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In This Issue of *Diabetes Care*

By Max Bingham, PhD

Sodium–Glucose Cotransporter Inhibitors and Diabetes Treatment Reviewed

The long history of the novel antidiabetic sodium–glucose cotransporter inhibitors (SGLTs) is charted by Mudaliar et al. (**p. 2344**) in this issue of *Diabetes Care*. They cover the development of the drug class all the way from the discovery of phlorizin in apple tree bark 200 years ago right through to the development and approval of SGLT inhibitors that are available today. While reporting that SGLT inhibitors are currently only approved for use in type 2 diabetes, the authors highlight other areas where they are being studied, including type 1 diabetes. They also provide a useful summary of the results of clinical trials that have completed to date and point out where further trials are taking place. SGLT2 inhibitors are notable, according to the authors, because they target glucosuria and inhibit renal glucose reabsorption, meaning that it is possible to reduce plasma glucose in a manner that is independent of insulin. The overall effects, which make them unique as antidiabetes agents, according to the authors, are that they improve glycemia, lead to caloric loss and weight and blood pressure reduction, and have a low risk of hypoglycemia. The result has meant widespread usage of the treatment in clinical practice often in combination with other agents such as metformin. Indeed, the authors even describe the introduction of SGLT2 inhibitors as a "paradigm shift in diabetes management." However, they highlight that for many aspects of these drugs, long-term studies are still needed, especially with respect to the long-term implications of increased glucosuria. Commenting more widely on the review, Dr. Mudaliar stated: "Due to the insulin-independent mechanism of these agents, they can be used across the spectrum of type 2 diabetes, from those with new-onset diabetes to those with long-duration disease in whom insulin secretion is greatly impaired. What is more exciting is the recent publication of the EMPA-REG OUTCOME study results that showed that SGLT2 inhibitors can significantly lower cardiovascular mortality and even all-cause mortality."

Mudaliar et al. Sodium–glucose cotransporter inhibitors: effects on renal and intestinal glucose transport—from bench to bedside. Diabetes Care 2015;38:2344–2353

HbA_{1c} May Predict Durable Glycemic Control in Adolescents With Type 2 Diabetes

A readily accessible clinical measurement, HbA_{1c} may allow those treating youth-onset type 2 diabetes to predict whether a patient will maintain durable glycemic control. Using data from 477 participants in the TODAY trial, Zeitler et al. (**p. 2285**) found that achieving an HbA_{1c} measurement of 6.3% or less a few months following commencement of treatment with metformin monotherapy was sufficient to predict whether a patient on oral medications would maintain glycemic control for at least 48 months. The authors suggest that this could be a "simple clinical measure to predict short- and medium-term outcome and allow better targeting of therapy to those adolescents at highest risk for loss of glycemic control." The outcome follows both univariate and multivariate analyses of a range of baseline characteristics (e.g., age, sex, race, BMI, waist circumference, etc.) and standard biochemical measurements including HbA_{1c}. Only HbA_{1c} and an insulinogenic index measure significantly differentiated those who maintained glycemic control on oral therapy from those who required insulin therapy within 48 months. The cutoff value of 6.3% was identified as predictive in the cohort as a whole, with a greater than fourfold risk of requiring insulin within 48 months for individuals above the cutoff. The same HbA_{1c} value held true for female participants but was lower for male participants at 5.6%. Commenting on the significance of their observations, Dr. Zeitler noted: "These results indicate that it is possible to distinguish youth early in the course of the disease who are likely to need intensification of therapy from those who can be expected to have durable control on oral therapy alone. This may allow better tailoring of therapeutic decisions. Most importantly, the HbA_{1c} cutoff that distinguishes youth who will likely need intensification is lower than might be expected, since an HbA_{1c} of 6.5% is well within the established treatment targets. It will now be important for clinicians to recognize that some youth who appear to have attained treatment targets may be at increased risk for decompensation over a relatively short time."

Zeitler et al. HbA_{1c} after a short period of monotherapy with metformin identifies durable glycemic control among adolescents with type 2 diabetes. Diabetes Care 2015;38:2285–2292

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Gestational Age and Birth Weight Linked to Type 1 Diabetes

Carrying on with the theme of diabetes in young populations, a large population-based cohort study by Khashan et al. (**p. 2308**) suggests that there may be a small association between premature birth (33–38 weeks) and occurrence of childhood type 1 diabetes. Low and high birth weight may also be associated with varying degrees of risk of type 1 diabetes. Of note with these conclusions is that they are based on data covering nearly all births in Sweden between 1973 and 2009. Furthermore, it was also possible to extract data for a sibling control study, meaning confounding factors relating to family could also be accounted for. Altogether 3.6 million singleton births were initially included in the study of which ~14,000 cases of type 1 diabetes were later identified. Around 11,000 cases were also included in the sibling control study (18,000 siblings). Modeling was then used by the authors to identify risk ratios for developing type 1 diabetes. Slightly elevated risk was identified in relation to preterm (33–36 weeks' gestation) and early-term (37–38) birth, and this remained significant after accounting for sibling controls. Large for gestational age was also associated with increased risk, but this effect disappeared once familial factors were accounted for. Very low birth weight, small for gestational age, and very preterm births (<33 weeks' gestation) conversely appeared to be associated with the reduced risk. In terms of mechanisms, the authors suggest that early life growth restriction and subsequent catch-up might affect insulin, which then manifests as type 1 diabetes. Alternatively, they suggest a link between the development of the human gut microbiome in infancy and the development of type 1 diabetes. Such a link has previously been suggested for both type 1 and type 2 diabetes. Commenting on the significance of their results, Dr. Khashan stated: "Our study provides new and intriguing data on the early life influences on the risk of developing diabetes. This will hopefully facilitate future studies to focus on the precise mechanism by which the in utero environment influences the pathophysiology of this disease."

Khashan et al. Gestational age and birth weight and the risk of childhood type 1 diabetes: a population-based cohort and sibling design study. Diabetes Care 2015;38:2308–2315

Depression in Youth With Type 1 or Type 2 Diabetes

Focusing on a slightly older population, Silverstein et al. (**p. 2341**) report in this issue of *Diabetes Care* that symptoms of depression may be routinely underdiagnosed in youth with type 1 or type 2 diabetes. As a result, they suggest that regular depression screening should be used to ensure appropriate referral and treatment for these patients. Using a validated self-reporting depression screening tool and statistical modeling, symptoms of depression were found in 13% of 261 patients with type 1 diabetes; however, of those, only 4% had received treatment from a therapist in the previous 12 months. For patients with type 2 diabetes, depressive symptoms were reported by 22% of 339 patients, of whom 9% had received treatment in a similar period. The study was carried out in children aged 10–17 years attending one of eight diabetes treatment centers in the U.S. that are part of the Pediatric Diabetes Consortium. Lower family income and obesity were both associated with depressive symptoms in type 1 diabetes. However, no such associations could be found in type 2 diabetes. In both type 1 and type 2 diabetes, there was no association of depressive symptoms with any of the other characteristics that were extracted from medical records or interviews. On the basis of the results, the authors suggest that routine screening of such young patients for depressive symptoms should now be carried out and that to assist in this, a self- administered electronic version of the survey could well be useful in busy diabetes practices. Commenting more widely on the results, Dr. Silverstein stated: "Despite recommendations from current treatment guidelines that routine screening for depression be done during clinic visits, the screening is not being performed frequently enough to allow us to adequately identify and recommend treatment for this at-risk population. Timely referral for psychological counseling could improve adherence and, ultimately, glycemic control."

Silverstein et al. Depressive symptoms in youth with type 1 or type 2 diabetes: results of the Pediatric Diabetes Consortium Screening Assessment of Depression in Diabetes study. Diabetes Care 2015;38:2341–2343

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