American Diabetes Month: November 2023

Each November, the American Diabetes Association (ADA) brings awareness to the diabetes mellitus epidemic by educating those at risk and bringing light to the stories of those who live with diabetes.¹

**Key Inforbits**
- What is Diabetes?
- Pathophysiology and Etiology
- New Medications
- Continuous Glucose Monitors
- Compounded Semaglutide
- AI in Diabetes Management

**What is Diabetes?**
Diabetes mellitus is a group of metabolic disorders characterized by chronically elevated glucose in the blood.² In addition to hyperglycemia, diabetes also involves abnormal protein and fat metabolism. When poorly controlled, diabetes can lead to microvascular complications such as retinopathy and nephropathy, as well as macrovascular complications such as ischemic heart disease and cerebrovascular disease.

**Background**
Diabetes remains one of the most prevalent disorders affecting individuals in the world. In 2021, 527 million adults aged 20-79 years old were living with diabetes, with the number expected to increase to 643 million by 2030, and 783 million by 2045.³ According to the ADA, in 2019, 37.3 million people in the United States had diabetes, with 28.7 million individuals being diagnosed and 8.5 million being undiagnosed.⁴ This number continues to grow in the United States with 1.4 million Americans being newly diagnosed with diabetes every year. Additionally, 1 out of 5 individuals with diabetes are unaware they have diabetes. While these numbers are startling, the
number of individuals who have prediabetes is even greater. In 2019, 96 million Americans aged 18 years and older had prediabetes, meaning their blood glucose levels were abnormally elevated, but not high enough to meet the diabetes diagnosis threshold.¹

![Image](https://www.cdc.gov/diabetes/library/socialmedia/infographics/diabetes.html)

### Types of Diabetes

There are 3 types of diabetes, including type 1 diabetes mellitus, type 2 diabetes mellitus, and gestational diabetes mellitus. These differ by pathophysiology, clinical presentation, and population affected. The classic symptoms of diabetes include polyuria, polydipsia, polyphagia, weight loss, and fatigue.¹

<table>
<thead>
<tr>
<th>Classification</th>
<th>Pathophysiology</th>
<th>Clinical Presentation</th>
<th>Population Affected</th>
<th>Prevalence</th>
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<tbody>
<tr>
<td><strong>Type 1 Diabetes Mellitus</strong></td>
<td>Autoimmune destruction of pancreatic β-cells leading to absolute insulin deficiency</td>
<td>-Family history in first-degree relatives is uncommon (&lt;10%).&lt;br&gt;-Symptoms are common and may be dramatic&lt;br&gt;-Lean body habitus&lt;br&gt;-Abrupt onset</td>
<td>Diagnosed primarily in children and those &lt; 20 years old.</td>
<td>5-10% of all diabetes cases</td>
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<tr>
<td><strong>Type 2 Diabetes Mellitus</strong></td>
<td>Progressive loss of β-cell insulin secretion function accompanied by</td>
<td>-Family history in first-degree relatives is common (&gt;80%).</td>
<td>Diagnosed primarily in adults &gt; 30 years old.</td>
<td>90-95% of all diabetes cases</td>
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¹ AU InforMed, vol.21, no. 7, Wednesday, November 1, 2023
resistance to insulin action - Symptoms are uncommon and often mild - Overweight or obese body habitus - Gradual onset

| Gestational Diabetes Mellitus | Hormone changes during pregnancy result in increased insulin resistance | - Symptoms are uncommon and mild. - Typically develops around 24th week of pregnancy - Overweight or obese body habitus | Pregnant Women | 9% of all pregnancies in the United States |

New Medications

**Small-molecule oral GLP-1 agonists:**
Two new oral nonpeptide GLP-1 agonists are currently in development. Unlike oral semaglutide (Rybelsus), both orforglipron and danuglipron do not have to be taken in the fasting state and have been shown to reduce weight. Orforglipron is currently in the recruiting phase for its phase 3 clinical trials, where it is being compared against placebo, oral semaglutide, and insulin glargine over the course of several years in patients with obesity and an increase in cardiovascular risk. In a phase 2 trial comparing a variety of orforglipron doses to both placebo and a once-weekly injection of dulaglutide for 26 weeks, orforglipron 12 to 45 mg once daily lowered HgA1c by 1.19 to 2.10% compared to 0.43% for placebo and 1.10% for dulaglutide. The 12 to 45 mg doses also lowered bodyweight by 8.14 to 22.22 lbs. compared to placebo (4.84 lbs.) and dulaglutide (8.58 lbs.) by the end of the 26-week period.

In a 16-week phase 2b clinical trial for danuglipron, doses from 2.5 mg twice daily to 120 mg twice daily were administered with food and compared to placebo to determine dose effects on change in HbA1c, fasting plasma glucose, and body weight. For HgA1c reduction, danuglipron 2.5 mg to 120 mg showed a decrease from 0.49% to 1.18% compared to placebo. Doses also decreased fasting plasma glucose from baseline by 12.81 up to 31.93 mg/dL (respectively) after 16 weeks compared to 1.31 mg/dL for placebo. For body weight, danuglipron 10 mg to 120 mg twice daily decreased body weight by 0.13 lbs. to 9.17 lbs. compared to 0.94 lbs. lost with placebo. The 2.5 mg dose showed a nonsignificant weight gain after 16 weeks.

It should be noted that as doses increased for both agents, adverse events also became more common. The most common adverse events seen were GI intolerances for both agents. In the danuglipron trial there was 1 report of acute cholecystitis. Otherwise, no reports of serious adverse events were given for either agent.
**Triple-acting GLP-1/GIP/glucagon receptor agonist:**
Retatrutide is a once-weekly injection that is most potent at the GIP receptor and less potent at human glucagon and GLP-1 receptors. In its phase 1 trials, it showed robust reductions in glucose and body weight. Retatrutide has been effective in lowering glucose in previous trials. Currently, there are phase 3 trials in the recruiting phase that are comparing the effects of retatrutide in obesity and type 2 diabetes (3-year study) as well as studying the agent’s effects in chronic kidney disease (31-week study). In a phase 2 trial of 275 patients lasting 36 weeks (plus a 4-week safety follow up), a variety of doses (0.5, 4, 8, and 12 mg) at different dose escalation speeds were compared to placebo and once weekly dulaglutide 1.5 mg injections for its impact on glucose reduction, bodyweight reduction, HgA1c, and insulin sensitivity among several other cardiometabolic risk factors. Retatrutide lowered A1c from baseline to 36 weeks by 0.54% for the 0.5 mg group up to 2.16% for the 12 mg group. This decrease was statistically significant across all groups compared to the decrease seen in both the placebo group (-0.30%) and dulaglutide group (-1.36%). For fasting glucose reduction, only the 4 mg escalation group (starting dose of 2 mg) was not statistically significant compared to placebo and dulaglutide. The 0.5 to 12 mg groups lowered fasting blood glucose from 17.51 to 41.2 mg/dL from baseline compared to 17.26 mg/dL for placebo and 27.53 mg/dL for dulaglutide. Every treatment group lowered the baseline body weight after 36 weeks (including placebo by 7.22 lbs.). The 0.5 mg retatrutide group only lowered it by 7.28 lbs. which was not significant from placebo. The 4 mg escalation group up to the 12 mg escalation group lowered body weight by 16 up to 37.77 lbs. compared to dulaglutide which lowered body weight by 4.33 lbs. from baseline. The investigators studied increased insulin sensitivity by measuring fasting insulin requirements after 36 weeks. They found that the placebo group lowered insulin requirements from baseline by 22.17%. The doses of retatrutide that were significant for lowering fasting insulin requirements were both 8 mg treatment groups (36.92% and 41.65%) and the 12 mg group (36.33%). Dulaglutide was significant for lowering fasting insulin requirements by 35.68%. For safety, the most common adverse events were nausea, diarrhea, decreased appetite, and constipation. Both 8mg study groups and the 12 mg group were about the same when it came to adverse event occurrence.

**Once-Weekly Insulin for T2DM:**
In a 78-week open label phase 3a clinical trial, 984 patients were studied for the effect of once weekly insulin icodex versus once daily insulin glargine U100 in combination with noninsulin glucose lowering treatments (GLP-1 agonists and SGLT2 inhibitors) in insulin naïve patients. The primary endpoint was change in HgA1C from baseline and secondary endpoints were percentage of time spent in the target glycemic range of 70-180 mg/dL in weeks 48 to 52 and change in fasting plasma glucose level from baseline to week 52. For the primary efficacy endpoint, insulin icodex lowered the HgA1C level by 1.55% compared to insulin glargine with 1.44% (p=0.05). For weeks 48-52, patients on insulin icodex were within the target glycemic range 71.9% of the time compared to 66.9% of the time for those on insulin glargine daily. At week 52, the estimated mean level of fasting plasma glucose had decreased by about 60 mg/dL for each treatment arm, which was not significant. For adverse events over the course of the study there were a total of 1882 adverse events occurring in 397 of the patients receiving icodex and 1823 events occurring in 389 of the patients receiving glargine. Most events in the mild to moderate severity category were determined to be unrelated to trial treatment. All serious adverse events (95 for icodex and 119 for glargine) were unlikely to be related to the trial treatment. Overall rated of hypoglycemic episodes remained below one event per person-year of exposure throughout the trial, which the authors claimed is similar to rates reported in other trials.
of daily basal insulin analogues for insulin-naïve patients. The incidence of clinically significant episodes of hypoglycemia were 12.4% for the icodex group and 13.4% for the glargine group over the course of the trial. The authors also noted that for the icodex group, 3 of the 492 participants had 105 of the 226 clinically significant hypoglycemic events. Overall, the authors found that once-weekly insulin icodex offered better glycemic control than once-daily insulin glargine U100 in patients with type 2 diabetes who had not previously received insulin.

**Continuous Glucose Monitors (CGM)**

**Devices:** Freestyle Libre 2 & 3, Dexcom G6 & 7, and Eversense E3

**When to use**

CGM should be considered in any patient that requires insulin. This eliminates the need for frequent finger pricks, reduces the risk of hypoglycemia, and allows for better glycemic control and easier dose adjustments.

**Benefits of CGM**

Patients with nocturnal hypoglycemia, hypoglycemia unawareness, and/ or frequent episodes of hypoglycemia may benefit the most from CGM. These devices have technology that will alert the patient when glucose levels are low potentially avoiding life threatening events.

**Additional uses**

Hemoglobin A1c (HgA1c) is the measure of glycated hemoglobin over a 3-month period. The lifecycle of red blood cells is around 120 days. This is why we only measure HgA1c every 3 months. There are various conditions that can affect the lifecycle of red blood cells such as anemias, asplenia, red blood cell transfusions, chronic alcohol consumption, chronic kidney disease, etc. HgA1c measurements rely on normal functioning red blood cells in order to accurately assess a patient's level of glycemic control. Continuous glucose monitoring has great utility in such conditions as it does not rely on HgA1c, but rather gives us a real-time data by continually monitoring blood glucose throughout the day as well as identifying trends over shorter intervals. Reports from CGM can be sent to healthcare providers which give more objective data to adjust therapy rather than collecting self-reported readings from patients.

**Compounded Semaglutide**

Since March of 2022, semaglutide along with other GLP-1 agonists used for weight loss have been in short supply. This has resulted in an increased demand for compounded semaglutide. Until recently, semaglutide was not a candidate for compounding under sections 503A and 503B of the FD&C Act because it was considered a biological product. In 2020 the FDA revised its definition of a “biological product” and semaglutide was no longer considered a biologic. Semaglutide is on the FDA’s drug shortage list, making it currently eligible to be compounded. Concerns have risen in regards to using the salt forms of semaglutide, including semaglutide acetate and sodium. The active ingredient in Wegovy and Ozempic is semaglutide in its base form, therefore compounding this medication using the salt form would not meet FD&C requirements for this drug. The FDA received reports of increased side effects associated with salt forms of semaglutide although they have not commented on the specifics of these side effects. It is likely that increased blood pressure will be the main side effect due to the increased salt intake with these formulations. Overall, it is acceptable to compound semaglutide for weight loss if the proper base form is being used.
Artificial Intelligence in Diabetes Management

Findings from a new clinical study conducted by Klick Labs revealed that the use of AI and voice recordings from patients could be a potential new screening tool for diabetes. The study published in *Mayo Clinic Proceedings: Digital Health*, investigated the potential of voice analysis as a prescreening or monitoring tool for type 2 diabetes mellitus by examining the differences in voice recordings between nondiabetic and T2DM individuals.

A total of 267 participants diagnosed as nondiabetic (79 women and 113 men) or T2DM (18 women and 57 men) were followed. Participants used a smartphone application to record their voices at least 6 times a day for 2 weeks, saying fixed phrases that were 6 to 10 seconds long (total recordings: 18,465). The data was segmented into an age-matched and BMI-matched dataset for both men and women in order to evaluate voice changes in those with T2DM, and not with confounders such as age and BMI. Voice features corresponding to pitch, harmonic noise ratio, intensity, shimmer, and jitter were extracted, with a total of 14 voice features extracted from each audio recording. Shimmer and jitter at increased absolute values are associated with increased perceived breathiness, roughness, and hoarseness of the voice.

A 3-vocal-feature logistic regression model was used for women and a 2-vocal-feature Gaussian Naïve Bayes model for men. Predictive features used for women were mean pitch, pitch SD, and RAP (relative average perturbation) jitter, while features used for men were mean intensity and apq11 (amplitude of perturbation quotient). These features were chosen for the model due to their significant difference between nondiabetic and diabetic individuals. Upon analysis, distinct differences between the voices of individuals with and without T2DM were found. Variation in model features found that women with T2DM had a slightly lower pitch with less variation, and men with T2DM had weaker voices with more variation. The researcher suggests that differences most likely stem from difference in disease symptoms manifestations between sexes. For example, swelling and edema reduces pitch and vibratory characteristics, while muscle weakness and atrophy are linked to vocal weakness.

Ultimately, the findings of this study suggest that the use of AI could be a valuable diabetes screening tool for the future. Implementing voice analysis could assist in the early detection and management of T2DM, as well as the improvement of healthcare outcomes.

The last “dose” ...

“I have high blood sugars, and Type 2 diabetes is not going to kill me. But I just have to eat right, and exercise, and lose weight, and watch what I eat, and I will be fine for the rest of my life.”

- Tom Hanks (American actor and filmmaker, 1956 - )
References:


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