to DKA and hypoglycemia per-

sists into adulthood. In fact, in adult series, mortality rates associated with DKA are in the 3.5–4.5% range (14). Furthermore, hypoglycemia unawareness increases with disease duration, and hypoglycemia-related mortality probably follows a similar trend. However, with time, the threat of micro- and macrovascular complications far exceeds that of DKA and hypoglycemia. Modifiable risk factors for these complications (i.e., poor metabolic control, hypertension, smoking, hyperlipidemia, and, perhaps, obesity and sedentary lifestyles) should be identified early on. Knowledge of the relationship between control and complications obtained through the DCCT and other studies allows us to provide patients and their families with the rationale for excellent metabolic control from day 1 of their diabetes (9). This needs to be tempered against the age and maturity of the child, their experience with hypoglycemia, and a host of other factors. We also need to provide these young people with counseling in regard to prevention of smoking, support for active lifestyles and avoidance of obesity, surveillance for both hyperlipidemia and hypertension, and screening for early microvascular changes (15).

Many questions remain unanswered. When does the clock start ticking on the long-term complications? While early data suggested that the prepubertal years may be relatively risk-free, more recent information is not as encouraging (16, 17). Do angiotensin-converting enzyme inhibitors provide the same renoprotection for adolescents with microalbuminuria as they do in adults? Data from at least five studies of the natural history of microalbuminuria in adolescents with type 1 diabetes show that about half "spontaneously" revert to normal over 3–10 years of follow-up (15). Will the drive for tight control in children and teens yield the desired health benefits 10–30 years from now? These and other issues will keep the diabetes research community busy for many years. But there is reason for optimism; Nishimura et al. (2) show a decreasing morality risk in those subjects diagnosed 20–25 versus 30–35 years ago. One could reasonably speculate that children being diagnosed today with type 1 diabetes face an even more optimistic future.

DENIS DANEMAN, MB, BCH, FRCPC

From the Division of Endocrinology, the Hospital for Sick Children, Toronto, Ontario, Canada.

Address correspondence to Denis Daneman, MB, BCh, FRCPC, Professor of Pediatrics, University of Toronto, Chief, Division of Endocrinology, The Hospital for Sick Children, 555 University Ave., Toronto, ON M5G 1X8, Canada. E-mail: denis.daneman@sickkids.on.ca.

References

1. Feudtner C: A disease in motion: diabetes history and the new paradigm of transmuted disease. *Perspect Biol Med* 39:158–170, 1996
2. Nishimura R, LaPorte RE, Dorman JS, Tajima N, Becker D, Orchard TJ: Mortality trends in type 1 diabetes: the Allegheny County (Pennsylvania) Registry 1965–1999. *Diabetes Care* 24:823–827, 2001
3. Matsushima M, LaPorte RE, Maruyama M, Shimizu K, Nishimura R, Tajima N: Geographic variation in mortality among individuals with youth-onset diabetes mellitus across the world: the DERI Mortality Study group. *Diabetologia* 40:212–216, 1997
4. Scibilia J, Finegold D, Dorman J, Becker D, Drash A: Why do children with diabetes die? *Acta Endocrinologica* 279 (Suppl.): 326–333, 1986
5. Sartor G, Dahlquist G: Short-term mortality in childhood onset insulin-dependent diabetes mellitus: a high frequency of unexpected deaths in bed. *Diabet Med* 12: 607–611, 1995
6. Edge JA, Ford-Adams ME, Dunger DB: Causes of death in children with insulin-dependent diabetes, 1990–96. *Arch Dis Child* 81:318–323, 1999
7. Glaser N, Barnett P, McCaslin I, Nelson D, Trainor J, Louie J, Kaufman F, Quayle K, Roback M, Malley R, Kuppermann N: Risk factors for cerebral edema in children with diabetic ketoacidosis. *N Engl J Med* 344:264–269, 2001
8. Levitsky LL, Ekwo E, Goselink CA, Solomon IL, Aceto T: Deaths from diabetes in hospitalized children (1970–1988). *Ped Res* 29 (Suppl.):A195, 1991
9. DCCT Research Group: Effect of intensive diabetes treatment on the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus: Diabetes Control and Complications Trial. *J Pediatr* 125: 177–188, 1994
10. Mortensen HB, Hougaard P, Hvidore Study Group on Childhood Diabetes: Comparison of metabolic control in a cross-sectional study of 2,873 children and adolescents with insulin-dependent diabetes from 18 nations. *Diabetes Care* 20:714–720, 1997
11. Vanelli M, Chiari G, Ghizzoni L, Costi G, Giacalone T, Chiarelli F: Effectiveness of a prevention program for diabetic ketoacidosis in children: an 8-year study in schools and private practices. *Diabetes Care* 22:7–9, 1999
12. Daneman D, Frank M: Defining quality of care in children and adolescents with type 1 diabetes. *Acta Paediatrica* 87 (Suppl. 425):11–19, 1998
13. Golden MP, Herrold AJ, Orr DP: An approach to the prevention of recurrent diabetic ketoacidosis in the pediatric population. *J Pediatrics* 107:195–200, 1985
14. Persisting: mortality in diabetic ketoacidosis. *Diabet Med* 10:282–284, 1993
15. Sochett E, Daneman D: Early diabetes-related complications in children and adolescents with type 1 diabetes: implications for screening and intervention. *Endocrinol Metab Clin North Am* 28:865–882, 1999
16. Kostraba JN, Dorman JS, Orchard TJ, Becker DJ, Ohki Y, Ellis D, Doft BH, Lobes LA, La Porte RE, Drash AL: Contribution of diabetes duration before puberty to development of microvascular complications in IDDM subjects. *Diabetes Care* 12: 686–693, 1989
17. Schultz CJ, Konopelska-Bahu T, Dalton RN, Carroll TA, Stratton I, Gale EA, Neil A, Dunger DB: Microalbuminuria prevalence varies with age, sex, and puberty in children with type 1 diabetes followed from diagnosis in a longitudinal study: Oxford Regional Prospective Study group. *Diabetes Care* 22:495–502, 1999