DIABETES IS PRIMARY

TIMELY NEWS AND NOTES FOR PRIMARY CARE PROVIDERS

from the American Diabetes Association

By Max Bingham, PhD

FROM THE JOURNALS

Is COVID-19 Causing Diabetes?

Since the earliest reports from China and Italy, there has been evidence of people with coronavirus disease 2019 (COVID-19) infection presenting with dangerously elevated blood glucose levels and requiring considerable insulin doses to control it. High numbers of cases of ketoacidosis at admission have also raised concerns that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19, might also be causing some form of diabetes in certain people.

As Domenico Accili explained in a recent *Nature Metabolism* commentary (doi.org/gjjw37), too much is yet unknown to fully pin these new cases of diabetes on SARS-CoV-2. For example, the hyperglycemia commonly seen in COVID-19 patients could have many causes, and many types of inflammation can cause issues with insulin resistance and glucose metabolism. Whether the coronavirus that causes COVID-19 can attack pancreatic β-cells is also an open question. The unusually high numbers of COVID-19 patients admitted with ketoacidosis might be explained by viral attack, but again the cause is probably multifactorial.

"We should not dismiss the possibility that SARS-CoV-2 can cause diabetes, but we should not contrive it out of thin air if it is not supported by evidence either," Accili wrote.

What is slightly clearer is that COVID-19 is uncovering new cases of diabetes. In a recent systematic review and meta-analysis, Sathish et al. (*Diabetes, Obesity and Metabolism*, doi.org/gjrbq4) examined data from 3,711 COVID-19 patients in eight studies and found 492 cases of newly diagnosed diabetes, giving a pooled proportion of 14.4%.

Of course, that number included both new-onset diabetes and previously undiagnosed diabetes. In the two studies for which it was possible to separate out new-onset from previously undiagnosed cases, one hospital in Wuhan, China, reported 25 new-onset cases (with admission A1C <6.5%) out of a cohort of 453 COVID-19 patients (5.5% of the cohort), whereas another hospital in Anhui, China, reported a rate of 27.5%. For previously undiagnosed diabetes, rates varied from 0.6 to 46.5% in various settings in China and the United States and for both combined (i.e., new-onset plus previously undiagnosed), rates varied from 2.9 to 16% in settings in China, the United States, and Italy.

In a subsequent letter published in *Diabetes & Metabolic Syndrome: Clinical Research & Reviews* (doi.org/f99d), Sathish and Cao provided an update to this analysis, this time extracting the rate of previously diagnosed diabetes as opposed to newly diagnosed diabetes. They found that 14.8% of COVID-19 patients had previously diagnosed diabetes.

"This study shows that newly diagnosed diabetes may be observed as frequently as preexisting diabetes in hospitalized COVID-19 patients," they wrote. "It is essential that frontline health care workers recognize that newly diagnosed diabetes is a common phenomenon in COVID-19 patients, and they are a high-risk group who should be managed early and appropriately to improve their prognosis."

Indeed, there has been sufficient concern about this phenomenon that researchers at King's College London in the United Kingdom and Monash University in Australia have now established the COVIDIAB Registry (bit.ly/2Rte89y), which is designed to capture suspected cases of new-onset diabetes in the setting of COVID-19 over time. According to media reports (bit.ly/3vNOyuN), more than 350 clinicians have submitted at least one case of suspected COVID-19–induced diabetes.

"Over the last few months, we've seen more cases of patients that had either developed diabetes during the COVID-19 experience, or shortly after that," COVIDIAB co-principal investigator Francesco Rubino told *The Guardian*. "We are now starting to think the link is probably true; there is an ability of the virus to cause malfunctioning of sugar metabolism."

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Time in Range Linked to Mortality in Type 2 Diabetes

Reduced time in range (TIR), a metric derived from continuous glucose monitoring (CGM) data, is associated with increased risks of all-cause and cardiovascular disease (CVD) mortality in individuals with type 2 diabetes, according to Lu et al. (*Diabetes Care*, doi.org/f99h). They suggest that TIR might serve as a surrogate marker for longer-term adverse clinical outcomes and that patients should be encouraged to aim for a higher percentage of TIR to reduce risks.

In their study, 6,225 hospitalized adult patients with type 2 diabetes had TIR measured over a 24-hour period at baseline and were then stratified accordingly. They were then followed up for just under 7 years to assess mortality outcomes.

A total of 838 deaths occurred in that time period, of which 287 were due to CVD. After adjusting for numerous factors, the investigators found that hazard ratios for all-cause mortality increased in a stepwise manner as TIR decreased to 1.83 (95% CI 1.48–2.28) when TIR was ≤50% when compared to TIR >85% (P <0.001 for trend). A similar trend was evident for CVD mortality.

The study had a number of limitations, including an issue with establishing causality, and the generalizability of its findings may be limited. Nevertheless, the authors concluded that "TIR, as an intuitive and valid measure of glycemic control, should be more widely accepted in both clinical practice and clinical studies."

Reflecting on these concerns, Elizabeth Selvin pointed out in a linked commentary (*Diabetes Care*, doi.org/f99k) that there is still much to learn about using CGM technologies in clinical practice, although linking CGM metrics to longer-term outcomes is a good first step.

"Epidemiologic studies and randomized clinical trials are needed to rigorously compare the prognostic value of CGM metrics to each other and to A1C and to demonstrate that using CGM can complement A1C and improve outcomes in patients with type 2 diabetes," she recommended. "This is the evidence we need to guide the use of this technology and facilitate wider adoption of CGM in clinical practice."

TREATMENTS + THERAPIES

STEP Trials Find Significant Weight Loss With Higher-Dose Injectable Semaglutide

The results of the STEP (Semaglutide Treatment Effect in People With Obesity) trials, which assessed the efficacy of semaglutide 2.4 mg for weight loss in obesity, were reported extensively at the March ENDO 2021 virtual conference. Briefly, weekly injections for 68 weeks resulted in significant weight loss in the settings of obesity (STEP 1), and in obesity with diabetes (STEP 2), but these effects wear off if the drug is withdrawn (STEP 4). Last year, similar effects were reported with the same dose in combination with intensive behavioral therapy and a low-calorie diet (STEP 3). Further studies (STEP trials 5–8) are either completed or underway, with reports expected later this year. The remaining trials look at the effects of the drug over 2 years, its effects in largely Asian populations, and its weight loss effects compared to liraglutide. STEP research program sponsor Novo Nordisk also recently announced (bit.ly/3gZWPYl) that it will also push ahead with a trial of oral semaglutide for weight loss. The company announced in December 2020 that it had applied for approval from the U.S. Food and Drug Administration (FDA) (bit.ly/3vMCpWM) and the European Medicines Agency (bit.ly/3tppRTQ) for the potential weight loss indication with the injectable version. Higher-dose liraglutide (sold under the brand name Saxenda) received FDA approval for a weight loss indication in obesity in 2014.

Higher-Dose Dulaglutide Yields Superior A1C, Weight Reduction

Results of the AWARD 11 (Assessment of Weekly Administration of LY2189265 [dulaglutide] in Diabetes-11) trial were also published recently (Frias et al., *Diabetes Care*, doi.org/f99v), showing that dulaglutide 3.0 and 4.5 mg reduces A1C and weight more than the standard dose of 1.5 mg in people with type 2 diabetes. Moreover, all three doses had similar safety profiles. (An approved dose of 0.75 mg is also available but was not included in this trial.)

In total, 1,842 individuals with type 2 diabetes and a mean BMI of 34.1 kg/m^2 were randomly assigned to one of the three doses for 52 weeks. The primary objective was to determine superiority of the two higher doses compared to the reference lower dose at 36 weeks for reduction in A1C. Secondary

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MARKETPLACE

Wearable Ketone Detector Deemed "Feasible"

A wearable continuous ketone monitoring (CKM) device is feasible, according to Alva et al. (*Journal of Diabetes Science and Technology*, doi.org/f99n), who recently reported an in vivo assessment of a CKM device's performance. Looking much like a continuous glucose monitoring (CGM) sensor, the device was tested by 12 individuals who wore it for 14 days on the back of their upper arm, while also following a low-carbohydrate diet.

According to the report, the device was stable and accurately tracked ketones when compared to capillary blood ketone reference levels. Using the same wired enzyme technology found in CGM systems, the CKM device is based on β-hydroxybutyrate dehydrogenase chemistry and measures the enzyme in interstitial fluid. It requires a single calibration to last 14 days, according to the authors. Although further study is needed, the authors note that, in theory, it might be possible to integrate CKM technology with sensors for other measures of interest such as glucose.

Higher-Dose Dulaglutide Yields Superior A1C, Weight Reduction, *continued from p. 245*

superiority objectives included assessment of weight changes with the three doses.

Dulaglutide 4.5 mg yielded superior A1C reduction (−1.77 vs. −1.54%) and weight loss (−4.6 vs. −3.0 kg) compared to the 1.5-mg dose. The 3.0-mg dose was not found to be superior but still yielded a clinically relevant reduction in A1C. Common adverse events were similar across doses and included nausea and vomiting.

The authors concluded, "The availability of four clinically efficacious dulaglutide doses provides additional tools to individualize patient care, helping patients achieve and maintain glycemic and weight-reduction goals and allowing those already taking 1.5 mg to intensify treatment while continuing to receive a familiar therapy."

ADA NEWS

New Tool May Help to Overcome Barriers to Diabetes Therapy Intensification

Timely therapy intensification has long-term health benefits for people with type 2 diabetes. Indeed, research has confirmed that a "legacy effect" associated with achieving A1C targets early can help to prevent or delay complications and improve quality of life for years to come. However, research has also shown that therapy intensification delays when people with diabetes fail to meet treatment goals are too often the norm. These delays, referred to as "therapeutic inertia," are a significant contributor to poor outcomes in diabetes.

To help address this challenge, the American Diabetes Association (ADA) has created a brief self-assessment tool that people with diabetes can use in a clinic waiting room. This tool helps identify misperceptions about diabetes and the diabetes therapy journey. It also brings to the surface social and emotional barriers for further discussion. A provider conversation guide accompanies this tool, offering action tips and talking points for responding to each self-assessment answer. This resource is available free of charge at https://professional.diabetes.org/sites/professional.diabetes.org/files/media/ada_providerguide_final-2021-03-17.pdf.

Video Series Focuses on Combination Injectable Therapy

The editors of *Clinical Diabetes* recently announced the publication of a digital program titled "Rationale for the Use of Combination Injectable Therapy in Patients With Type 2 Diabetes Who Have High A1C (≥9%) and/or Long Duration (>8 Years)." In this short video series, Vivian A. Fonseca, MD, FRCP, Minisha Sood, MD, FACE, and Rodolfo J. Galindo, MD, discuss the pathophysiological changes that occur during the progression of type 2 diabetes, with a particular focus on the key role of declining β-cell function, as well as the clinical characteristics—long duration of type 2 diabetes and A1C ≥9%—that are

CONFERENCE SPOTLIGHT

The virtual ENDO 2021 conference took place March 20–23 and included many presentations on diabetes-related topics. The following is a roundup of some particularly relevant reports.

Glycemic Control Improved During Lockdown for Children With Type 1 Diabetes

Children with type 1 diabetes experienced improved blood glucose control in the first 12 weeks of the first coronavirus disease 2019–related lockdown in the United Kingdom, according to a report by Lawrence et al. (Abstract P22-1, bit.ly/2QNuvhj).

Concerned that pandemic-caused changes in care practices might affect how children and families manage the disease, the researchers compared glycemic control for children and teenagers in the 3 months before the lockdown versus the 3 months after it began. They found that, after lockdown, blood glucose levels and glycemic variability decreased, along with longer-term average blood glucose (A1C). The proportion of time in the target glycemic range

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indicative of diminishing β-cell function. They also review the clinical data supporting the use of available treatment options for these individuals and specifically examine the role of fixed-ratio combination therapies of a basal insulin and a glucagon-like peptide-1 receptor agonist.

The videos and an executive summary of the panel's recommendation are available on the *Clinical Diabetes* website at https://clinical.diabetesjournals.org/content/combination-injectable-therapy.

Diabetes and COVID-19 Article Collections Available

The ADA's four journals cover breaking research on diabetes research, treatment, and education and the effect of the coronavirus disease 2019 (COVID-19) pandemic. Articles on diabetes and COVID-19 are continually added to freely accessible collections available on the diabetesjournals.org website. The most recent articles include obesity and COVID-19 in adults with diabetes (https://doi.org/10.2337/db20-0671), associations between dipeptidyl peptidase 4 inhibitors and COVID-19 outcomes in type 2 diabetes (https://doi.org/10.2337/dc20-1824), implementing a pediatric diabetes clinic via telehealth (https://doi.org/10.2337/ds20-0060), and isolation and education during a pandemic for new-onset type 1 diabetes and concomitant COVID-19 (https://doi.org/10.2337/cd20-0044), among others.

ADA Launches Eye Health Facebook Page

Clinicians and their patients with diabetes are invited to join ADA's new Facebook group for people with diabetes who are interested in eye health. Individuals who join the site can interact with others in the diabetes community, ask questions about diabetes and eye health, and access helpful resources. The page can be accessed at https://www.facebook.com/groups/660493001405846.

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increased, while time below range did not change. In short, glycemic control improved.

"Children and families found it easier to manage this disease when they were forced to stay home," lead author Neil Lawrence said. "This helps us to understand the pressure that is put on patients and families when trying to live normal busy lives with activities outside of home. We need to give them extra support at school and when they go out socializing to prevent them from developing unfortunate complications later in life."

Rehospitalization Common for Diabetic Ketoacidosis

In further reporting from the ENDO 2021 conference, a study focusing on diabetic ketoacidosis found that one in five adults with type 1 diabetes who were hospitalized with the life-threatening condition were hospitalized again within 1 month. These patients were also twice as likely to die during the second hospitalization.

"We were surprised to find that the readmission rate after diabetic ketoacidosis treatment is so high," said Hafeez Shaka, lead author of the study (Abstract OR09-2, bit.ly/33h8cmv). "Efforts should be channeled toward identifying the risk factors for readmission in hospitalized adult patients with diabetic ketoacidosis, as well as ensuring proper discharge planning to decrease the burden of readmissions."

Language Barriers May Increase Obesity Rates in Spanish-Speaking Families

Li et al. (Abstract P02-31, bit.ly/3tkXHt7) examined long-term prevalence trends of obesity in children and teenagers in the United States and found that overall rates increased from ~15% in 1999 to ~20% in 2018. Strikingly, obesity rates among Spanish-speaking families reached ~25%, significantly higher than in English-speaking families. Lower household education and household income levels were also associated with higher obesity rates.

Lead author Hang-Long Li suggested that language barriers may be a key factor to consider given that most health promotion resources in the United States are presented in English. Even food labels tend to be in English only, he noted.

"Public health measures specifically catering to children from Spanish-speaking families should be put in place to raise awareness of childhood obesity and implement health interventions," he said.