



# DIABETES IS PRIMARY

TIMELY NEWS AND NOTES FOR PRIMARY CARE PROVIDERS  
from the American Diabetes Association

By Max Bingham, PhD

## FROM THE JOURNALS.....

### **Remission With Weight Loss Lifestyle Intervention “Should Be the Primary Therapeutic Aim” in Prediabetes**

A lifestyle intervention focused on weight loss can lead to the remission of prediabetes and a substantial risk reduction for developing type 2 diabetes, according to Sandforth et al. (*The Lancet Diabetes & Endocrinology*, doi.org/k3sw). However, unlike the remission of type 2 diabetes, prediabetes remission is characterized by improvement in insulin sensitivity and reduction in visceral adipose tissue, and it appears there are also responders and nonresponders to the approach.

The findings come from a pre specified post hoc analysis of the Prediabetes Lifestyle Intervention Study (PLIS), with validation using data from the Diabetes Prevention Program (DPP) study. Only individuals who lost  $\geq 5\%$  of their body weight during 12 months of intervention were included in the analysis. The authors then defined responders and nonresponders as those who returned or did not return, respectively, to normal fasting plasma glucose levels based on three separate measures.

“We aimed to explore the feasibility of commencing earlier and implementing preventive measures already at a stage that precedes type 2 diabetes, namely prediabetes, with the aim of reversing it,” senior author Andreas Birkenfeld said.

Just over one-fourth of PLIS participants ( $n = 298$ ) achieved a weight loss  $\geq 5\%$ , and of those, 43% were responders. In contrast, the DPP validation cohort had 683 participants who achieved the same weight loss target, of whom 19% were responders.

The authors then looked at a series of outcomes and found that responders experienced increased insulin sensitivity and reduced visceral adipose tissue compared to nonresponders. BMI reduction and insulin secretion did not differ between the groups, and intrahepatic lipid

content decreased in both groups. The authors note that 2 years after the interventions ended in PLIS, the responders had a 73% lower risk of developing type 2 diabetes compared to nonresponders.

As in PLIS, participants in the DPP cohort who were responders had improved insulin sensitivity compared to nonresponders but no difference in terms of insulin secretion.

“Since the responders showed a reduction in abdominal fat in particular, it will be important in the future to identify the factors that promote the loss of this fat depot,” first author Arvid Sandforth said. Indeed, although the authors discuss some of the potential mechanisms involved, they note that the study design precludes the identification of unmeasured confounding factors.

“Based on the new data, remission should be the new therapeutic target in people with prediabetes,” co-first author Reiner Jumpertz von Schwartzberg said. “This has the potential to change treatment practice and minimize the complication rate for our patients.”

### **Rotavirus Vaccine in Finland Linked to Decrease in Type 1 Diabetes Incidence in Young Children**

A decrease in exposure to rotavirus brought on by the introduction of a rotavirus vaccine in Finland appears to be associated with a decrease in the incidence of type 1 diabetes, according to Parviainen et al. (*Diabetes Care*, doi.org/k3s3).

The findings come from a national register-based ecological study involving birth cohorts in Finland from 1995 through 2015. The authors then compared outcomes in those born before and after the vaccine became commercially available in 2006 and its introduction nationally in 2009. Just over 1 million children were included in the analysis.

The authors found that 18,154 children  $< 5$  years of age were exposed to rotavirus infection, of whom 82% were in the pre-vaccine birth cohorts. The peak of infection was in the 2001–2005 cohorts, with a rate of 2,522 per 100,000 children. However, this rate dropped to 171 per 100,000 children in the post-vaccine cohorts.

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<https://doi.org/10.2337/cd24-dp01>

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The incidence of type 1 diabetes in children <5 years of age changed in parallel with infection rates, with incidence 21% lower in the post-vaccine 2010–2015 cohorts compared to the pre-vaccine 2001–2005 cohorts. Based on these findings, the authors calculated that a 1% reduction in exposure to rotavirus was associated with a decrease of 8% in incidence of type 1 diabetes in children <5 years of age.

Although this study has considerable strengths, including its size and statistical power, the authors note that it was designed to explore the association at a population level; thus, their findings cannot be interpreted as indicative of causality at an individual level. For that reason, the authors call for further research.

## TREATMENTS + THERAPIES



### Gastrointestinal Issues Associated With Off-Label Use of GLP-1 Receptor Agonists

Glucagon-like peptide 1 (GLP-1) receptor agonists, when used off-label for weight loss, appear to be associated with increased risks for serious gastrointestinal issues, according to Sodhi et al. (*JAMA*, doi.org/k2rc). The drugs appear to raise risks for stomach paralysis, pancreatitis, and bowel obstruction when used in patients without diabetes.

Prior studies have highlighted the gastrointestinal issues associated with the drugs when used in people with diabetes. However, none have specifically assessed these risks in individuals without diabetes who are using the drugs for weight loss.

“Given the wide use of these drugs, these adverse events, although rare, must be considered by patients thinking about using them for weight loss,” first author Mohit Sodhi said. “The risk calculus will differ depending on whether a patient is using these drugs for diabetes, obesity, or just general weight loss. People who are otherwise healthy may be less willing to accept these potentially serious adverse events.”

Using data from the PharMetrics Plus database, the authors used a random sample of 16 million patients over the period 2006–2020 to identify new users of semaglutide or liraglutide or the active comparator bupropion-naltrexone that is used for weight loss via a different mechanism. Individuals were included if they had documented obesity and excluded if they had documented diabetes or use of antidiabetic medications. Outcomes were incidence of biliary disease, pancreatitis, bowel obstruction, and gastroparesis.

For all four outcomes, there was an elevated incidence with the GLP-1 receptor agonists compared to the comparator drug. Based on adjusted hazard ratios (HRs), the authors found increased risks for pancreatitis (HR 9.09, 95% CI 1.25–66.00), bowel obstruction (HR 4.22, 95% CI 1.02–17.40), and gastroparesis (HR 3.67, 95% CI 1.15–11.90), but not biliary disease (HR 1.50, 95% CI 0.89–2.53).

The authors note that, although these events were rare, the popularity of the drugs could still mean that many hundreds of thousands of individuals might experience the conditions.

*continued on p. 7 →*

# MARKETPLACE.....

## Low-Cost Decision Support Tool Cuts Hypoglycemia Risks and Medication Needs in Older Adults With Type 2 Diabetes

Older adults with type 2 diabetes are often considered at risk for hypoglycemia when they remain on glucose-lowering drugs when their A1C is <7%. Multiple previous studies have shown that many—perhaps most—older adults with type 2 diabetes are overtreated. However, a distinctly analogue clinical decision support tool, combined with shared decision-making, can lower the risk of hypoglycemia resulting from overtreatment in these individuals, according to Kohn et al. (*Journal of the American Geriatrics Society*, doi.org/k37k). Specifically, use of the tool helped individuals reduce or eliminate their use of glucose-lowering drugs and with it their risk for hypoglycemia. Study participants also reported significant improvements to daily life after intervention with the tool and the subsequent reduction in hypoglycemia episodes.

The findings come from a small, single-arm pilot study that investigated the use of the tool in combination with extensive shared decision-making over a 6-month period in a primary care setting. Clinicians used the tool with patients to assess

hypoglycemia risk, set individualized A1C targets, and adjust glucose-lowering medication use. They also used a validated patient outcomes tool to assess how changes in the risk of hypoglycemia affected six domain scores of daily life.

Ninety-four individuals were included at baseline, and 90 completed the study. The authors found that nearly all of the participants set individualized A1C goals and that 20% decreased or eliminate their use of insulin or a sulfonylurea. Just over half reached their A1C goal, with the mean A1C increasing by 0.53%. The number of participants who were at risk before the intervention because they had an A1C <7% and used glucose-lowering medications decreased by 46% with intervention. The impact of hypoglycemia on daily life also decreased.

“This study demonstrates that a low-cost clinical decision support tool, without the additional use of continuous glucose monitoring technology, can decrease the number of patients at high risk for hypoglycemia and reduce overtreatment with insulin and diabetes medications that cause hypoglycemia,” study author Jeffrey B. Boord said (bit.ly/40twB5m).

The tool and instructions are freely available in the supplementary materials of the article (bit.ly/3sl1EDI).

### Treatments + Therapies, *continued from p. 6*

“These drugs are becoming increasingly accessible, and it is concerning that, in some cases, people can simply go online and order these kinds of medications when they may not have a full understanding of what could potentially happen,” Sodhi said. “This is critical information for patients to know so they can seek timely medical attention and avoid serious consequences.”

The Ozempic (semaglutide) label has since been updated to include an intestinal blockage warning (cnn.it/3QufMm8).

### Regulators Warn of Fake GLP-1 Receptor Agonist Drugs

The U.K.’s Medicines and Healthcare Products Regulatory Agency (MHRA) has issued a public warning about fake and potentially harmful injectable versions of Ozempic (semaglutide) and Saxenda (liraglutide) (bit.ly/49lmEuD). This follows similar warnings largely about Ozempic from the European Medicines Agency (EMA) (bit.ly/49lsBI3) and national authorities in Germany (bit.ly/47mCe7E), Austria (bit.ly/49m3nJv), and Switzerland (bit.ly/49id8IR).

British authorities report that they have seized hundreds of potentially fake Ozempic pens since January 2023, and there have been many reports of fake

Saxenda pens obtained by members of the public via “non-legitimate” routes without prescription. Authorities have also received a small number of reports of individuals hospitalized after using the purported semaglutide pens for weight loss with serious side effects, including hypoglycemic shock and coma, raising suspicion that the pens contained insulin rather than semaglutide.

The medicines, which were originally developed to treat type 2 diabetes and obesity, have become increasingly popular with the general public for largely off-label use for weight loss, causing shortages of the drugs throughout Europe, the United States, and elsewhere (bit.ly/3MxK32e). The drugs can cost ~\$1,000 per month in the United States without insurance, opening opportunities for illegal traders to proliferate and profit. Both Novo Nordisk (bit.ly/3RyZ4CD) and Eli Lilly, the manufacturer of the dual GLP-1/glucose-dependent insulinotropic polypeptide Mounjaro (tirzepatide) (bit.ly/3QpbPPr), have filed lawsuits against various medical spas, wellness centers, and compounding pharmacies to stop them from selling knock-off versions of the drugs.

The MHRA, EMA, and German, Austrian, and Swiss authorities are urging the public not to buy such prefilled pens and instead to consult a health care professional and obtain a prescription.



## ADA NEWS

### New Article Collection Maps Out CGM's Role in Transforming Diabetes Management

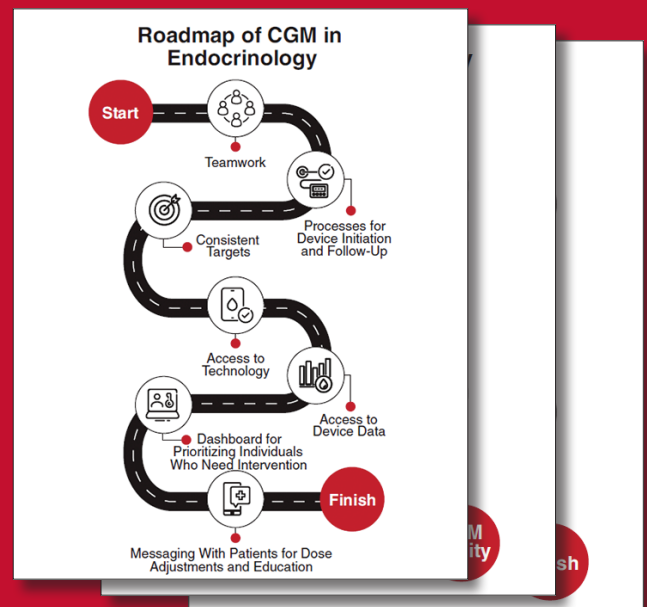
The global diabetes pandemic is challenging health care professionals to transform current care practices to improve outcomes in an ever-expanding population living with the disease. In a recent *Diabetes Spectrum* From Research to Practice article collection (*Diabetes Spectrum*, [bit.ly/49pnhz](https://bit.ly/49pnhz)), esteemed Guest Editor Richard M.

Bergental, MD, Associate Editor Anastasia Albanese-O'Neill, PhD, APRN, CDCES, and a team of expert authors explain how continuous glucose monitoring (CGM) can play a pivotal role in that transformation.

Titled "Roadmaps to Continuous Glucose Monitoring's Role in Transforming Diabetes Management," the collection opens with a preface in which Bergental explains that transforming care requires clearly defined, step-by-step processes moving from innovation to investigation to implementation. From there, expert authors present such roadmaps to the expanded and optimized use of CGM in five key areas: diabetes specialty care, primary care, pregnancy care, education, and care equity. The authors map out recent advances, discuss remaining barriers, and describe their hopes and expectations for the future. The collection ends with an insightful article in which Bergental reflects on the 25-year evolution, current impact, and future promise of CGM as a driver of transformation in diabetes care.

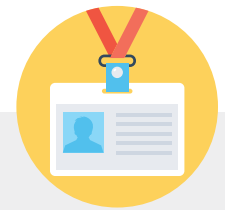
Bergental's review, and the other articles in the collection, highlight "what the diabetes

community has achieved, what we are still working on, and what we need to tackle next, including innovations we all hope will materialize before much longer," Bergental said. "I imagine the destination for all such CGM roadmaps will be a place and time when all who can benefit from the use of CGM or other life-changing approaches to diabetes management have equal access to these transformative therapies."



### Safe at School: Updated CGM Guidance

The ADA's Safe at School Working Group has recently updated its guidance for schools, clinicians, and parents on the use of CGM in school settings ([bit.ly/3FLOa8D](https://bit.ly/3FLOa8D)). In addition to an overview of CGM systems, the guidance provides suggestions for monitoring and responding to CGM data and for ensuring appropriate communication between schools and parents/guardians.



## CONFERENCE SPOTLIGHT

### ***ISPAD: Antibody Slows $\beta$ -Cell Loss in Children Newly Diagnosed With Type 1 Diabetes***

Teplizumab appears to preserve  $\beta$ -cell function when given shortly after a diagnosis of type 1 diabetes, according to Ramos et al., who presented at the 2023 meeting of the International Society for Pediatric and Adolescent Diabetes in Rotterdam, the Netherlands, and also published their findings (*New England Journal of Medicine*, doi.org/k37p).

The course of the drug resulted in 59.3% less  $\beta$ -cell function loss compared to placebo at 78 weeks, and nearly all teplizumab patients (94.9%) had peak C-peptide (a  $\beta$ -cell proxy measure) of  $\geq 0.2$  pmol/mL, compared to 79.2% of those taking placebo. The study also included a series of secondary end points such as insulin dose, hypoglycemia, and A1C change, but none were significantly different between the treatment and placebo groups. There was also little difference between the groups in quality-of-life scores.

“Type 1 diabetes is a chronic autoimmune disease, driven by the destruction of the insulin-producing  $\beta$ -cells, and, as such,  $\beta$ -cell preservation remains a meaningful unmet need for all patients with diabetes,” author Kevan Herold said in a statement (bit.ly/466ADSa) “These new results build on the findings from multiple studies across

different stages of the disease process, further supporting [teplizumab’s] potential to modulate the progression of [type 1 diabetes].”

The findings come from a phase 3 randomized controlled trial called PROTECT, which included 328 individuals aged 8–17 years with stage 3 type 1 diabetes. Individuals were assigned 2:1 to either teplizumab or placebo dosed in two 12-day courses, with the first administered within 6 weeks of diagnosis.

According to the authors, the study was complicated by the coronavirus disease 2019 pandemic, which caused missed visits and disrupted data collection. There were also difficulties with blinding, and the trial was likely underpowered for the secondary outcomes. Nevertheless, the authors conclude that there were still benefits in terms of the primary outcome of maintenance of  $\beta$ -cell function.

Further research appears to be inevitable for the drug to make progress with this indication (i.e., its use after rather than before diagnosis of clinical type 1 diabetes), but success could substantially expand its use into primary care, where most new cases of type 1 diabetes are identified. An observational extension study is ongoing and will follow participants for an additional 42 months.

To learn more about ADA’s continuing education opportunities, including Diabetes Is Primary events in your community, please visit [professional.diabetes.org/ce](http://professional.diabetes.org/ce).