

Steps to redressing an imbalance: GLP-1 analogues for obesity in East Asia

Obesity is a global disease and is particularly prevalent in Asia. It is estimated that 1 billion people across Asia have a body mass index (BMI) of $>25 \text{ kg/m}^2$ ¹. Obesity affects 1 in 3 Chinese, with a significant increase in recent years², this trend is also seen across other countries in Asia³. The relationship of BMI to diabetes and other manifestations of metabolic syndrome is different in East Asian populations, where the prevalence of metabolic syndrome is much higher compared to other ethnicities even at non-obese BMIs⁴. This phenomenon is linked to the higher accumulation of visceral adipose tissue (VAT) relative to subcutaneous adipose tissue in East Asians⁵. Recognising this, the definition of 'obesity disease' by professional societies in Japan (JASSO) and Korea (KSSO) sets the cut-off of BMI at 25 kg/m^2 , with additional criteria relating to obesity comorbidities and measurements of VAT, for example radiographic measurement of visceral fat area (VFA) or waist circumference.

Analogues of glucagon-like peptide-1 (GLP-1) are now licensed in the US and Europe for the treatment of obesity, based on successful Phase 3 trials of liraglutide 3.0 mg daily⁶ and semaglutide 2.4 mg weekly⁷. In the STEP series of trials of semaglutide that have been published to date, participants from Asia have been a decided minority, which is not reflective of the global situation with obesity. In this issue of *The Lancet Diabetes and Endocrinology*, Kadowaki and colleagues report on the STEP 6 randomised, double-blinded, placebo-controlled trial of semaglutide for obesity in an East Asian population. Participants were recruited from Japan and Korea; they had had at least one attempt at dietary weight loss and had BMI $\geq 27.0 \text{ kg/m}^2$ with two or more treated or untreated weight related comorbidity, or $\geq 35.0 \text{ kg/m}^2$ and one or more treated or untreated weight related comorbidity. One comorbidity had to be hypertension, dyslipidaemia or diabetes. Furthermore, two specified subgroups of participants from Japan were recruited, one with who had a diagnosis of diabetes, with a glycated haemoglobin (HbA1c) of 7.0-10% (53-86

mmol/mol) and receiving treatment with up to 3 oral hypoglycaemics; the other had measurements of VFA using CT scanning as a specified secondary endpoint. Between Jan 21 and Jun 4 2019, 401 eligible participants were randomised to semaglutide 1.7 mg weekly (n=101), 2.4 mg weekly (n=199) and placebo (n=101); all were given advice on exercise and a hypocaloric diet aiming for a 500 kcal/day deficit. Baseline characteristics were well balanced between groups. Notably, the mean BMI in this trial was 31.9 kg/m², less than in previous reported STEP trials (35.7 to 38.5 kg/m²), despite the BMI inclusion criteria being similar. As per other trials of semaglutide, participants were dose-escalated in a fixed regimen every four weeks to the final dose of 1.7 mg or 2.4 mg. Treatment was continued for up to 68 weeks, followed by a 7 week follow-up period after treatment was stopped. Notably, trial adherence was high, with 98.5% completing. The adverse events with semaglutide were mainly gastrointestinal (as per previous experience), mostly mild and led to permanent discontinuation in only 2.5-3.0% of participants.

The primary endpoint, percentage change of bodyweight from baseline to 68 weeks, was -13.2% with the 2.4 mg dose, -9.6% with 1.7 mg and -2.1% with placebo (estimated treatment difference [ETD] -11.1% and -7.5% respectively, p<0.0001 for each dose). 82.9% of participants treated with 2.4 mg lost at least 5% bodyweight, compared to 72.4% with 1.7 mg and 21.0% with placebo. These results are compatible with the other STEP trials. Interestingly women lost more weight (-15.79% with 2.4 mg, -12.71% with 1.7 mg) than men (-8.47% and -5.19% respectively, p=0.0002 and p=0.0008 for the interaction) and this has never been reported in other STEP trials. It is unclear if this indicates a differential effect by sex in this population. Semaglutide reduced HbA1c in those with diabetes (n=99), by -2.2% (-24 mmol/mol) with 2.4 mg and -2.1% (-23 mmol/mol) with 1.7 mg compared to +0.3% (+3.3 mmol/mol) with placebo, but only had a minor effect in those without diabetes reflective of its glucose-dependent insulinotropic effect. People with diabetes did not lose as much weight as those without. Abdominal VFA was analysed in a subgroup of 180 participants. This was reduced by 40% with 2.4 mg and 22.2% with 1.7 mg, compared to 6.9% with placebo (ETD of 33.2% and 15.3% respectively, p<0.0001 for both). Parallel with this, semaglutide treatment was associated with improvements in surrogate markers for cardiovascular risk and inflammation such as systolic blood pressure, total and LDL

cholesterol, C-reactive protein and plasminogen activator inhibitor-1 in the overall trial population.

Overall, the trial shows that semaglutide is as effective for the treatment of obesity in Japanese and Korean people as in other ethnicities tested so far. The results are likely generalisable to other Asian populations, but further information will come from the forthcoming STEP 7 trial (ClinicalTrials.gov NCT04251156) which has recruited from centres in China and Brazil. The direct demonstration of improvements in VAT does suggest that semaglutide has clinically significant impacts on the pathophysiology of metabolic syndrome. We look forward to the results of the SELECT trial (ClinicalTrials.gov NCT03574597; due to complete in 2023), which should provide some answers on semaglutide's effect on cardiovascular disease. Importantly, SELECT will recruit from centres across the Americas, Europe and Asia (including South and South East Asia): another step, albeit incomplete, to addressing the global ethnic imbalances in GLP-1 analogue trials to date.

Declaration of interests

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