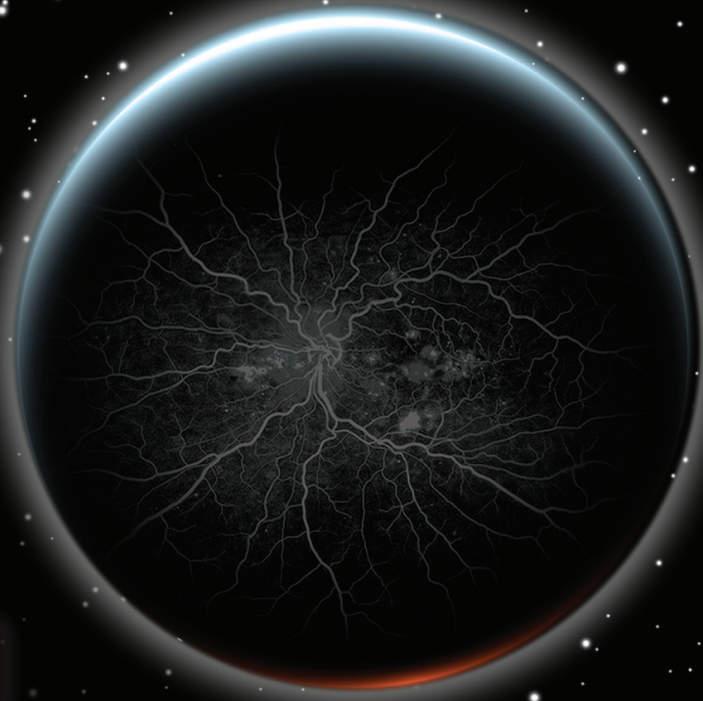


MODERN DIABETES CARE: WHAT YOU NEED TO KNOW



The changing landscape of systemic diabetes care is affecting ocular complications such as diabetic retinopathy.

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With new therapies and devices changing diabetes care, there is growing interest in how they affect ophthalmic outcomes for patients with diabetic retinopathy (DR). Here, we discuss continuous glucose monitoring (CGM) devices, next-generation systemic pharmacotherapy, and digital diabetes management platforms (DDMPs).



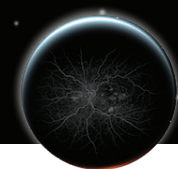
CONTINUOUS GLUCOSE MONITORING

Managing diabetes requires maintaining a strict diet and regularly monitoring blood glucose. Today, CGM devices are minimally invasive monitors that can be implanted subcutaneously to monitor blood glucose levels in real time.

AT A GLANCE

- ▶ Research shows that the use of continuous glucose monitoring devices is linked with lower odds of progression to diabetic retinopathy (DR) and proliferative DR.
- ▶ The DR-related adverse effects of new therapies are still under investigation, and various studies have yielded mixed, sometimes conflicting, findings.
- ▶ Digital diabetes management platforms integrate telemedicine, personalized coaching, connected technologies, and glycemic monitoring to help patients manage their diabetes.





For example, the G6 CGM device (Dexcom) was shown to enable more precise insulin dose adjustment and improve glycemic control.¹ Other positive effects, such as prolonged duration within the target glycemic range and reduced hypoglycemic events, were also seen.¹

CGM can also improve DR management. One cohort study examined the odds of patients with type 1 diabetes developing DR and proliferative DR (PDR) when using CGM, insulin pumps, or both.² CGM use was linked with lower odds of progression to DR and PDR. Additionally, CGM with an insulin pump was linked with lower odds of PDR when compared with no CGM use.² Overall, CGM use was associated with slower disease progression, even after controlling for other health and demographic factors.

Another study examined whether metrics obtained with CGM were associated with DR severity. Data obtained from the FreeStyle Libre Pro CGM device (Abbott Japan) showed that intra- and inter-day glucose variability in patients with diabetes was significantly associated with DR severity, even after adjusting for risk factors. Thus, CGM may aid in identifying patients at the highest risk for developing diabetic eye disease, reinforcing its utility in diabetes care.³

As enthusiasm for and acceptance of CGM continues to grow, we have seen further expansion of its capabilities and integration into modern diabetes management. For example, a CGM device can now be paired with a smart insulin pump in a closed-loop system to automatically adjust insulin delivery. This tandem unit helps regulate blood glucose levels in real time, essentially functioning as an artificial pancreas.⁴

Recently, access to these devices have improved with the FDA approval of the first over-the-counter CGM, the Stelo Glucose Biosensor System (Dexcom).⁵ Furthermore, various health startup companies are now using CGM technology for patients without diabetes to help users better understand how diet and lifestyle choices affect their glycemic levels.⁶

NEXT-GENERATION SYSTEMIC PHARMACOTHERAPY

In the past decade, FDA-approved novel classes of therapies for diabetes have expanded the armamentarium of diabetic pharmacotherapy. Although some of these newer treatments have been praised for their protective effects on mortality, cardiovascular, and renal outcomes,⁷ DR-related adverse effects are still under investigation, and various studies have yielded mixed, sometimes conflicting, findings.

The introduction of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) has been met with significant positive reception due to their ability to significantly reduce hemoglobin A1c, major adverse cardiovascular events, and weight.⁸ In the SUSTAIN-6 trial investigating the cardiovascular safety of semaglutide, patients receiving the study drug experienced fewer cardiovascular adverse effects but significantly more retina-related complications,

including vitreous hemorrhage, blindness, and conditions requiring additional ocular treatments.⁹

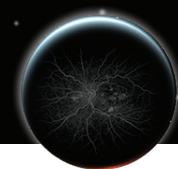
However, limitations of the study, such as a short follow-up time, call into question these adverse ocular findings. Notably, the worsened/increased DR events have yet to be corroborated by other randomized controlled trials. In addition, a dilated fundus examination was not required in the study, and the classification of DR status was not uniform at the study onset; thus, patients with PDR or diabetic macular edema (DME) at baseline were likely included, rendering any true tabulation of vision-threatening complications during the study nebulous.¹⁰ Finally, SUSTAIN-6 was a cardiovascular outcome trial, and DR was not a primary outcome measure. The 5-year FOCUS trial is now investigating the long-term effects of semaglutide on DR in approximately 1,500 patients with type 2 diabetes.¹¹ (For more on this topic, see *GLP-1 Receptor Agonists and the Eye* on page 28.)

Sodium-glucose co-transporter 2 (SGLT2) inhibitors have also been gaining significant popularity in the medical community largely due to their nephroprotective effects. Mechanistically, SGLT2 inhibitors prevent glucose reabsorption in the renal proximal tubule of the kidney, resulting in increased urinary glucose excretion.¹²

Several studies have found diminished DR risk and slower DR progression with SGLT2 inhibitor use in patients with type 2 diabetes.¹³⁻¹⁶ These observations were corroborated by an aggregate electronic health record (EHR) retrospective clinical cohort study (n = 6,481) using the TriNetX Research Network. Patients on GLP-1 RA monotherapy had significantly higher rates of PDR progression and new-onset DME compared with those on SGLT2 inhibitor monotherapy.¹⁷ In contrast, a 2024 retrospective cohort study found no significant difference in the risk of developing vision-threatening DR between patients newly initiated on SGLT2 inhibitors versus other non-insulin diabetic medications.¹⁸

Dipeptidyl peptidase-4 (DPP-4) is an enzyme that degrades endogenous GLP-1. This class of inhibitors mechanistically increases GLP-1 bioavailability and downstream insulin secretion. A recent analysis in Taiwan revealed that patients with newly diagnosed diabetes who were treated with a DPP-4 inhibitor demonstrated an increased risk of DR compared with those who were treated with a sulfonyleurea.¹⁹ One possible explanation for this is DPP-4's role in cleaving other endogenous substrates, including stromal cell-derived factor-1 alpha (SDF-1 α). DPP-4 inhibitors, therefore, may increase levels of SDF-1 α , which has been shown to promote pathologic angiogenesis in animal models of DR.²⁰ Yet, not all evidence supports a causal relationship. For instance, a 2024 meta-analysis of seven real-world studies found no association between DPP-4 inhibitors and DR risk, suggesting the mechanistic concerns may not translate to clinical harm.²¹

While there have been ample retrospective observational



series and aggregate EHR-based analyses on the effects of these novel therapeutic classes on the retinal microcirculation, we still lack formal prospective evaluations in randomized clinical trials. Ongoing research efforts are necessary to better understand the multifactorial effects of these novel systemic agents on the development and progression of DR.

DIGITAL PLATFORMS

DDMPs integrate telemedicine, personalized coaching, connected technologies, and glycemic monitoring to help patients manage their diabetes. Many companies have developed their own DDMP (eg, Virta Health, Livongo Health, Omada Health, and Glooko, to name a few), each with its own unique approach to personalized diabetes care.

Virta Health delivers an individualized approach to carbohydrate intake and nutritional ketosis. In the company's 5-year study, 122 patients participated in a continuous care intervention via telemedicine that included counseling on a strict, very low-carbohydrate diet with nutritional ketosis. Maintenance of hemoglobin A1c less than 6.5% with either no medication or metformin alone was achieved in 32.5% of the patients who completed the study, highlighting the value of telemedicine-based interventions.²² However, nearly 30% of patients who initially consented to participate in the study dropped out before the 5-year mark, emphasizing that these rigorous interventions are not feasible for all patients.

Livongo Health provides a self-monitoring blood glucose device with real-time glucose readings. Abnormal readings trigger an alert to a certified diabetes educator who provides resources or escalates to a consultation with a provider or emergency services. In a 2021 study, patients using Livongo Health and a cohort receiving specialized care from the University of Massachusetts Medical Center Diabetes Center of Excellence had similar reductions in hemoglobin A1c, suggesting the digital tool could be an alternative for those who do not have access to specialty clinics.²³

Omada Health focuses on providing a structured curriculum and peer-group support. The platform helps patients manage their diabetes and other chronic conditions by combining data from their CGM, weekly goals, lab tests, and other sources and then sending it to the patient's primary care provider. Of patients who used the Omada Health app, 76% met their hemoglobin A1c reduction goal and experienced a 1.17 kg/m² mean reduction in body mass index over 12 months.^{24,25}

CARE FOR THE WHOLE PATIENT

It is essential that retina specialists be knowledgeable about the changing landscape of modern systemic diabetes care to best care for their patients with DR. Future studies that investigate the ongoing effects of these new therapies and devices on DR will help us better tailor treatment to the individual patient. ■

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