A STEP in the right direction for people with prediabetes

Treatment with weekly subcutaneous semaglutide 2.4 mg for 52 weeks in those with obesity and prediabetes achieved an 81% prediabetes remission rate compared with 14% in the lifestyle-only group, and more than 11% greater mean weight loss, in the STEP 10 randomised controlled trial published in *Lancet Diabetes & Endocrinology*. During a further 28-week period off treatment, some weight gain occurred in both groups, with persistent normoglycaemia observed in 44% of those previously treated with semaglutide versus 18% of those in the lifestyle-only group at 80 weeks. Fewer people were diagnosed with type 2 diabetes at both 52 and 80 weeks amongst those treated with semaglutide. As expected, there were more gastrointestinal adverse events reported in the semaglutide group but no previously unrecognised serious adverse events of interest were recorded. These findings add to the evidence base that prediabetes remission, with return to normoglycaemia rather than just prevention of progression to type 2 diabetes, achievable with intensive lifestyle advice, semaglutide 2.4 mg or bariatric surgery, is an important and emerging goal in reducing future levels of type 2 diabetes.

Pam Brown
GP in Swansea

Return to normoglycaemia, rather than prevention of progression to type 2 diabetes, is an emerging goal for people with prediabetes (non-diabetic or intermediate hyperglycaemia), given that rates of this condition continue to rise in parallel with rising rates of obesity and that any elevation of glucose increases the risk of developing not just type 2 diabetes but also cardiovascular disease. Achieving and maintaining this with lifestyle and behaviour change is possible but can be challenging, as at least 7% weight loss and 150 minutes per week of moderate physical activity such as brisk walking is recommended for prevention (American Diabetes Association Professional Practice Committee, 2024).

STEP 10 was a randomised, double-blind, placebo-controlled trial to compare the efficacy and safety of once-weekly semaglutide 2.4 mg versus placebo in people with obesity and prediabetes (but not type 2 diabetes) at trial sites across Canada, Denmark, Finland, Spain and the UK (McGowan et al, 2024). People aged ≥18 years, with BMI ≥30 kg/m^2, who met at least one of the UK criteria for prediabetes – HbA_{1c} 42–47 mmol/mol (6.0–6.4%) or fasting plasma glucose 5.5–6.9 mmol/L – were randomly assigned 2:1 to receive semaglutide 2.4 mg once weekly or placebo, alongside diet and physical activity counselling, for 52 weeks followed by a 28-week follow-up whilst off treatment. The primary endpoints were percentage weight change and the proportion of participants achieving prediabetes remission/normoglycaemia (HbA_{1c} <42 mmol/mol or fasting plasma glucose <5.5 mmol/L) at 52 weeks.

Study results

A total of 138 people were randomised to semaglutide 2.4 mg and 69 to placebo. Mean age at baseline was 53 years and mean body weight 111.6 kg, with mean BMI just over 40 kg/m^2. Mean HbA_{1c} was just below 42 mmol/mol, with a mean fasting glucose of 5.9 mmol/L.

Overall, 93% completed the study in both groups. At the end of the active treatment period, 84% of those remaining on semaglutide were on the full 2.4 mg dose.

From baseline to week 52, semaglutide 2.4 mg plus lifestyle counselling resulted in a 13.9% mean reduction in body weight, compared with 2.7% in the placebo arm. This is similar

Citation: Brown P (2024) Diabetes Distilled: A STEP in the right direction for people with prediabetes. *Diabetes & Primary Care* **26**: [Early view publication]

Table 1. Weight loss and glycaemic outcomes after 52 weeks of treatment and a further 28 weeks off treatment.

	Mean weight loss (52 weeks)	Mean weight loss (80 weeks)	Normoglycaemia (52 weeks)	Normoglycaemia (80 weeks)	Type 2 diabetes (52 weeks)	Type 2 diabetes (80 weeks)
Semaglutide 2.4 mg + lifestyle interventions	13.9%	7.9%	81%	44%	1% (1 of 127)	3% (3 of 120)
Placebo + lifestyle interventions	2.7%	1.3%	14%	18%	3% (2 of 64)	8% (5 of 60)

to the weight loss achieved with semaglutide in the STEP 1 and 3 studies. At the end of the study period at 52 weeks, 81% of participants in the semaglutide 2.4 mg group had reverted to normoglycaemia, compared with 14% in the placebo group. Likewise, fewer people progressed to type 2 diabetes in the semaglutide group than with placebo (*Table 1*). Nobody who lost 5% body weight or more progressed to type 2 diabetes.

Weight regain (around 6.0% of original body weight in the semaglutide group and 1.4% in the placebo group) occurred in the 28 weeks following treatment discontinuation, such that the mean change in body weight from baseline was 7.9% for semaglutide 2.4 mg and 1.3% for placebo, with an ongoing upward trend at the end of 80 weeks. Overall, 44% of those treated with semaglutide remained in prediabetes remission at 80 weeks, compared with 18% in the placebo group. By week 80, three of 120 participants in the semaglutide group had progressed to type 2 diabetes compared with five of 60 in the placebo group (2.5% vs 8.3%).

Those treated with semaglutide 2.4 mg had greater beneficial changes in HbA_{1c}, fasting glucose, waist circumference and systolic blood pressure than the placebo group at week 52, and off treatment these parameters increased but did not reach baseline levels at week 80.

Safety profile

Serious adverse events were reported by 9% in each group, with serious gastrointestinal events only reported by those in the semaglutide group. Adverse events leading to permanent discontinuation of treatment occurred in 6% of those on semaglutide and 1% of those on placebo. No previously unrecognised serious adverse events of interest were recorded in the semaglutide group.

Two malignant neoplasms were diagnosed during the study in those taking semaglutide, but both were deemed unrelated to the study drug. In the SELECT study, in a much larger population and over a longer treatment period, there was no increased risk of cancer identified with semaglutide 2.4 mg treatment. Likewise, a systematic review and meta-analysis of cancer rates in semaglutide randomised controlled trials and real-world studies did not identify an increased cancer risk (Nagendra et al, 2023). Two cases of acute pancreatitis and one of gallbladder disease were identified during the study. Two deaths were reported in the semaglutide group but were deemed unrelated to the study drug.

Study strengths and limitations

Strengths of the study were that it included follow-up after 28 weeks off treatment, and the high rates of treatment adherence and trial completion. Key limitations were that most people in the study were White and female; participants' fasting glucose and HbA_{1c} levels were at the lower end of the prediabetes/intermediate hyperglycaemia range (those with higher values may have had greater treatment effects); the 80-week study period was short whereas obesity is a long-term condition; there was no active comparator such as metformin, which has previously been demonstrated to reduce progression to type 2 diabetes; and it was not clear how much of the HbA_{1c} reduction was due to weight loss and how much due to the effects of the high-dose semaglutide.

It should also be noted that nine sessions of dietitian counselling were provided to both groups during the study, which is a significant input unlikely to be achievable in routine clinical practice and which likely supported the weight loss and remission rates achieved in the placebo group.

Discussion

In an accompanying commentary, Bergman (2024) reminds us that it remains important to consider all options for achieving prediabetes remission in those with obesity, since 14% of the

control group in STEP 10 achieved remission at 1 year with an intensive lifestyle intervention, while bariatric surgery has demonstrated a 58% rate of prediabetes remission 4 years after surgery (Borges-Cana et al, 2024). Bergen highlights the importance of earlier identification of people at risk of diabetes and prediabetes.

In the SELECT randomised controlled trial of semaglutide 2.4 mg in people with obesity or overweight and established cardiovascular disease but without type 2 diabetes, two-thirds of participants had prediabetes at baseline according to the lower US threshold of HbA_{1c} ≥39 mmol/mol (5.7%). Overall, 65.7% of those with prediabetes and treated with semaglutide 2.4 mg achieved normoglycaemia at 102 weeks compared with 21.4% of those in the placebo group. A reduction in risk of cardiovascular disease was demonstrated across all baseline HbA_{1c} levels, including in those with prediabetes (Lingvay et al, 2024).

Guidelines such as the ADA Standards of Care recommend ≥7% weight loss and 150 minutes of moderate physical activity per week for those with prediabetes. Using data from the US Diabetes Prevention Program (DPP), Jumpertz von Schwartzenberg et al (2024) demonstrate that combining this weight loss goal with a glycaemic goal of prediabetes remission according to US criteria (fasting plasma glucose <5.6 mmol/L or HbA_{1c} <39 mmol/mol) would be more effective in reducing the risk of type 2 diabetes development than achieving the weight loss goal alone. In total, 480 participants in the original DPP achieved ≥7% weight loss by 1 year, and 114 of these also achieved normoglycaemia. At 4 years, 11.5% of those who achieved only the weight loss target had developed type 2 diabetes, compared with only 0.9% of those who achieved both the weight loss and prediabetes remission.

Implications for practice

Type 2 diabetes is largely preventable in those who develop prediabetes, with a 58% risk reduction over 3 years in the those at high risk in the original DPP. There is increasing interest in targeting remission to normoglycaemia, rather than mere prevention of progression to type 2 diabetes, in those with prediabetes, not only because this further reduces the risk of developing type 2 diabetes, but also because prediabetes is itself associated with the development of microvascular complications and cardiovascular disease.

Many people at risk of prediabetes or diabetes are completely unaware of their risk. Using simple tools such as the Leicester Risk Assessment (available on the Diabetes UK website) will help us identify those at highest risk and guide us in arranging HbA_{1c} testing.

The additional value in supporting people to achieve both 7% weight loss and normoglycaemia (i.e. prediabetes remission), to reduce short-term risk as well as future diabetes development, is now clearer, and this may be an appropriate time to update our goals in managing prediabetes. Within the NHS, diabetes prevention programmes are already well established, and there is increasing access to weight loss drugs and bariatric surgery.

What can we do? We can be more proactive in searching for and testing those at high risk of diabetes and prediabetes. Every person we support to accept referral to a prevention programme is one more opportunity to prevent development of type 2 diabetes, with all its inherent health risks. We need to know how to refer for weight loss therapy and bariatric surgery in our local area, and to share this information with people who may want to pursue these options. By coupling this with proactive referral to remission services, perhaps we really can help reduce the burden of type 2 diabetes. ■

Diabetes prevention programmes across the UK

England: Healthier You Diabetes Prevention Programme
Wales: All-Wales Diabetes Prevention Programme
Northern Ireland: Type 2 Diabetes Prevention Programme
Scotland: My Diabetes My Way

American Diabetes Association Professional Practice Committee (2024) 3. Prevention or delay of diabetes and associated comorbidities: Standards of Care in Diabetes – 2024. *Diabetes Care* **47**(Suppl 1): S43–51

Bergman M (2024) Prediabetes remission in people with obesity. *Lancet Diabetes Endocrinol* **12**: 603–5

Borges-Canha M, Neves JS, Silva MM et al; CRIO group (2024) Prediabetes remission after bariatric surgery: A 4-years follow-up study. *BMC Endocr Disord* **24**: 7

Jumpertz von Schwartzenberg R, Vazquez Arreola E, Sandforth A et al (2024) Role of weight loss-induced prediabetes remission in the prevention of type 2 diabetes: Time to improve diabetes prevention. *Diabetologia* **67**: 1714–8

Lingvay I, Deanfield J, Kahn SE et al; SELECT trial investigators (2024) Semaglutide and cardiovascular outcomes by baseline HbA_{1c} and change in HbA_{1c} in people with overweight or obesity but without diabetes in SELECT. *Diabetes Care* **47**: 1360–9

McGowan BM, Bruun JM, Capehorn M et al; STEP 10 study group (2024) Efficacy and safety of once-weekly semaglutide 2·4 mg versus placebo in people with obesity and prediabetes (STEP 10): A randomised, double-blind, placebo-controlled, multicentre phase 3 trial. *Lancet Diabetes Endocrinol* **12**: 631–42

Nagendra L, Bg H, Sharma M, Dutta D (2023) Semaglutide and cancer: A systematic review and meta-analysis. *Diabetes Metab Syndr* **17**: 102834

Efficacy and safety of once-weekly semaglutide 2·4 mg versus placebo in people with obesity and prediabetes (STEP 10): A randomised, double-blind, placebo-controlled, multicentre phase 3 trial

Click here to read the study in full (subscription access or purchase required)