Since 2005, glucagon-like peptide 1 (GLP-1) receptor agonists have been clinically available, which has resulted in a significant transformation in diabetes care, both in terms of weight management and glucose control. The emergence of sodium–glucose cotransporter-2 (SGLT2) inhibitors in 2013 has led to significant reductions in Hba1c levels and modest weight loss. Subsequent investigations revealed that both drug classes have beneficial effects on cardiovascular and kidney diseases. A recent meta-analysis examining 816 trials with 471,083 patients and 13 different drug classes found that SGLT-2 inhibitors (odds ratio 0.88, 95% confidence interval (CI) 0.83 to 0.94) and GLP-1 receptor agonists (0.88, CI 0.82 to 0.93) reduced all-cause death. The study confirmed the known benefits of SGLT-2 inhibitors and GLP-1 receptor agonists in reducing cardiovascular death, non-fatal myocardial infarction, hospital admission for heart failure, and end-stage kidney disease. Only GLP-1 receptor agonists reduced non-fatal stroke, and SGLT-2 inhibitors were superior to other drugs in reducing end-stage kidney disease. GLP-1 receptor agonists and probably SGLT-2 inhibitors have the potential to improve the quality of life [1].

The next significant advancement in diabetes care occurred in 2018, with the initiation of the first randomised clinical trial of tirzepatide, a novel dual GIP and GLP-1 agonist [2]. This agent was significantly superior to semaglutide in the SURPASS 2 trial [3], showcasing greater reductions in HBA1c levels by 0.45% and greater weight loss of 5.5 kg at the highest dose (15 mg). Significant differences were also observed between the 5 and 10 mg doses. Subsequent meta-analyses of 7–8 trials of terzepatide have demonstrated similar benefits [4,5]. In a study analysing eight trials, tirzepatide exhibited a significant reduction in the risk of major adverse cardiovascular events by 48% compared to the control (RR 0.52, 95% CI 0.38 to 0.72); tirzepatide also displayed a significantly attenuated risk of cardiovascular death by 49% (RR 0.51, 95% CI 0.29 to 0.89) and all-cause death by 49% (RR 0.51, 95% CI 0.34 to 0.77) [6].

Tirzepatide demonstrated significant long-term body weight reduction among adults with obesity and type 2 diabetes in the SURMOUNT-2 phase 3 randomised placebo-controlled trial. In this trial, 938 adults with a body mass index of 27 kg/m² or higher and an HbA1c level of 7 to 10 percent were randomly assigned to receive once-weekly subcutaneous doses of tirzepatide at 10 or 15 mg, or placebo for 72 weeks. The mean change in body weight at week 72 was –12.8% with 10 mg of tirzepatide and –14.7% with 15 mg of tirzepatide compared to –3.2% with placebo (p < 0.0001 for both comparisons). A higher percentage of tirzepatide-treated participants (79 to 83 percent) achieved a body weight reduction of 5 percent or more compared to placebo-treated participants (32 percent). Tirzepatide was associated with a higher frequency of gastrointestinal-related adverse events, although less than 5 percent of these events led to treatment discontinuation [7]. Tirzepatide was also found to improve the quality of life [1].

This year, a significant advancement in knowledge was achieved via the presentation at the 83rd Annual Scientific Sessions of the American Diabetes Association (ADA) meeting and the publication of phase II trial results for retatrutide, a GIP/GLP1 and glucagon receptor agonist, in NEJM and The Lancet. Phase I trials also showed excellent results [8].

In the diabetes study, 281 participants with type 2 diabetes were randomised to receive 0.5 mg, 4 mg, 8 mg, or 12 mg doses of retatrutide, 1.5 mg dose of dulaglutide, or a placebo...
for 36 weeks. A total of 4–12 mg of retatrutide lowered HbA1c by 1.3% to 2.0% after about six months compared to no change with placebo and a 1.4% HbA1c reduction with dulaglutide. Those who received retatrutide also experienced greater weight loss than those who received placebo. The average weight reduction in the 12 mg group was 16.9% (17.2 kg) compared to 3.0% (3.3 kg) in the placebo group. Retatrutide exhibited an overall safety and tolerability profile comparable to that of incretin-based therapies like dulaglutide [9].

In the obesity study, 388 participants with obesity, but without diabetes, received 1, 4, 8, or 12 mg over 48 weeks. Participants who received the two highest doses lost more than 24% of their body weight, whereas all participants lost at least 5% of their body weight [10]. An additional important result at the same meeting was a trial of a 50 mg oral semaglutide, a GLP-1 receptor agonist marketed as Rybelsus (already available for type 2 diabetes at 7 and 14 mg doses), in participants with obesity but without diabetes. An average weight loss of 15% was observed after 68 weeks of treatment, with 34% of participants experiencing a 20% weight reduction [11].

Novo presented an array of preliminary studies examining new agents for type 2 diabetes and obesity at the ADA meeting (26 presentations in total). The weekly basal insulin (BIF LY3209590 or Icodec) was comparable to insulin degludec (ONWARDS 3 (Oral 178-OR)) and insulin glargine (ONWARDS 1 (Oral 179-OR)) in insulin-naïve patients with type 2 diabetes. The safety profile was comparable to that of daily insulin [12–14].

CagriSema is a once-weekly subcutaneous combination of semaglutide and a new amylin analogue called cagrilintide. A recent trial investigated the safety and efficacy of a fixed-dose combination of CagriSema, comprising 2.4 mg of semaglutide and 2.4 mg of cagrilintide, compared to the individual components of semaglutide and cagrilintide. The trial involved 92 overweight subjects with type 2 diabetes and lasted for 32 weeks [15]. Subjects were randomised equally into the three treatment arms of the trial. Those who received CagriSema achieved a 2.18% decline in HbA1c compared to 1.79% and 0.93% for semaglutide and cagrilintide, respectively. Subjects in the CagriSema arm demonstrated a 15.6% decline in body weight compared to 5.1% and 8.1% with semaglutide and cagrilintide, respectively.

Lilly’s new agents currently undergoing clinical trials include an oral non-protein GLP-1 agonist called orforglipron (LY3502970) in a placebo-controlled study, known as Attain 2, involving 1500 obese or overweight adults with type 2 diabetes. The results of this trial will be reported in June 2025. Another trial, Achieve 4, is studying the comparison between orforglipron and insulin glargine in 2620 obese or overweight adults with type 2 diabetes and increased cardiovascular risk, the results of which will be reported in August 2025. LY3502970 was tested in a 12-week proof-of-concept study involving patients with type 2 diabetes. The mean change in HbA1c was -1.8% from baseline and a 4.7 kg weight loss. In the phase 1 trial involving 24 volunteers, the administration of an acylated peptide analogue of oxyntomodulin-a, a GLP-1 and glucagon receptor agonist (Mazdutide, LY3505677), showed a weight loss of 11.2 kg, with an increasing dose of up to 10 mg/day over 16 weeks, in comparison to a weight loss of 2 kg in the placebo group. A 1% reduction in HbA1c levels was observed compared to that in the placebo group [16].

A further advancement in the care of diabetic and non-diabetic patients with chronic kidney disease is fineronone, a novel non-steroidal mineralocorticoid receptor antagonist available since 2021 [17]. In patients with chronic kidney disease, fineronone showed the potential to reduce mortality (0.89, 0.79 to 1.00), hospital admissions for heart failure, end-stage kidney disease, and possibly cardiovascular death [1].

A new disease that has emerged over the past decade is checkpoint inhibitor-associated autoimmune diabetes mellitus (CIADM). Wu et al. [18] conducted a study on 192 patients who met the following criteria: (1) evidence of hyperglycemia (blood glucose level > 11 mmol/L or HbA1c ≥ 6.5%); and (2) evidence of insulin deficiency (diabetic ketoacidosis (DKA) and/or C-peptide < 0.4 nmol/L). The authors found that >99% of the patients were treated with anti-PD-1 or anti-PD-L1, either as monotherapy or in combination with anti-CTLA-4, but rarely with anti-CTLA-4 alone. The median time for the onset of CIADM was 12 weeks after
initiating ICI therapy, with most patients presenting with DKA (69%, which is higher than that of T1D). Over 90% of patients exhibited C-peptide < 0.4 nmol/L at presentation, and over a period of months, there was a significant decline in C-peptide levels in all patients, as observed in follow-ups. All patients were treated with insulin, which could not be discontinued during follow-up. Only 59% of the patients possessed the classic susceptible haplotypes associated with T1D, and only 40% tested positive for T1D autoantibodies, with the majority showing positivity for a single autoantibody. Most patients (69%) also demonstrated elevated lipase levels, indicative of exocrine pancreatic inflammation.

Finally, future agents could include biodegradable hollow nanoscavengers that restore liver function by reversing insulin resistance in fat-fed streptozotocin-treated diabetic mice [19]. Improving hepatic insulin resistance by reducing oxidative stress is a promising strategy for T2D treatment. For this purpose, liver-targeted biodegradable silica nanoshells embedded with platinum nanoparticles (Pt-SiO2) and 2,4-dinitrophenol-methyl ether (DNPME, a mitochondrial uncoupler that reduces reactive oxygen species (ROS) production) were injected into the mice. The treatment resulted in reduced hepatic steatosis and oxidative stress.

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