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In This Issue of *Diabetes Care*

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DCCT/EDIC: Mortality Rates in Type 1 Diabetes Cohort Are the Same as in General Population

Rates of mortality in the Diabetes Control and Complications Trial (DCCT) and the follow-up Epidemiology of Diabetes Control and Complications (EDIC) cohort appear to be similar to that of the current general U.S. population, according to the latest report from the DCCT/EDIC Study Research Group (**p. 1378**). Specifically, mortality in the intensive therapy group appeared lower (although nonsignificantly) but mortality was significantly higher in the conventional therapy group. Mortality also increased significantly with increasing mean HbA_{1c}, especially among women in the cohort. The DCCT was a major intervention study that compared the effects of an intensive treatment approach to normalize glycemia and a "conventional" treatment approach (for the time) aimed at maintaining clinical well-being (EDIC is the extended follow-up study of the DCCT cohort). Together the studies demonstrated major benefits of intensive treatment, with the DCCT results in particular having a major influence on clinical practice—achieving HbA_{1c} levels <7% is now considered central for treating both type 1 and type 2 diabetes. According to the authors, the leading primary causes of death in the type 1 diabetes cohort were cardiovascular disease and cancer—both, of course, leading causes of death in the general population. Mortality risk also appeared to correlate with increased HbA_{1c}. The authors stress however, that establishing relationships between HbA_{1c}, other underlying risk factors, and mortality in the cohort will require more time as at the moment the number of deaths is too small to achieve sufficient power and precision in the analysis. Commenting more widely on the results, John M. Lachin told *Diabetes Care*: "While historical cohorts with type 1 diabetes experienced markedly increased mortality relative to the general population, the DCCT/EDIC cohort, with a mean HbA_{1c} of about 8% since the close of the DCCT in 1993, shows little increased mortality with the suggestion that current treatment guidelines aimed at near normal HbA_{1c} will yield mortality rates no different from the general population."

The Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Study Research Group. Mortality in type 1 diabetes in the DCCT/EDIC versus the general population. Diabetes Care 2016;39:1378–1383

HbA_{1c}: Research Gaps, Future Directions, and Opportunities?

HbA_{1c} has been used successfully for decades in the management and more recently, in the diagnosis of patients with diabetes. And yet, the measurement is not without weaknesses, meaning that careful consideration of results is needed. Welsh et al. (**p. 1299**) chart the development of HbA_{1c} and its use in diabetes and specifically highlight where the measure has its weaknesses and the research gaps that should be addressed to progress the method further. They also highlight potential alternative glycated proteins, particularly fructosamine, glycated albumin, and advanced glycation end products (AGEs) that might have potential to improve the predictive capacity of HbA_{1c}, or to even replace it in certain situations. HbA_{1c} reflects average blood glucose concentration over the preceding 3–4 months. In comparison to direct spot measurement of blood glucose levels, which can be influenced by many different factors, it is considered a more robust method for assessing glycemia in diabetes. Nevertheless, according to the authors, a range of factors need to be considered in terms of HbA_{1c} data for the purposes of diabetes management. These include factors that may influence the interpretation of HbA_{1c} and factors that may influence HbA_{1c} measurement. While HbA_{1c} has certainly proved invaluable in diabetes management and has proven clinical usage on the basis of a number of landmark trials, controversies do remain, according to the authors. They highlight two opposing views, which are also published in this issue of *Diabetes Care* (**pp. 1458 and 1462**), that center on whether HbA_{1c} might vary according to racial grouping or age—raising the pointed question of what exactly HbA_{1c} means for different groups. Commenting more widely on this study, author David B. Sacks stated: "Optimal use of any laboratory test requires an understanding of its limitations. Awareness of the conditions that may influence HbA_{1c} results enables clinicians and other health care providers to derive valuable information from HbA_{1c} measurements that assists in treatment decisions. Future studies are likely to enhance our comprehension of the clinical value of other glycated proteins in patients with diabetes."

Welsh et al. Role of glycated proteins in the diagnosis and management of diabetes: research gaps and future directions. Diabetes Care 2016;39:1299–1306

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Lixisenatide for Intensive HbA_{1c} Reduction but Reduced Side Effects

While HbA_{1c} remains a central measure for the management of diabetes and intensive treatment to reduce it to 7% or less is a central target to reduce diabetes complications, how one actually achieves this remains open to question. The results of the GetGoal Duo-2 trial, as reported by Rosenstock et al. (**p. 1318**), should help clarify matters with the suggestion that short-acting glucagon-like receptor agonists (in the form of lixisenatide) as an add-on to basal insulin might represent a preferred treatment intensification option. This is because in the head-to-head comparison it could achieve substantial reductions in HbA_{1c} but with fewer hypoglycemic events and without weight gain in comparison to "standard" approaches involving insulin alone. The three-arm randomized open-label study compared HbA_{1c} outcomes in patients with type 2 diabetes on basal (optimized) insulin glargine and either lixisenatide once daily or insulin glulisine given once or three times daily. Primary end points after 26 weeks were the noninferiority of lixisenatide to reduce HbA_{1c} versus that of glulisine given once or three times per day. Lixisenatide was also examined for superiority in body weight change versus glulisine three times per day. Plasma glucose, efficacy/safety end points and adverse events were also tracked. According to the authors, HbA_{1c} improved in the run-in baseline glargine optimization period (8.5–7.9%) and then over the following 26 weeks of intervention, all three treatments resulted in further improvements in HbA_{1c} (7.0–7.2%) (i.e., lixisenatide was not inferior to the other treatments). Significantly though, symptomatic hypoglycemia and body weight were reduced in the lixisenatide group in comparison with the other glulisene groups. Hypoglycemia and body weight increases are a significant issue in many patients when intensification of treatment is commenced. The authors concluded by suggesting that lixisenatide may represent a "valuable alternative to treatment intensification" and "may become a preferred therapeutic option."

Rosenstock et al. Prandial options to advance basal insulin glargine therapy: testing lixisenatide plus basal insulin versus insulin glulisine either as basal-plus or basal-bolus in type 2 diabetes: the GetGoal Duo-2 trial. Diabetes Care 2016;39:1318–1328

Hidden Information in Glucose Tolerance Tests Suggests Curves Might Predict Type 2 Diabetes

The shape of the oral glucose tolerance test (OGTT) response curve may contain hidden metabolic information and is potentially a predictor for type 2 diabetes in adults. According to Kim et al. (**p. 1431**), this may also be the case in youth, and it seems a monophasic OGTT curve is indicative of all the risk biomarkers in youth with type 2 diabetes. The study examined 277 obese adolescents without diabetes who completed a 2-h OGTT. They were then categorized according to whether they had a monophasic or a biphasic OGTT curve. A whole range of body composition and metabolic parameters where then compared. A subset (n = 106) of the volunteers also underwent clamp procedures to accurately determine insulin sensitivity and secretion and β-cell function. According to the authors, the group that had the monophasic OGTT response had many classic signs of risk for type 2 diabetes, while the biphasic group did not (even though they were obese). As well as confirming the existence of these different response patterns, the researchers suggest these patterns may represent a simple but effective biomarker for identifying type 2 diabetes risk or even prediabetes. However, they caution that both prospective longitudinal and intervention studies will likely be needed to confirm their observations and whether it is possible to use interventions to shift from monophasic to biphasic profiles, presumably because this is a "healthier" phenotype. Commenting more widely on the outcomes of the study, Silva Arslanian said: "Our study informs that despite similar fasting and 2-h OGTT glucose concentrations, the monophasic group harbors much higher risk of prediabetes and type 2 diabetes than the biphasic group. This suggests that regardless of the accepted and standard criteria for prediabetes or diabetes diagnosis by the World Health Organization and the American Diabetes Association, the OGTT glucose response curve in youth might unravel abnormalities much earlier than impairments in fasting and 2-h glucose concentrations, a stage that might be too late for effective intervention and prevention efforts in youth."

Kim et al. The shape of the glucose response curve during an oral glucose tolerance test heralds biomarkers of type 2 diabetes risk in obese youth. Diabetes Care 2016;39:1431–1439

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