The Changing Face of Young-Onset Diabetes: Type 1 Optimism Mellowed by Type 2 Concerns

Until recently the outlook for a youth or young adult diagnosed with diabetes, which was almost universally type 1, was bleak. Indeed, using data from the National Health Interview Survey as recent as from 1984 to 2000, it was estimated that U.S. children diagnosed with diabetes at 10 years of age had a life expectancy approximately 19 years less than seen in the general population (1). However, more recent data from the Pittsburgh Epidemiology of Diabetes Complications (EDC) study suggest those diagnosed with childhood-onset diabetes between 1965 and 1980 have a life expectancy of almost 69 years, which is less than 4 years lower than the comparable U.S. population (2). This good news has been accompanied by the observation from the Finnish Diabetic Nephropathy (FinnDiane) study that virtually all of the excess mortality seen in type 1 diabetes is related to the development of micro- or macroalbuminuria (3). This seminal observation has been confirmed and extended for up to a 20-year period in the EDC population (4).

The improved prognosis, in terms of mortality, has been accompanied by a dramatic reduction (5) or delay (6) in the incidence of end-stage renal disease. Interestingly, the decline in cardiovascular disease (CVD), the leading cause of overall mortality in diabetes, is less marked (5). One cautionary note, however, has to be made concerning the improvement in mortality of patients with type 1 diabetes. In a recent analysis of over 17,000 individuals in Finland, diagnosed between 1970 and 1999, Harjutsalo et al. (7) compared the time trends of mortality for those diagnosed at an age less than 15 years to those diagnosed at an age of 15 through 29 years. Although a very significant fall was seen in mortality over time for the young-onset group, consistent with the Pittsburgh EDC population (who were all diagnosed before the age of 17), mortality for the older-onset group increased over time reflecting an increasing number deaths related to alcohol, drugs, and acute complications (7). This raises the possibility that

type 1 diabetes mortality patterns may differ markedly by age of onset.

The picture becomes more confusing, and disturbing, when one considers the recent increased incidence of apparent type 2 diabetes occurring in youth and young adults (8). One major challenge is that of typology, or our ability to distinguish between type 1 and type 2 diabetes, which is particularly difficult in an overweight or obese young adult. The SEARCH for Diabetes in Youth (SEARCH) study has examined this issue in some depth and described four groups based on the presence or absence of diabetes autoantibodies and of insulin resistance (9). How well this schema would work in the future in terms of predicting outcome remains to be seen but it is likely to be quite relevant as a number of studies have suggested that even in clear type 1 individuals it is those with evidence of insulin resistance or an insulin resistance/type 2 diabetes family background that have increased cardiovascular and renal disease (10–15). The complexity of this issue is further demonstrated by the observation that many classic type 1 diabetic subjects may retain some residual β-cell function for many years after diagnosis (16), which may partly relate to the benign natural history seen in many of the patients from the Joslin 50-Year Medalist Study who have survived 50 years of type 1 diabetes (17).

So what do we know about the prognosis of type 2 diabetes in youth and young adults? A number of studies have suggested that individuals with type 2 diabetes have worse cardiovascular risk factors than similarly aged individuals with type 1 diabetes. Indeed, the SEARCH study has shown more adverse cardiovascular risk profiles, including blood pressure (18) and lipid levels (19), and a higher prevalence of microalbuminuria (20) in youth-onset type 2 diabetes compared with type 1. Up to now, however, there have been few data on mortality or major outcomes of diabetes comparing type 1 and type 2 diabetes where onset occurred in youth or young

adulthood. Hillier and Pedula (21) some years ago suggested that type 2 diabetes with an onset between age 18 and 44 years ran a more aggressive course than cases diagnosed later, particularly in terms of relative impact compared with the age-matched general population. The results of the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study support such a conclusion in terms of metabolic deterioration and have been recently reviewed (22).

In this issue, Constantino et al. (23) now provide further data concerning young adult–onset type 2 diabetes. Using a diabetes clinical database, and matching to the Australian National Death Index, these investigators were able to compare clinical and mortality outcomes from 354 patients with type 2 diabetes and 470 with type 1 diabetes.

Strikingly there was a twofold greater mortality in the type 2 cohort predominantly due to an excess of cardiovascular deaths. Although the clinical data were largely collected through routine encounters, a standardized protocol was used and the data quality is thus likely to be generally high. Likewise, the linkage with the Australian National Death Index is validated and mortality ascertainment data are likely to be complete. A significant weakness of the study, however, is the reliance purely on death certificates alone for cause of death, which were only available for 72% of deaths at the time of analysis. A number of studies have demonstrated the pathways and contributors to death are quite complex in diabetes (24) and the study would be greatly enhanced by the investigation and standardized recording of causes of death. Nevertheless, these data are unique and extremely valuable and support the growing concern that type 2 diabetes with a youth/young adult–onset has a particularly high risk of adverse vascular outcomes. Some of the figures from Constantino et al. (23) are quite concerning with prevalence rates of ischemic heart disease reaching as high as 13% at an age of 40 years compared with only 3% in

the comparable group with type 1 diabetes whose mean age was 39 years.

In an interesting further analysis, the authors looked at the prevalence of risk factors 2–5 years after diabetes diagnosis when mean age was 28 years. Significant differences between the two types of diabetes were seen with the type 2 subjects having significantly higher blood pressures, lipids, and greater albuminuria. In contrast, smoking rates were marginally lower in those with type 2 diabetes. Finally, it should be noted that although the blood pressures and lipids were generally higher in type 2 diabetes than type 1 diabetes, they were only moderately elevated (e.g., mean blood pressures were 120/78 mmHg and total cholesterol was 210 mg/dL).

These data therefore raise very significant clinical questions that need urgent answers. First and foremost, it is important that we do not adopt the narrow "glucocentric" approach that for so many years dominated our approach to diabetes management and CVD prevention in type 2 diabetes. It should be noted these very divergent vascular outcomes in the current study's data occurred with an identical updated HbA$_{1c}$ of 8.1% in both groups of subjects.

Second, we need to know more about the relative contribution of predictors of adverse outcomes in young-onset type 2 diabetes. Unfortunately the data from Constantino et al. on risk factors measured early on in the course of diabetes were available for only 29% of subjects thus precluding prospective, definitive multivariable risk modeling. Third, we need to address the lack of guidelines and evidence-based goals on which to base cardiovascular intervention. This has been a long-standing problem in type 1 diabetes because, with the exception of the Heart Protection Study (HPS) (25), there are no cardiovascular risk factor intervention trials in young-onset type 1 diabetes with clinical outcomes on which to base treatment goals and strategy. While clearly the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) studies intensive insulin therapy intervention in early-onset type 1 is of great benefit, CVD still develops in the intervention group at a high rate (26) and, as noted earlier, CVD rates do not seem to be declining as rapidly as renal disease rates (5). It is thus quite possible that lower blood pressure and lipid goals may be more appropriate in type 1 diabetic subjects than now appear to be the case in older type 2 diabetic subjects, the group on which guidelines are loosely based. In the light of the recent Constantino et al. and TODAY (22) studies, data current guidelines and goals maybe even more out of tune for those with young-onset type 2 diabetes. Fourth, an implication of the results in Constantino et al. is the need to continue the search for other avenues to reduce the mortality and cardiovascular morbidity seen in diabetes in general. Clearly, the enhanced risk in type 2 diabetes may largely relate to insulin resistance itself, and as noted this is also an important risk factor in type 1 diabetes.

A further focus should be to better identify and target those with a genetic predisposition. Recent data concerning the combination of haptoglobin genotype 2–2 and diabetes (either type 1 or type 2) leading to enhanced coronary artery disease risk (27,28) and renal risk (in type 1 diabetes) (29) offers some hope in this regard. This is particularly encouraging as the CVD risk may be ameliorated by vitamin E therapy (so far tested only in type 2) (30). This is unlikely, however, to explain the differential risk between type 1 and type 2 diabetes.

So where do we go from here? While guidelines and CVD risk factor goals clearly need to be revisited in terms of their applicability to both young-onset type 1 and type 2 diabetes, they would be best based on clinical trial evidence. Thus, a CVD prevention trial evaluating both intensive blood pressure and lipid control versus current management would be helpful. The outcomes could also include renal disease while further randomized arms might address new approaches (e.g., insulin sensitization and/or vitamin E therapy in those with haptoglobin susceptibility). The target population should comprise young adults with either type 1 or type 2 diabetes though the former should have longer diabetes duration to provide comparable and sufficient event rates.

Constantino et al. (23) should serve not only as an alarm bell for the development of appropriate management strategies for young-onset type 2 diabetes but also—especially given the disappointing results of the TODAY study (22) of management of adolescent type 2 diabetes—a call to further our prevention efforts in terms of type 2 diabetes and insulin resistance in general. While we can probably still conclude that those with type 1 diabetes and an onset in youth may have a normal life expectancy, particularly if micro- or macroalbuminuria is avoided, it seems doubtful that the same optimism can be extended to those developing type 2 diabetes at a similarly young age.

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