Editorial Commentary

GLP-1 analogue liraglutide as adjunct treatment in diabetes type 2 after failed bariatric/metabolic surgery

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Obesity with its negative effect on health (1) has become a major challenge to physicians as well as surgeons throughout the world. Today more than 650 million people worldwide are obese (1). To the physician, the individuals' positive energy balance with a greater energy intake than expenditure means an increased rate of diabetes type 2 and insulin resistance along with debilitating complications such as hypertension, stroke and cardiac disease, sleep respiratory disorders including sleep disturbance, blood lipid abnormalities and non-alcoholic fatty liver disease. To the surgeon, the problem mainly deals with the stigmatizing body composition, excessive accumulation of adipose tissue and immobility. Furthermore, there is a link to a number of cancers, such as endometrium, breast, ovary, prostate, liver, gallbladder, kidney, and colorectal cancer.

Obesity is most commonly caused by a combination of over-eating, limited physical activity, and genetic susceptibility (1,2). Metabolically, obese people have a greater energy expenditure than their normal counterparts due to the huge energy required to maintain an increased body mass in a vicious circle (3,4). The excessive food intake will put an extra requirement on the capacity of inner organs, such as the liver and pancreas, in order to meet the unrestricted load of nutrients that is delivered through the stomach and small intestine. Therefore, food restriction seems to be the obvious way to tackle the problem and move forward. At the individual level, WHO recommends limitation of the energy intake with less total fats and sugars as well as increased intake of fruit, vegetables and legumes, as well as whole grains and nuts (1). Experience is telling that this is hard to come by.

In the clinic, bariatric surgery is today the only method considered effective and reliable enough to achieve substantial weight loss and relief of obesity-related co-morbidities, with superior outcomes as compared to dieting (5,6). Gastric bypass surgery (7) usually results in durable weight loss (8), along with marked hormonal changes that develop immediately after surgery, even before demonstrable weight loss takes place (9). As an alternative, sleeve gastrectomy as a stand-alone procedure has gained popularity to achieve large weight loss (10). Sleeve gastrectomy is considered as effective as gastric bypass surgery, including improvements in glucose homeostasis even before substantial weight loss ensues. The two operations are both permanent, reduce hunger and cause similar weight loss. The weight-loss independent benefits are related to a diminished gastric volume, gut peptide release, and expression of genes entangled in intestinal glucose absorption (11,12).

Through research on gastrointestinal peptide hormones, accumulating evidence show that there is also a pharmacological way forward to bring about weight loss. Glucagon-like peptide-1 (GLP-1) is an anorexigenic and insulinogenic hormone and neuropeptide released from the distal gastrointestinal tract. GLP-1 slows gastric emptying, an effect that may be due hormonal as well as transmitter actions within the myenteric plexus (13,14). Postprandial GLP-1 levels are suppressed in obese subjects as compared

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to the lean (9). Fasting levels of GLP-1 increase after bypass surgery as well as after diet-induced weight loss, and stay high after even one year of weight maintenance (9,15). Studies employing GLP-1 analogues have shown liraglutide to be effective for weight-reducing purposes, even though a relatively high dose of 3 mg was used to achieve a significant weight loss of 8% after 56 weeks (16). Recently, data was launched showing that another analogue, semaglutide, at a daily dose of 0.4 mg was able to further reduce body weight by 16.2% (17). This pharmacological development makes GLP-1 analogues really interesting for weight reduction purposes and true competitors to surgery. To this end, since the metabolic effects of bariatric surgery aside from weight control are strong, the term *metabolic surgery* has now been coined for the enhanced metabolic control and glucose homeostasis after bariatric surgery.

In *The Lancet Diabetes & Endocrinology*, Alexander D. Miras and colleagues report the results of a well-conducted randomised, double-blind, placebo-controlled clinical trial on the adjunctive use of liraglutide as a treatment in patients with persistent or recurrent type 2 diabetes after metabolic surgery (18). The basic standpoint for the article is the fact that after surgery 30–63% of diabetic patients attain remission to normoglycaemia without any additional glucose-lowering medications, but also that 37–70% do not attain remission. Furthermore, in those who achieve normoglycaemia to remission, 21–43% relapse within 3–9 years (19,20). Hence, the management of persistent or recurrent diabetes type 2 after metabolic surgery represents a clinical challenge because post-surgical conditions may compromise regular pharmacokinetics with erratic drug absorption, why an injectable such as liraglutide would be the natural choice. However, in the absence of a randomized trial this condition still leaves the diabetologist with no available guidelines or specific recommendations for further treatment. Against this background the GRAVITAS (*GLP-1 Receptor Agonist interVentIon for poor responders afTer bariAtric Surgery*) clinical trial was set out to examine the safety and efficacy of subcutaneous injections of the GLP-1 receptor agonist liraglutide on glycaemic control in patients with persistent or recurrent diabetes type 2 after bariatric Roux-en-Y gastric bypass or vertical sleeve gastrectomy.

All in all, 80 adult participants out of a total number of 303 pre-screened individuals, were recruited who had undergone bariatric surgery at least 12 months before enrolment, had diabetes type 2 with HbA_{1c} over 48 mmol/mol (>6.5%), treatment with metformin or long-acting insulin, and had given informed consent. Of those assigned, 71 completed the trial reaching a statistical power of at least 80% at the $P<0.05$ level. The study design was parallel with an initial run-in period for assessing the patients' adherence to self-administration of the injectable study drug or placebo once daily. Then, the participants were randomised to either liraglutide or placebo in a 2:1 fashion, starting with a daily dose of 0.6 mg liraglutide increasing 0.6 mg per week up to 1.8 mg or maximum tolerated dose for 26 weeks in a row. All patients were overseen by a diabetologist-endocrinologist, dietician, and psychiatrist. The key aspect of the simultaneous nutritional approach aimed at an intake deficit of 500 kcal per day from their baseline consumption, with advice on adequate intake of protein, vegetables and fruit, along with reduced amounts of high-glycaemic index foods, alcohol, salt and saturated fat.

The primary outcome of the study was the change in HbA_{1c} after 26 weeks of treatment. The secondary outcomes were assessment of changes from baseline in bodyweight, systolic and diastolic blood pressure, blood lipid profile, the number of glucose-lowering drugs, the number of patients on insulin and insulin dosage, the obesity-related co-morbidity score, behavioural traits, quality of life, sweet taste detection, food reward ratings, the number of hypoglycaemic episodes, and collected adverse events assessed by reporting at each trial study visit.

There were no differences in baseline features or properties between patients in the liraglutide and placebo groups. Over the treatment period there was a parallel decrease in HbA_{1c} and body weight throughout the study reaching highly significant nadirs at 18 and 26 weeks, respectively. The effect on HbA_{1c} with a mean difference of –13.3 mmol/mol was striking as was the mean difference of in body weight between the two groups with –5.26 kg. Other outcomes did not show any significant changes.

The strength of this study is the generalizability that is shown by the similar response rate to liraglutide irrespective of the type of metabolic surgery. Since the two operations, i.e., gastric bypass and sleeve gastrectomy, are so divergent in nature, with one restricting the stomach size to a minimum, and the other leaving a considerable part of the stomach in place, it seems that a common mechanism of action of liraglutide (and similar GLP-1 analogues) on gastric functions is unlikely. The fact that both operations would permit a rapid delivery of foodstuffs into the small intestine where a host of gastrointestinal peptides [e.g., incretins such as glucose-dependent insulinotropic peptide (GIP) and GLP-1] are released, opens the possibility

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of a common peripheral mechanism of action. Such a mechanism would be expected to cause dumping effects but no adverse effects alike were found in the study. The paucity of a dumping syndrome rules out this possibility as a weight-reducing mechanism. Hence, it would have been of interest to see how the bioavailability of various nutrients or pharmaceuticals behave under these two circumstances. Experiments using glucose or paracetamol for absorption tests would possibly give some more insight into the mechanism of action of liraglutide. Even if peripheral mechanisms may be in operation for weight control, a centrally-mediated action of liraglutide, primarily in the nucleus of the solitary tract, may also be necessary in order to accomplish the substantial weight loss seen with different GLP-1 analogues. To summarize, irrespective of the type of previous metabolic surgery, treatment with liraglutide at doses of 1.2–1.8 mg per day seems to overcome persistent or recurrent diabetes type 2 after bariatric surgery along with a needful weight loss.

In terms of weight loss, bariatric surgery is no guarantee for success. Experience show that even with highly standardized surgery which results in a maintained weight loss for most patients (8) some degree of postsurgical weight regain is commonplace, as noted in one-half of patients two years after surgery (21). Results show that after 5 years, about one-fifth of operated patients will have lost no more than half of their preoperative overweight (22), considered a hallmark of failing bariatric surgery (23). Amongst gut peptide hormones in the proximal gastrointestinal tract, ghrelin is higher in the obese than in normal-weight individuals (24), whereas GLP-1 is low (9,14). In a recent study of non-responders to bariatric surgery, an early rise of ghrelin to baseline levels in conjunction with decreasing leptin levels below baseline during an oral glucose tolerance test have been suggested as a possible appetite-stimulating effect, thus contributing to undesired weight gain after surgery (25).

The present study by Miras and co-workers shows that the GLP-1 mechanism as brought about by liraglutide is able to overcome basic pathophysiological aberrations in obese subjects with low plasma GLP-1 levels (9,14). The stimulation of GLP-1 receptors controls not only glucose homeostasis, but also body weight maintenance with a very limited risk of adverse effects (18). Even if change in bodyweight was stated as a secondary outcome of the study, anyone skilled in the field would recognise this as an important coeffect to the reduced HbA_{1c}. However, in order to make this finding a fully acceptable discovery, a clinical study according to the regulatory construct would require the change in body weight as a primary study endpoint. There is no single superior method of how to evaluate postoperative weight results. Measurements of change in excess BMI, total body weight and degree of weight regain are all different approaches developed for this purpose. The percent of excess BMI loss (%EBMIL), although criticized for giving better results in lightweight subjects as compared to the heavyweights, is today considered a reliable measurement as primary endpoint of weight regain after weight loss. In addition, beyond changes in %EBMIL, successful weight loss should also comprise remission of co-morbidities and improvement of quality of life as secondary endpoints. Since we today much too often meet patients who experience poor long-term weight results after bariatric surgery, and since we do not have a clear picture of the underlying mechanisms for surgery failure, treatment with GLP-1 analogues, be it liraglutide or semaglutide, or similar compounds, stand out as effective treatment with little side-effect burden, largely limited to nausea and constipation, which might be easily overcome by dose-adjustments in the clinical setting.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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