Fat – pharmacological therapies

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It was a pleasure to be asked to speak at the ABCD celebration of the discovery of insulin and its subsequent rapid adoption into clinical practice, truly a major advance in medicine. My remit was to discuss pharmacological therapies for weight reduction. Given the time constraints, I chose to focus on the glucose-lowering therapies which are now being licensed for the management of obesity, how they are being positioned in guidelines and future developments, including ongoing trials.

The introduction of glucagon-like peptide 1 receptor agonists (GLP-1RAs) into the UK in 2007, followed by sodium-glucose co-transporter-2 (SGLT2) inhibitors in 2012, finally gave clinicians glucose-lowering therapies that had the additional benefit of weight reduction. The initial phase 3 trials suggested similar mean weight loss for both drug classes of 2-3 kilograms (kg) over six months. The mode of weight loss for the SGLT2 inhibitors was thought to be calorific loss due to induced glucosuria and so their potential for weight reduction in people with normal glucose tolerance was limited. A recent systematic review and meta-analysis in non-diabetic adults with overweight or obesity has confirmed modest changes in body weight (-1.42kg, confidence intervals [CI] -1.70 to -1.14) and body mass index (BMI) -0.47 kg/m^2 (CI -0.63 to -0.31). I am not aware of any plans for SGLT2 inhibitors to be marketed for weight loss.[1]

In contrast, the impact of GLP-1RAs on weight is not dependent on hyperglycaemia. At a higher dose than that licensed for glucose lowering, subcutaneous liraglutide 3mg OD was found to lower food intake by reducing hunger and increasing satiety, predominantly through effects on the central nervous system rather than slowing gastric emptying.[2] This led to the SCALE phase 3 clinical trial programme in people with obesity/overweight, either alone or with co-morbidities of pre-diabetes, diabetes or sleep apnoea.[3-5] In all groups studied, liraglutide produced statistically superior weight loss compared to placebo, with 46.3–63.2% of trial recruits achieving a weight loss >5%, which is the Food and Drug Administration (FDA) minimum requirement for an anti-obesity licence. Between 23.4% and 33.1% of participants lost more than 10% of their baseline weight.[6] The 3mg dose of liraglutide was generally well tolerated, with the anticipated adverse gastrointestinal effects of nausea, vomiting, diarrhoea and constipation, and was marketed as Saxenda® in 2015.

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Semaglutide

When the once-weekly GLP-1RA, semaglutide, was being assessed in the SUSTAIN phase 3 trial programme, it became clear that this agent had the potential for greater weight loss than liraglutide.[7] As a result, the STEP programme of clinical trials was initiated in people with overweight or obesity, using high-dose (2.4mg) semaglutide, given by subcutaneous weekly injection.[8] Each of the STEP 1-4 trials was placebo- controlled and lasted for 68 weeks; the mean change in body weight from baseline was -9.6% to 17.4%, the lowest reduction being seen in those people with T2DM, as is typically the case.[9-12] In the STEP 1, 3 and 4 studies of people without diabetes, between 50.5% and 63.7% of trial participants achieved >15% weight loss compared with 4.9-13.2% of participants on placebo. The superiority of semaglutide 2.4mg QW over daily Saxenda® was confirmed by the head-to-head STEP 8 trial in people with overweight or obesity without T2DM, treated for 68 weeks.[13] The mean weight reductions were 15.4% versus 6.4%, statistically favouring semaglutide 2.4mg QW, which is now licenced as Wegovy®. The National Institute for Health and Care Excellence (NICE) recommended Wegovy® for 'adults with at least one weight-related condition and a BMI of at least 35 kg/m^2' on 8th February 2022, although it has not yet been launched in the UK (currently anticipated in 2023).[14]

The oral version of semaglutide (Rybelsus®) was launched as a daily glucose- lowering therapy in 2020 and is currently being assessed in the OASIS 1 trial of people who are overweight or living with obesity.[15] This is a placebo-controlled trial of a 50mg dose (compared with the maximum glucose-lowering dose of 14mg OD) in 660 participants, and is expected to complete in May 2023. Other activities in the GLP-1RA space include: the REDEFINE 2 study of CagriSema, a combination of subcutaneous cagrilinitide (an amylin analogue) and subcutaneous semaglutide (both 2.4 mg QW) in people who have T2DM and a body weight above the healthy range, expected to start in 2022;[16] and the unexpected development of an oral small molecule GLP-1RA, danuglipron.[17]

Dual agonists

The most recently developed class of glucose-lowering therapies is the GLP-1/ glucose-dependent insulinotropic polypeptide (GIP)

Table 1 GLP-1 co-agonists in development (phase 1 and beyond)

Drug	Administration	Status	Therapeutic areas
GLP-1/Glucagon Dual Agonists			
Pemvidutide (ALT-801)	sc weekly	phase 1b, 2	NASH, obesity
Cotadutide	sc daily	phase 2b	NASH, T2D w CKD
BI456906	sc weekly	phase 2	T2D, obesity, NASH
Mazdutide (LY3305677)	sc weekly	phase 2	T2D, obesity
Efinopegdutide	sc weekly	phase 2	NASH
OPK8803	sc weekly	completed phase 2/2b	T2D, obesity
DD01	sc weekly	phase 1	T2D w NAFLD
PB-718	sc weekly	phase 1	NAFLD, obesity

Key messages

- Glucose lowering therapies are now being re-purposed as weight loss therapies for people who do not have diabetes
- The weight loss achieved by modern therapies is phenomenal and side-effect profiles are tolerated
- Evidence that weight loss achieved with pharmaco therapy equates to cardiovascular and total mortality benefits is awaited but should emerge in the near future

dual agonists, the first of which was approved in Europe in 2022. Tirzepatide is a 39 amino acid peptide which binds to both the GLP-1 and GIP receptors and *in vitro* has greater potency for GIP. It is conjugated to a 20-carbon fatty diacid moiety which allows for once-weekly subcutaneous dosing.[18] It has been assessed in a large (>27,000 participants) clinical trial programme examining both glucose lowering (SURPASS studies) and weight management (SURMOUNT 1-4). The SURPASS programme has demonstrated impressive glucose lowering across the T2DM spectrum from monotherapy to insulin add-on, with 86-92% of study recruits achieving an HbA_{1c} ≤48mmol/mol on the highest dose (15mg QW).[19] This was superior to active treatment with both insulin degludec and subcutaneous semaglutide 1mg QW and, as a result, the European Medicines Agency (EMA) granted approval in September 2022. Weight reduction, a secondary endpoint in the SURPASS studies of people with T2DM, was equally impressive, with 27-43% of those on the highest dose achieving ≥15% weight loss.

For reasons that are unclear, people recruited into the SURMOUNT studies who did not have T2DM fared even better. In the SURMOUNT-1 trial, the mean percentage weight reduction from baseline to 72 weeks in the tirzepatide 15mg QW arm was 20.9%, compared with 3.1% for placebo.[20] This reflected 56.7% of subjects in this arm achieving a weight reduction of ≥20% and one third (36.2%) losing ≥25% of baseline weight. This led commentators to state that the impact of this weekly drug was equivalent to that of bariatric surgery and the FDA to grant fast-track designation, which will probably lead to an obesity licence in 2023. The dual agonist pipeline is also a very active one, with GLP-1/Glucagon agonism a major therapeutic target (see table 1).

At this point, it may be appropriate to question the widely held view that weight loss will inevitably reduce major cardiovascular (CV) events. This consensus was challenged in May 2022 by Park and colleagues, who reported on a longitudinal follow-up of a nationwide cohort of more than 1.5 million people in South Korea.[21] They found that both weight gain and weight loss of >5% within two years were associated with an increase in major CV outcomes in people with T2DM. This was followed by publication of the 21-year median follow-up of people in the Diabetes Prevention Programme (DPP) and Diabetes Prevention Programme Outcomes Study (DPPOS); this reported that there was no impact of lifestyle modification (or metformin use) on major CV events.[22] Fortunately, the current vogue for cardiovascular studies (CVOTs) in T2DM has extended into the obesity field and so this question should be definitively addressed. The SELECT study is examining the impact of subcutaneous semaglutide 2.4mg QW versus placebo in people with overweight or obesity but not T2DM (HbA_{1c} <48mmol/mol).[23] The trial cohort is large (17,500 individuals) and they all have established CV disease (prior myocardial infarction [MI] or stroke ≥60 days before inclusion) or peripheral vascular disease. The primary endpoint is time to the first occurrence of the composite endpoint of CV death, non-fatal MI or non-fatal stroke (the standard 3-point MACE used in diabetes CVOTs) and the results are expected by 2023.

Finally, back to diabetes: how do these data impact on diabetes guidelines? Judging by the latest iteration of the ADA/EASD consensus report in 2022, the answer is quite profoundly.[24] The report now gives the same standing to glycaemia and weight management as it does to cardiovascular risk reduction. Moreover, semaglutide and tirzepatide are named as 'very high efficacy drugs' for weight reduction though the latter drug does not have any CVOT data and is not due for review by NICE until 2023. Times are indeed a-changing….

Conflict of interest SCB reports receiving grant income and speaker honoraria from Novo Nordisk and Eli Lilly, manufacturers of the medicines forming the main focus of this talk.
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