International Journal of Obesity www.nature.com/ijo

PERSPECTIVE

Clinical Research

Prediabetes: a new indication for GLP-1s?

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International Journal of Obesity; https://doi.org/10.1038/s41366-025-01930-2

Prediabetes is a condition defined by the American Diabetes Association (ADA) based on one of the following criteria: impaired fasting glucose (IFG) with fasting blood glucose (FBG) of 5.6–6.9 mmol/L (100–125 mg/dL), impaired glucose tolerance (IGT) with 2h-plasma glucose (PG) during a 75 g oral glucose tolerance test (OGTT) of 7.8–11.0 mmol/L (140–199 mg/dL), or HbA1c of 39–47 mmol/mol (5.7–6.4%). Other medical organizations have slightly different criteria for prediabetes but all agree prediabetes is prevalent worldwide [1].

In 2018, 34.5% of U.S adults had prediabetes [2] which confers a substantial risk of progression to overt type 2 diabetes (T2DM) [3]. Nearly 90% of those with prediabetes are unaware they have it [4]. The problem with this is that in those aged 45 years, the lifetime risk of progression from prediabetes to T2DM is 74.0% [4]. Better detection is certainly needed. But what can providers do when it is detected? The ADA recommendations to treat prediabetes include lifestyle and the medication metformin, although it is not approved by the Food and Drug Administration (FDA) for prediabetes [5]. Is this enough for a condition that is associated with an increased risk for all cause mortality and cardiovascular disease?

We have an obesity epidemic which has been driving up the prevalence of T2DM as well for which the treatment landscape has changed dramatically over the past few years due to the advent of glucagon-like peptide-1 (GLP-1) medications. The latest study to show beneficial effects of GLP-1 medications on progression to T2DM in patients with prediabetes is a phase 3 double-blind randomized controlled trial by Jastreboff and colleagues [6]. This study is an extension of the tirzepatide trial SURMOUNT-1 in a subset of 1032 participants with obesity and prediabetes who either continued once weekly tirzepatide or placebo for a total of 176 weeks followed by a 17-week off treatment period. The results showed that 10 participants (1.3%) randomized to pooled tirzepatide groups developed T2DM versus 36 (13.3%) in the placebo group, representing a 93% reduction (HR of 0.07) in the risk of developing T2DM. Depending on the dose of tirzepatide, weight losses were between 12.3 and 19.7%. During the 17 week off treatment period, an average 7% weight regain was observed, and an additional 8 participants from the tirzepatide group developed T2DM for a total of 18 participants (2.4%) as compared with 37 placebo participants (13.7%). Further, 15.5% of patients reverted from normoglycemia back to prediabetes.

In other words, almost 99% of participants with prediabetes treated with tirzepatide did not develop T2DM over the 3 year period of the study as compared with 87% of the placebo group.

This trial is the latest in a series of studies showing that treating patients with prediabetes through focusing on weight reduction with GLP-1 receptor agonists prevented progression to T2DM. The degree of risk reduction of developing T2DM appeared to track with the degree of weight reduction. In a previously published three-year study liraglutide led to a 6.1% body weight reduction associated with a HR of 0.34 for progression to T2DM in patients with prediabetes [7]. Semaglutide in several studies of various durations resulted in weight losses of between 9.7 and 15.2% associated with a HR of 0.27 for developing T2DM in those with prediabetes [8–10]. Importantly an analysis of the Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity Trial (SELECT) showed that semaglutide increases rates of regression to normoglycemia and decreases progression to T2DM in those with prediabetes and preexisting cardiovascular disease [11]. Thus, we have come a long way since the Diabetes Prevention Program (DPP) trial, in which a 58% reduction over three years in the risk of developing T2DM in those with prediabetes, achieved a 5–7% weight loss with lifestyle intervention alone, which was superior to the effect of metformin [12]. Longer term, the DPP Outcomes Study (DPPOS) showed that over 21 years of follow up, cumulative incidence of T2DM was reduced by 24% and 17% in the lifestyle and metformin groups but there were no effects on microvascular or cardiovascular outcomes. However, prevalence of microvascular complications was significantly lower in those who did not progress to T2DM as compared with those who progressed to T2DM [13].

Degree of weight reduction is highest and most durable with metabolic bariatric surgery which has been shown to prevent T2DM, to prevent micro and macro angiopathic diabetes complications and to prevent cardiovascular events [14].

The liraglutide, semaglutide and now tirzepatide studies [6–10] show progressive reduction in risk of T2DM with degree of weight reduction in those with prediabetes.

Tirzepatide's performance in those with prediabetes continues to assure that more weight reduction leads to greater reduction in risk of T2DM as evidenced by metabolic bariatric surgery. Second, beyond metabolic parameters, the Jastreboff study also evaluated quality of life, finding improvements in all domains, most notably physical function. These findings offer reassurance that the use of

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Received: 10 June 2025 Revised: 3 September 2025 Accepted: 29 September 2025
Published online: 09 October 2025

tirzepatide to achieve weight reduction and delay in development of T2DM is beneficial beyond laboratory findings and metabolic parameters. Further, all other trials in patients with prediabetes (DPP, liraglutide and semaglutide) have shown that despite the intervention and weight reduction maintenance, participants had progressive decline in beta-cell function over time as evidenced by dysglycemia. The tirzepatide study showed that tirzepatide delivered a sustained effect on glycemia over three years of treatment. Tirzepatide is unique among these agents in that it is both a GLP-1 receptor agonist and glucose-dependent insulinotropic polypeptide (GIP) agonist. Dual-action on insulin sensitivity and the beta-cell might explain durability, but further studies are needed [6].

It is hopeful that this latest trial may expand the indication for use of an obesity medication to delay or prevent T2DM and highlights the ability of tirzepatide to do so. The FDA has distributed an updated draft guidance (January 2025) for industry, aiming to assist in the trial design and efficacy and safety parameters for medications to achieve approval for obesity with other indications [15]. The section on seeking an indication for the delay or prevention of T2DM clearly states the need to establish clinical benefit of a delay in development of T2DM on quality of life, disease management burden or psychosocial functioning and not just metabolic parameters. Jastreboff et al. [6] have made a case for the clinical benefit of tirzepatide for the treatment of obesity and prediabetes by demonstrating robust weight reduction and improvements in metabolic measures, quality of life and a 93% reduction in risk of developing T2DM in patients with prediabetes over three years of treatment. Shouldn't this be enough evidence for tirzepatide to gain approval for the novel indication of a T2DM preventive therapy?

Indeed, any medication approved for the prevention of T2DM in those with prediabetes will incur a cost burden for insurers before the benefits translate into reduction in T2DM and CVD burden. The DPP program for lifestyle intervention in prediabetes with multidisciplinary teams of highly trained professionals is estimated to cost 2600–2800 dollars per person for the first year and 1900–2100 for subsequent years for a 5–10% weight reduction and this needs to be sustained indefinitely. Medications such as GLP-1s approved for prediabetes would also need to be sustained indefinitely to ward off T2DM and cardiovascular disease to ensure continued weight loss maintenance [1]. In order to reduce these costs, certainly lifestyle interventions such as DPP have been and should be recommended first for those 34% of US adults with prediabetes. This will not suffice for a good percentage of this population however. The Lancet Commission on Obesity [16] does not include prediabetes among their core complications that define clinical obesity requiring pharmacotherapy. This perspective has given a number of good reasons why prediabetes should be identified as more than just a risk factor but a condition that leads to T2DM and cardiovascular mortality that should be treated with a proven remission agent such as tirzepatide.

Tirzepatide as distinguished from liraglutide and semaglutide, has been shown in trials to have a better efficacy profile and in the real world to incur less gastrointestinal side effects which would enhance long term compliance [17].

In the end, it may take an oral version of tirzepatide which can be manufactured with less resources to build a case for cost effectiveness and access to GLP-1s for prevention of T2DM for the growing population with prediabetes in the US and worldwide.

The approval of a GLP-1 for prediabetes will change the landscape for prevention of T2DM and its complications for due to early detection. Currently, most individuals at risk of T2DM are not identified promptly and therefore do not receive adequate referrals for lifestyle interventions based on ADA guidance. The approval of a new drug for prediabetes would prompt providers not just to test HbA1c but to then act more promptly with lifestyle in addition to treatment with a GLP-1. Timely intervention is necessary to reverse the T2DM epidemic in the US and worldwide.

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AUTHOR CONTRIBUTIONS

CMA is responsible for all aspects of this manuscript.

COMPETING INTERESTS

In the past 36 months, CMA has participated on advisory boards for AbbVie Inc., Altimmune, Inc., Arrowhead Pharmaceuticals, Inc., BioAge, Biolinq Incorporated, Caribou Biosciences, Inc., CinFina Pharma, Inc., Covidien LP, Cowen and Company, LLC, Currax Pharmaceuticals, LLC, EPG Communication Holdings Ltd., Form Health, Inc., Fractyl Health, Inc., Keros Therapeutics, Inc., Lilly USA, LLC, L-Nutra, Inc., Mediflix

Inc., NeuroBo Pharmaceuticals, Inc., Neurocrine Biosciences, Inc., NodThera Limited, Novo Nordisk, Nutrisystem, OptumRx, Inc., Pain Script Corporation, Palatin Technologies, Inc., Pursuit By You, Redesign Health Inc., ReShape Lifesciences Inc., Riverview School, Roman Health Ventures Inc., Scholar Rock, Inc., Terns, Inc., Verily Life Sciences LLC, Veru Inc., Vida Health, Inc., Wave Life Sciences, WondrHealth, Xeno Biosciences and Zyversa Therapeutics, Inc. CMA has received research funding from PCORI and GI Dynamics, Inc.

ADDITIONAL INFORMATION

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