Management & prevention of type 2 diabetes

Pharmacological approaches to weight loss

Jason Gill
Reader in Exercise and Metabolism, Institute of Cardiovascular and Medical Sciences, University of Glasgow

Obesity is the most important modifiable risk factor for type 2 diabetes (Abdullah et al, 2010), and large-scale randomised controlled trials (RCTs) have demonstrated that lifestyle interventions incorporating weight loss and increased physical activity are effective at reducing the incidence of diabetes in individuals at high risk over the long term (Lindström et al, 2013; Diabetes Prevention Program Research Group, 2015).

However, in interventions undertaken under more pragmatic, "real-world" conditions, the extent of weight loss observed, while still clinically significant in general, has been only 30–50% of that achieved in the large-scale clinical efficacy trials (Dunkley et al, 2014). In this context, the potential of pharmacotherapy to enhance the effects of lifestyle intervention on weight loss and diabetes prevention warrants consideration. This has been tested in two recent trials.

In a phase IIa, double-blind, placebo-controlled RCT (summarised on page 44), Hollander and colleagues assessed the efficacy and safety of canagliflozin and phentermine, both as monotherapies and in combination, on top of a standardised lifestyle intervention (a 600-kcal/day energy-deficit diet and 150 minutes of exercise per week). Weight loss and safety outcomes were assessed at 26 weeks in 335 overweight or obese adults without T2D.

Participants were randomised 1:1:1:1 into placebo, canagliflozin, phentermine and canagliflozin plus phentermine intervention arms. The rationale was that the two drugs would potentially induce weight loss via complementary mechanisms: canagliflozin, a sodium–glucose cotransporter 2 inhibitor, would aid weight reduction via calorie loss through urinary glucose excretion, while phentermine, a sympathomimetic amine anorectic, would act by increasing satiety and thereby reduce energy intake.

Mean weight loss was 0.6% of body weight with placebo, 1.9% with canagliflozin, 4.1% with phentermine and 7.3% with the canagliflozin/phentermine combination. Furthermore, 66.7% of participants in the combination group achieved at least 5% weight loss, compared to 17.5% on placebo, 17.9% on canagliflozin and 41.7% on phentermine. The canagliflozin/phentermine combination, but not the individual drugs on their own, led to a significant reduction in systolic blood pressure compared with placebo (by 4.2 mmHg), but there was a significant increase in heart rate in the phentermine and canagliflozin/phentermine groups.

Intriguingly, the extent of weight loss (and blood pressure reduction) with coadministration of canagliflozin and phentermine was greater than the additive effects of canagliflozin and phentermine monotherapy, which the authors hypothesised may be due to the phentermine's effects on appetite and satiety acting synergistically to offset potential adaptive increases in energy intake in response to increased urinary glucose excretion with canagliflozin.

Longer-term studies are needed to determine the effects on cardiovascular and diabetes outcomes, but these data suggest that coadministration of canagliflozin and phentermine may be a viable approach for long-term weight management.

In a longer-term study (also summarised), le Roux and colleagues undertook a 3-year, double-blind RCT in 2254 people with prediabetes. They were randomised 2:1 to liraglutide or placebo in addition to lifestyle intervention (a 500-kcal/day energy-deficit diet and 150 minutes per week of physical activity). The time to onset of type 2 diabetes and weight loss were assessed.

The probability of developing type 2 diabetes over the 160-week follow-up was 3% in the liraglutide group and 11% in the placebo group, with time to diabetes onset while on treatment being 2.7 times longer with liraglutide than placebo. Mean weight loss was greater in the liraglutide group (6.1% of body weight) than the placebo group (1.9%); thus, the relative contributions of liraglutide's effect on glucose metabolism and its effect on body weight to the diabetes risk reduction are unclear and warrant further investigation. Interestingly, most individuals who developed type 2 diabetes lost less weight than the treatment group's mean.

Thus, there is increasing evidence that pharmacotherapy in addition to lifestyle intervention can enhance weight loss and, in the case of liraglutide, reduce or delay the incidence of type 2 diabetes. Whether such therapies gain widespread use for weight loss and diabetes prevention will depend on cost-effectiveness, available resources and views on the extent to which prevention, as opposed to treatment, of type 2 diabetes should be medicalised. ■

Abdullah A, Peeters A, de Court, Stoelwinder J (2010) The magnitude of association between overweight and obesity and the risk of diabetes: a meta-analysis of prospective cohort studies. *Diabetes Res Clin Pract* **89**: 309–19

Diabetes Prevention Program Research Group (2015) Long-term effects of lifestyle intervention or metformin on diabetes development and microvascular complications over 15-year follow-up: the Diabetes Prevention Program Outcomes Study. *Lancet Diabetes Endocrinol* **3**: 866–75

Dunkley AJ, Bodicoat DH, Greaves CJ et al (2014) Diabetes prevention in the real world: effectiveness of pragmatic lifestyle interventions for the prevention of type 2 diabetes and of the impact of adherence to guideline recommendations: a systematic review and meta-analysis. *Diabetes Care* **37**: 922–33

Lindström J, Peltonen M, Eriksson JG et al (2013) Improved lifestyle and decreased diabetes risk over 13 years: long-term follow-up of the randomised Finnish Diabetes Prevention Study (DPS). *Diabetologia* **56**: 284–93

"The generalisability and longer-term efficacy of these findings still need to be established; however, interrupting sitting with either walking or resistance exercise appears to have significant benefits in terms of glucose control."

Diabetes Care

Canagiflozin and phentermine for weight management

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! Factor	✓✓✓✓

1 This 26-week study aimed to assess the efficacy and safety of coadministration of canagliflozin (a sodium–glucose cotransporter 2 inhibitor) and phentermine (an appetite suppressant) compared with placebo, canagliflozin monotherapy and phentermine monotherapy in 231 overweight and obese adults without T2D. Participants were randomised 1:1:1:1 into each group.

2 The primary endpoint was percentage change in body weight from baseline to week 26. Key secondary endpoints were the proportion of participants achieving ≥5% weight loss and change from baseline in systolic blood pressure.

3 The combination therapy led to superior weight loss from baseline versus placebo at week 26. Furthermore, it led to a greater proportion of participants achieving ≥5% weight loss compared with the placebo group, as well as a greater reduction in systolic blood pressure.

4 The difference in treatment effects on body weight was observed as early as week 6, the first on-treatment follow-up visit. Weight loss with combination therapy continued until the end of the study period.

5 The drugs used in combination were generally well tolerated, with a safety profile consistent with the individual components.

6 The clinically significant reductions in body weight over 26 weeks produced by the combination therapy suggest potential use in long-term weight management.

Hollander P, Bays HE, Rosenstock J et al (2017) Coadministration of canagliflozin and phentermine for weight management in overweight and obese individuals without diabetes: a randomized clinical trial. *Diabetes Care* **40**: 632–9

Lancet

Liraglutide: T2D risk reduction in obese people with prediabetes

Readability	✓✓✓✓
Applicability to practice	✓✓✓
WOW! Factor	✓✓✓

1 In this randomised, double-blind, placebo-controlled trial, overweight and obese adults with prediabetes were randomised 2:1 to either once-daily subcutaneous liraglutide 3.0 mg or placebo, as an adjunct to a reduced-calorie diet and increased physical activity.

2 Half of those initially enrolled completed the 160-week study. The main reason for withdrawal was mild-to-moderate gastrointestinal symptoms in the liraglutide group (118 of 1501 individuals [8%] in the liraglutide group vs 11 of 747 [2%] in the placebo group).

3 By week 160, 26 of 1472 individuals (2%) in the liraglutide group versus 46 of 738 (6%) in the placebo group were diagnosed with diabetes while on treatment.

4 The time to onset of diabetes over 160 weeks among all study participants was 2.7 times longer with liraglutide compared with placebo (95% confidence interval [CI], 1.9–3.9), corresponding to a hazard ratio of 0.21 (95% CI, 0.13–0.34).

5 Liraglutide induced greater weight loss than placebo at week 160 (6.1% of body weight [standard deviation, 7.3] vs 1.9% [6.3]).

6 Serious adverse event rates were similar between the two groups (15% vs 13%).

6 The authors conclude that liraglutide 3.0 mg might be used to reduce risk of diabetes in individuals with obesity and prediabetes.

le Roux CW, Astrup A, Fujioka K et al (2017) 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial. *Lancet* **389**: 1399–409

Diabetologia

Glycaemic effects of interrupting sitting every 30 minutes

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓

1 This randomised, crossover study examined the effect of interrupting prolonged sitting with brief bouts of walking or resistance activities on 22-hour glucose homeostasis in adults with T2D.

2 A total of 24 participants were randomised and completed all trial conditions: (1) prolonged sitting for 7 hours after breakfast; (2) sitting interrupted with 3-minute bouts of light-intensity walking (3.2 km/hour) every 30 minutes; and (3) sitting interrupted with 3-minute bouts of simple resistance activities every 30 minutes.

3 Continuous glucose monitoring was used to track glucose homeostasis throughout the study.

4 Over the entire 22-hour period, mean glucose concentrations were significantly lower in the walking (8.9 mmol/L) and resistance (8.7 mmol/L) arms compared with the sitting arm (11.6 mmol/L).

5 The total area under the blood glucose curve and mean time spent in hyperglycaemia (>10 mmol/L), were also significantly reduced in the activity groups. Postprandial glucose excursions were lower and mean glucose reductions were sustained nocturnally until morning.

6 There were no significant differences in glycaemia between the walking and resistance groups.

7 The generalisability and longer-term efficacy of these findings still need to be established; however, interrupting sitting with either walking or resistance exercise appears to have significant benefits in terms of glucose control.

Dempsey PC, Blankenship JM, Larsen RN et al (2016) Interrupting prolonged sitting in type 2 diabetes: nocturnal persistence of improved glycaemic control. *Diabetologia* **60**: 499–507.

Diabetes Care

Depression, anxiety and mortality risk in people with T2D

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓✓

1 In this large, population-based study in Norway, the authors evaluated the excess risk associated with T2D and comorbid depression and/or anxiety compared with the general population.

2 Of 64 177 participants, 1133 had T2D. All received a physical examination and filled in questionnaires on affective disorders. Deaths were monitored via a national registry.

3 After adjustment for demographic risk factors, compared with the population without T2D or affective disorders, mortality risk was higher in people with affective disorders, higher still in those with T2D alone, and highest in those with both combined.

4 Among people with T2D, excess mortality risk was lowest in those with anxiety (hazard ratio [HR], 1.66) and highest in those with depression (HR, 2.10). Interestingly, those with both anxiety and depression had a slightly lower risk than those with depression alone (HR, 2.01).

5 The latter finding is supported by literature suggesting that anxiety may have a protective effect in the general population, as it may lead to health-seeking behaviours.

6 The negative effects of affective symptoms were greater in men than women with T2D: HRs ranged from 2.14 to 3.47 for the different comorbidities in men, and from 1.14 to 1.86 in women.

7 This was proposed to be because men are less likely to be diagnosed or treated for depression, and may also have greater inflammation than women in the presence of anxiety disorders.

Naicker K, Johnson JA, Skogen JC et al (2017) Type 2 diabetes and comorbid symptoms of depression and anxiety: longitudinal associations with mortality risk. *Diabetes Care* **40**: 352–8

Diabetes Res Clin Pract

Postmeal exercise effects in people with advanced T2D

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! Factor	✓✓

1 Previous studies of the effects of postmeal exercise in T2D have mostly enrolled people with new-onset diabetes controlled with only diet or metformin. This study was conducted to assess the effects in people with more advanced diabetes who had already escalated beyond metformin, but not onto insulin.

2 Eight people underwent continuous glucose monitoring for 2 days. On the first, they remained sedentary after all meals, while on the second they performed three 10-minute bouts of treadmill walking, separated by 3-minute rest periods, after breakfast. This was designed to be tolerable for people unaccustomed to exercise.

3 During the exercise, glucose peaked at significantly lower levels compared with the exercise-free day (9.9 mmol/L vs 13.8 mmol/L; P=0.02). The glucose area under the curve (AUC) was also significantly lower during exercise (357 vs 500 mmol/L × 40 minutes).

4 These effects appeared to be transient, however, and did not extend beyond 2 hours after exercise.

5 The authors suggest that longer periods of exercise, or more intensive activity (treadmill speeds were set to achieve 50% of maximal oxygen uptake), may be required.

6 Further studies to determine the optimal exercise strategies to reduce postprandial excursions, as well as to assess the effects of these on diabetes outcomes, are warranted.

Erickson ML, Little JP, Gay JL et al (2017) Effects of postmeal exercise on postprandial glucose excursions in people with type 2 diabetes treated with add-on hypoglycemic agents. *Diabetes Res Clin Pract* **126**: 240–7

Diabetes Care

Personalising T2D management using electronic records

Readability	✓✓
Applicability to practice	✓✓✓
WOW! Factor	✓✓✓

1 There is growing interest in using clinical evidence to comprehend the effects of pharmacological treatments in various populations with T2D.

2 The authors of this study used Boston Medical Center's electronic medical records for 10 806 patients to model the outcomes of 13 pharmacological therapies. Data from between 1999 and 2014 were used to create an algorithm for personalised diabetes management.

3 The *k*-nearest neighbour approach was used to model the outcomes from each visit. The neighbours that maximised similarity based on individual patient characteristics and outcome-related medical history were selected. The regimen with the best predicted outcome was prescribed by the algorithm when the threshold for switching regimens was reached. The effect of recommendations on matched patient outcomes from unseen data were evaluated.

4 The algorithm's recommendation mirrored the observed standard of care in 68.2% of 48 140 patient visits.

5 When the algorithm differed from the standard of care, the mean post-treatment HbA_{1c} was 4.8±0.3 mmol/mol (0.44%±0.03%) lower than the standard of care P<0.001).

6 Compared to the standard of care, the personalised approach to diabetes management using the algorithm resulted in substantial HbA_{1c} improvements. The prototype dashboard can be used by healthcare professionals to inform diabetes care.

Bertsimas D, Kallus N, Weinstein AM et al (2017) Personalized diabetes management using electronic patient records. *Diabetes Care* **40**: 210–7

> *"The authors conclude that liraglutide 3.0 mg might be used to reduce risk of diabetes in individuals with obesity and prediabetes."*