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Semaglutide is precipitating a revolution in obesity care

The prevalence of obesity has rapidly surged with almost one in seven of people on earth now considered as having obesity.[1] The biology of the disease of obesity is being unravelled,[1] but treating the disease is also important because of the devastating complications which includes type 2 diabetes, cardiovascular disease and several malignancies.[2–7] Previously, obesity was thought to be a disorder of willpower, resulting in significant discrimination against people with obesity even among clinicians.[8] We now understand that satiety and hunger signals are generated in parts of the brain that are not related to conscious awareness. Obesity is thus considered a consequence of a subcortical brain disease, particularly of the hypothalamus, area postrema, and nucleus tractus solitarius.[9,10] Genetic disorders resulting in loss of the melanocortin 4 receptor (MC4R) activity in the hypothalamus leading to severe obesity in close to 5% of the affected patients, supports this concept of a subcortical brain disease.[11] Targeting the disease itself in the subcortical areas by nutritional therapies, pharmacotherapy or surgical therapies results in significant and sustained weight reduction and remarkable improvements in the quality of life.[8,12–14] By understanding the pathogenesis of obesity and the responsible organ, more focused management approach can be provided for patients with obesity.

Semaglutide 2.4 mg is a once-weekly analogue of the glucagon-like peptide-1 (GLP-1) which has been approved as a treatment for obesity in conjunction with lifestyle modifications by the FDA (United States), Health Canada, the Medicines and Healthcare products Regulatory Agency (United Kingdom), and most recently by The European Medicines Agency.[15] The drug appears to act on the dysregulated central and or peripheral neuronal pathways which causes obesity, because it initially stimulates satiety, reduces energy intake and hunger, and ultimately allows patients to maintain a lower fat mass.[16,17] Therefore, semaglutide should be considered as a treatment for the disease of obesity rather than a weight reduction medication.

The Semaglutide Treatment Effect in People with Obesity (STEP) program is an assembly of 15 multinational, phase-III, randomized, double-blind, placebo-controlled trials.[12,15,18] The STEP trials established two primary efficacy endpoints: (i) the mean body weight change from baseline until the measurement date, and (ii) the rate of participants who experienced body weight loss of $\geq$5% from baseline until the measurement date. Compared with the placebo arm, the results from these STEP trials showed semaglutide to effectively treat obesity. Overall, the mean weight change from baseline to end of treatment was −13.2% with semaglutide versus −1.6% with placebo across the seven published STEP trials. Moreover, the proportion of participants treated with semaglutide achieving $\geq$5% was 82.9%, but more than 30% achieved $\geq$20% weight loss. Analysis of exploratory secondary endpoints depicted several favourable impacts on a diverse array of anthropometric (e.g., body mass index and waist circumference), inflammatory (e.g., C-reactive protein), lipid (e.g., low-density lipoprotein cholesterol and total cholesterol), glycaemic (e.g., fasting plasma glucose and glycated haemoglobin A1c), and blood pressure (e.g., systolic and diastolic) indices. Across all published STEP trials, semaglutide 2.4 mg showed significant reductions in waist circumference (−11.82 cm), BMI (−4.4 kg/m^2), systolic and diastolic blood pressure (−5.36 mmHg and −3.09 mmHg, respectively) and HbA1c (−0.61%). In terms of safety profile, semaglutide was tolerable without a substantial risk of serious adverse effects or drug discontinuation. Mild to moderate gastrointestinal related symptoms were the most frequent adverse events. The frequencies of injection−site reactions, hypoglycaemia, and gall bladder related symptoms were comparable in the semaglutide group and placebo group.[12,15,18]

In Untied States of America (USA), since FDA approval of semaglutide in 2021 as a reliable drug for chronic body weight management, the adoption of the treatment has exceeded expectations. Consequently, in March 2022, the manufacturing company Novo Nordisk USA declared significant supply shortages owing to the exceptional product demand.[19] Novo Nordisk USA advised healthcare providers to temporarily delay starting new patients on semaglutide and rather focus on supporting the current semaglutide individuals who have already started treatment so they can stay on therapy.[19] This is consistent with the STEP 1 continuation studying showing that if the drug is stopped the disease of obesity relapses and weight regain follows,[20] but it shows how semaglutide may be a foundation drug for the management of obesity which can revolutionise the care of the disease because it is effective, safe and easy to use.

This is reminiscent of statins, which are among the most extensively prescribed drugs universally, because they are well tolerated and have proven cardiovascular event and mortality benefits.[21] Initially simvastatin was shown to have a mortality benefit in the 4S study,[22] which caused a dilemma for healthcare systems, because how was a new expensive drug going to be prescribed to a quarter of

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the population who had dyslipidaemia, which at the time was not considered a disease but rather a self-inflicted condition. The solution was that initially those patients at highest risk of dying such as those with existing cardiovascular disease and a total cholesterol above 7 mmol/L was targeted first. A few years later the medication was considered for patients with total cholesterols above 7 mmol/L who didn't have existing cardiovascular disease, and another couple of years later patients with type 2 diabetes was added to the list.[23,24] This natural iterative process was informed by high quality randomized controlled trials, but ultimately it allowed expensive but cost-effective medications such as statins to be introduced to almost a quarter of the European population. Likewise, semaglutide has the potential to transform the field of obesity care and change the paradigms of managing obesity. Semaglutide, similar to simvastatin, is anticipated to be a foundation drug, because it is likely to be tolerate by a large portion of patients while effectively treating the disease of obesity without much effort from the patients.

A frequently asked question is whether semaglutide will displace the need for bariatric surgery. The International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) estimates that only 1% of the eligible population receive bariatric surgery.[25] Semaglutide is unlikely to be the preferred option for these patients but is more likely to be prescribed to those who may not wish to have surgery. Thus, if semaglutide penetrates only 10% of the eligible population with obesity, then approximately 20% of these (2% of the total population with obesity) may have a suboptimal response. Consequently, many of these patients with a suboptimal response to the medication may wish to escalate their therapy to include surgery. Thus, it is likely that the total number of patients wanting surgery may double in the short term.

In conclusion, semaglutide is likely to revolutionise obesity treatment in the same way statins impacted the treatment of cardiovascular disease. The drug is likely to be well tolerated, highly effective, and require very little effort from patients or clinicians. Similar to statins the hope is that semaglutide will allow patients to live longer with better quality of life.

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Conflicts of Interest

ClR reports grants from the Irish Research Council, Science Foundation Ireland, Anabio, and the Health Research Board. He serves on advisory boards of Novo Nordisk, Herbalife, GI Dynamics, Eli Lilly, Johnson & Johnson, Sanofi Aventis, AstraZeneca, Janssen, Bristol-Myers Squibb, Glia, and Boehringer Ingelheim. ClR is a member of the Irish Society for Nutrition and Metabolism outside the area of work commented on here. He is the chief medical officer and director of the Medical Device Division of Keyron since January 2011. Both of these are unremunerated positions. ClR was a previous investor in Keyron, which develops endoscopically implantable medical devices intended to mimic the surgical procedures of sleeve gastrectomy and gastric bypass. He continues to provide scientific advice to Keyron for no remuneration.

RPV has received Honorarium for educational lectures and seminars from Novo Nordisk, UK.

Author contributions

All authors contributed equally and approved the final version.

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