Age-related differences in glycaemic control in diabetes

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Abbreviation

NHANES National Health and Nutrition Examination Survey

There has been a dramatic increase in the global burden of type 2 diabetes over the past three decades [1]. In addition to obesity, age is one of the most important risk factors for type 2 diabetes and the burden of the disease is very high in older age groups. Among adults in the USA aged 65 or older, the prevalence of diagnosed diabetes in 2011 was 20%, or more than eight times higher than the prevalence among adults 18 to 44 years of age (2.4% prevalence) [2]. The strong association of diabetes with age is of particular concern given the global ageing of the population [3]. Nevertheless, the incidence and prevalence of type 2 diabetes is also increasing among young persons [1, 4–6].

The article by Berkowitz et al [7] in this issue of *Diabetologia* examines whether younger age at diabetes diagnosis is associated with worse glycaemic control. They analysed data from the 2005–2010 National Health and Nutrition Examination Survey (NHANES), a nationally representative sample of the civilian non-institutionalised population of the USA. The authors concluded that persons diagnosed with diabetes between the ages of 30 and 65 years had worse glycaemic control than those diagnosed at 65 years of

age or older. This raises an important question: why might younger people have inferior glycaemic control compared with their older counterparts?

Berkowitz et al found that the use of insulin was much higher and treatment with sulfonylurea medications much lower among individuals with a younger age at diagnosis. In addition, even though people diagnosed with diabetes younger than 65 had inferior glycaemic control, they had fewer comorbid conditions, such as end stage renal disease, congestive heart failure and chronic obstructive pulmonary disease. Persons with younger-onset diabetes were also more likely to be obese, to be ethnically either Hispanic or non-Hispanic black, and to have a longer duration of diabetes. It is important to note that, in this study, the diagnosis of diabetes, medication use and comorbid conditions were all self-reported. A concern is that there are age-related differences in screening and diagnostic practices. Indeed, older age is explicitly incorporated into some diabetes screening recommendations; for example, the American Diabetes Association and Diabetes UK both recommend that, in the absence of major risk factors, routine screening for diabetes should begin in middle-age [8, 9]. It is unclear to what degree possible detection bias may have influenced the observed results. Furthermore, as the authors acknowledge, certain segments of the US population were not included in NHANES, such as people residing in nursing homes or long-term care facilities. The current national prevalence of diabetes among residents of nursing homes and long-term care facilities is unknown but is undoubtedly high [10].

Diabetes is progressive and glucose levels are known to increase with age [8, 11]. However, there is also evidence for differences in the pathophysiology of type 2 diabetes in older compared with younger individuals. It is unclear to what degree diabetes in the elderly may primarily result from an age-related decline in beta cell function. It has been hypothesised that impaired insulin secretion, rather than insulin resistance, commonly leads to diabetes in elderly adults

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compared with their younger counterparts [12, 13]. This may, in part, explain the relative lack of effectiveness of metformin therapy (which decreases hepatic glucose output and increases insulin action) in older participants in the landmark Diabetes Prevention Program (DPP) Trial [14, 15]. Persons diagnosed with type 2 diabetes at younger ages may have a more severe form of the disease, associated with a higher degree of insulin resistance, more rapidly increasing glucose levels, and worse glycaemic control that is more resistant to current treatment modalities [16].

Survival bias is also a critical issue in the interpretation of age-related effects in any cross-sectional study. People who are ill—including the most severe, complicated and/or uncontrolled cases of diabetes—are more likely to die at a younger age compared with individuals with late-onset and/or well-controlled diabetes. By definition, these persons will be under-represented in a large, population-based survey. Prospective follow-up of individuals over time does not resolve this issue entirely, since differential entry into the study and/or loss to follow-up can lead to survival bias in prospective cohort studies. Previous studies have reported a slowing of diabetes incidence with age [17]. It is possible that some (or all) of this plateau is attributable to higher rates of study dropout among persons with newly developed disease.

To address survival bias in their report, Berkowitz et al controlled for duration of diabetes. The authors also conducted several sensitivity analyses. First, they restricted analyses to persons older than 70 years of age, to increase the representation of people who had had diabetes for a significant amount of time, particularly among those diagnosed at a younger age. In a second analysis, they included only those persons who had had diabetes for fewer than 5 years, since it is unlikely that death within 5 years of diagnosis would be due to diabetes, thus limiting the potential for survival bias to arise. In a third analysis, they restricted analyses to people taking insulin, to limit the study population to those with more severe diabetes.

Unfortunately, these analytical approaches cannot fully overcome the possible profound selection and survival issues. Adjustment for duration of diabetes may actually exacerbate the survival bias effect. This adjustment necessarily invokes a comparison between an older and younger cohort: a person who has had diabetes for 10 years but was diagnosed with diabetes at under 65 years of age will be younger than a person who has had diabetes for 10 years but was diagnosed at an age above 65 years. In the USA, life expectancy is approximately 78 years and, inevitably, those who live longer are generally healthier. Thus, the older group (who developed diabetes later in life) may have better general health than the younger group, having survived to a more advanced age.

So where do we go from here? Berkowitz et al colleagues' concluding points about individualisation of treatment and the

need for prospective studies are good ones. Most of our current evidence in the field of type 2 diabetes comes from studies of middle-aged adults. Diabetes in older individuals is often complicated by comorbid conditions, frailty, multiple medications, frequent hypoglycaemia and cognitive or functional impairment. Thus, older people with diabetes are commonly excluded from clinical trials and epidemiological studies. Consequently, we have limited understanding of the incidence and natural progression of diabetes and the best approaches to treatment in older people. Compounding these knowledge gaps is the fact that randomised clinical trials have shown little benefit of (and perhaps even harm caused by) very intensive glycaemic control in the risk of macrovascular outcomes [18–22]. There is controversy regarding whether a focus on very tight glycaemic control results in overall benefit in type 2 diabetes, particularly among the elderly and those with long-standing disease [8, 23, 24].

At the other end of the age spectrum, the increase in overweight and obesity in young people in many countries has been dramatic. In the 1970s in the USA, only about 5% of children were overweight or obese. Now, the prevalence is almost 20% [5, 6]. Consequently, type 2 diabetes among children and adolescents—once a rare condition—is now more common than type 1 diabetes in some subgroups of the population [4, 25, 26]. Unfortunately, little is known about this expanding population, particularly in relation to best approaches to treatment. Results of a recent clinical trial showed that adolescents with type 2 diabetes may respond to treatment differently from adults: young people with type 2 diabetes may not respond as well to monotherapy and may be more likely to need combination or insulin therapy to achieve glycaemic control [27]. An additional sobering trend is the growing prevalence of pre-diabetes in youth [28–30]. The best approach to the prevention of diabetes and complications in these high-risk young people is uncertain [31].

Ultimately, in light of these many uncertainties, we think it is imperative that policy-makers and research funding agencies turn their attention to new-onset diabetes in both the young and the old to further our understanding of pathophysiology and inform management of the disease in these growing populations.

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