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Diabetes Care®

In This Issue of *Diabetes Care*

By Max Bingham, PhD

Hypoglycemia Unawareness and Glucose Variability as Key Risk Factors for Hypoglycemic Events in Older Adults

A combination of physiological hypoglycemia unawareness and increased glucose variability is likely associated with the common occurrence of severe hypoglycemic events in older adults with type 1 diabetes, according to Weinstock et al. (**p. 603**), who also found that patients who had had a severe hypoglycemic event over the past year scored worse on certain tests of cognition. Using a case-control study, the authors investigated a range of hypoglycemia risk factors. Cases included older (≥60 years of age) patients with long-standing type 1 diabetes who had experienced at least one severe hypoglycemic episode in the previous 12 months. In contrast, matched control subjects had had no severe hypoglycemia in the previous 3 years. Both HbA_{1c} and mean glucose were found to be similar between the case and control subjects. However, hypoglycemia unawareness, where a person with diabetes does not experience the usual physiological warning signs of an impending hypoglycemic episode, was much more common in the case subjects. At the same time, greater glucose variability was also detected in the case subjects. Current guidelines suggest that higher HbA_{1c} targets should be considered in older adults with long-standing type 1 diabetes because hypoglycemia risk is so high in this group. However, according to the authors, their results now call into question whether increased HbA_{1c} targets are likely to be sufficient alone for reducing hypoglycemia in this population. The authors conclude that frequent home glucose measurements might well be the best available approach to manage hypoglycemia risk in the face of hypoglycemia unawareness. Commenting more widely on the outcomes of the study, Dr. Weinstock stated: "Older adults with type 1 diabetes are an understudied population. It is important to be aware of their increased risk for severe hypoglycemia and for us to investigate ways in which this risk can be reduced. Studies using newer technologies such as continuous glucose monitoring with threshold suspend insulin pumps in this population are needed."

Weinstock et al. Risk factors associated with severe hypoglycemia in older adults with type 1 diabetes. Diabetes Care 2016;39:603–610

Nasal Spray With Glucagon May Replace Injections in Hypoglycemia Emergencies

The results of a phase 1 clinical study suggest that a needle-free glucagon nasal powder delivery approach could be as effective as intramuscular glucagon injections for treating severe hypoglycemia in children. The study by Sherr et al. (**p. 555**) was mainly designed to assess safety and dose-response relationships of glucagon delivered via the nose as a spray in comparison with standard glucagon injections. Involving 48 children with type 1 diabetes (aged 4 to <17 years), the study then assessed how effective different doses of glucagon and administration routes were for raising blood glucose after it was artificially lowered to <80 mg/dL. The study was clinically based and involved seven U.S. diabetes centers. The majority of doses of glucagon produced an increase in blood glucose of >25 mg/dL within 20 min of administration, irrespective of delivery route. The one dose that did not work was in a 6-year-old boy who blew his nose directly after receiving a nasal spray of glucagon. Times to peak glucose and glucagon levels were similar for both routes of administration. The results of the study "support the potential efficacy of a needle-free glucagon nasal powder delivery system for treatment of hypoglycemia in youth with type 1 diabetes." The authors conclude that "the next step will be to determine its effectiveness when used in the treatment of real-life outpatient hypoglycemic events in youth with [type 1 diabetes]." Commenting more widely on the outcomes of the study, Dr. Sherr stated: "As our youth with type 1 diabetes spend nearly one-third of their day outside of the care of their parents, this single-step intranasal glucagon preparation could make treatment of severe hypoglycemia more feasible for the myriad individuals involved in their care including parents, other family members, teachers, bus drivers, and coaches."

Sherr et al. Glucagon nasal powder: a promising alternative to intramuscular glucagon in youth with type 1 diabetes. Diabetes Care 2016;39:555–562

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Once-Weekly Long-Acting C-Peptide for Neuropathy in Type 1 Diabetes

A once-weekly dose of a long-acting C-peptide results in a marked improvement in a measure of peripheral neuropathy in patients with type 1 diabetes, according to the results of a large multicenter phase 2 randomized controlled trial conducted by Wahren et al. (**p. 596**). The C-peptide intervention resulted in a 25% improvement over 52 weeks in vibration perception threshold (VPT), a measure of peripheral neuropathy. Meanwhile, another measure, bilateral sural nerve conduction velocity (SNCV), also improved in patients receiving C-peptide. However, unexpectedly the corresponding value for the placebo group also increased and the differences between groups did not differ significantly. Trying to explain the results, the authors suggest that they expected the SNCV measure to slow during the 12 months of the study in the placebo group due to the natural progression of peripheral neuropathy. Follow-up work into potential confounding factors then suggested that simply taking part in the study might possibly have been enough to induce significant effects on SNCV. They suggest that their observations, along with other studies where such a placebo effect was observed, raise questions about the usefulness of SNCV as a primary outcome variable in studies of diabetic neuropathy. Despite the setback, the authors go on to suggest that the improvements in VPT are significant clinically and represent what could be interpreted as a targeted improvement for a key aspect of sensory function in peripheral neuropathy in type 1 diabetes. Commenting more widely on the study, Dr. Wahren stated: "There is no disease-modifying therapy available for diabetic neuropathy, and the unmet medical need is great. The present results and earlier findings suggest that future development of C-peptide as a therapeutic agent for diabetic nerve impairment should focus on small fiber neuropathy and early stages of the disorder."

Wahren et al. Long-acting C-peptide and neuropathy in type 1 diabetes: a 12-month clinical trial. Diabetes Care 2016;39:596–602

Uric Acid Levels Reduced in Adolescents With Type 1 Diabetes but Not Associated With Cardiovascular Risk Factors

A clinical study by Lytvyn et al. (**p. 611**) reveals that plasma uric acid levels may already be reduced in adolescents with type 1 diabetes, likely as the result of increased clearance by the kidneys into urine. At the same time, however, no relationships were evident between uric acid levels and a range of cardiovascular parameters. While the healthy control participants registered an average plasma uric acid level of 306 µmol/L, the adolescent patients with type 1 diabetes had an average level of 242 µmol/L. There was also an inverse relationship of plasma uric acid levels with estimated glomerular filtration rate when type 1 diabetes was present, which, the authors suggest, might reflect increased urinary clearance. They suggest that while there maybe few type 1 diabetes complications evident at an early stage in childhood, their study shows that underlying pathogenic processes may have already started. Previously, little was understood about the relationship between uric acid and renal/cardiovascular parameters in adolescents. According to the authors, establishing such relationships could potentially reveal predictors of future complications and also possibly treatment options. Commenting more widely on the study, Dr. Cherney stated: "Unlike in adults with type 1 diabetes, plasma uric acid levels were not associated with early cardiovascular abnormalities in an adolescent cohort. Given the accumulating evidence in adult patients with type 1 or type 2 diabetes linking plasma uric acid with hypertension, atherosclerosis, and chronic kidney disease, it is important to identify whether the effects of plasma uric acid on cardiorenal risk are modified over time and to determine causal relationships. Moreover, to better understand uric acid as a cardiorenal risk factor, renal and cardiovascular protective effects of plasma uric acid lowering are being investigated in an ongoing clinical trial in adult patients with type 1 diabetes with microalbuminuria in the Preventing Early Renal Loss in Diabetes (PERL) study (NCT02017171)."

Lytvyn et al. Association between plasma uric acid levels and cardiorenal function in adolescents with type 1 diabetes. Diabetes Care 2016;39:611–616

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