Exenatide at mealtimes in type 1 diabetes—no MAG1C with exenatide, or with other glucagon-like peptide-1 receptor agonists

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In type 1 and 2 diabetes mellitus, reduced insulin secretion, insulin action, or the combination lead to chronic hyperglycaemia, and this is characterised by failure of the eyes, kidneys, nerves, and cardiovascular system. In type 1 diabetes mellitus (T1DM), the lack of insulin secretion is due to cellular-mediated autoimmune destruction of the pancreatic β-cells. This is accompanied by an increased secretion of glucagon from the pancreatic α-cells which releases glucose from the liver. Lowering this could reduce hyperglycaemia (1). With a reduction or no insulin secretion in T1DM, the logical treatment is to replace the insulin. However, despite insulin replacement therapy in T1DM, the incidence and prevalence of cardiovascular disease is still raised, and this includes myocardial infarction, coronary revascularisation, death from coronary heart disease or stroke, non-fatal stroke, and peripheral vascular disease (2). Damage to the kidney (2), eye (3) and peripheral nervous system (4) in T1DM is also associated with the increase in cardiovascular/microvascular disease.

Hypoglycaemia episodes limit the use of insulin replacement therapy in T1DM. These episodes are more common with intense/higher than with conventional/lower doses of insulin. However, if the lower doses of insulin are used to prevent hypoglycaemia there is poor glycaemic control (5). Weight gain is another factor limiting insulin replacement therapy use in T1DM. This is increasingly being observed and may increase cardiovascular risk (6).

Consequently, the search for better treatments for T1DM continues. Adjunct therapy to insulin is one approach to improve glycaemic control and prevent the use of high doses of insulin prior to meals, which are responsible for the excessive hypoglycaemia. Adjunct therapy is used to reduce insulin dose and the consequent weight gain. In T1DM, a group of drugs being tested as adjuncts to insulin are the glucagon-like peptide-1 receptor (GLP-1R) agonists such as exenatide. With a meal, the intestinal hormone glucagon-like peptide 1 (GLP-1) is secreted, which in turn increases glucose-mediated insulin secretion and suppresses glucagon secretion from the pancreatic α-cells to reduce glucose levels. In addition, GLP-1 inhibits gastric emptying and reduces appetite. These actions of GLP-1, especially augmenting insulin secretion, may make the GLP-1R agonists beneficial in the treatment of T2DM. Although the GLP-1R agonists liraglutide (7) and semaglutide (8) have been shown to reduced cardiovascular outcomes in T2DM, exenatide has not.

There are some major limitations when considering using GLP-1R agonists in T1DM. Firstly, with the pancreatic β-cells are failing, as in the progression to T1DM, the GLP-1R agonists may be able to increase insulin secretion, but when they stop functioning, as in established T1DM, the GLP-1R agonists cannot increase insulin secretion. Secondly, although suppression of glucagon secretion is a physiologic response to GLP-1, it is not a consistent finding that the GLP-1R agonists suppress glucagon secretion in T1DM (9).

The MAG1C clinical trial (Meal-time Administration of Exenatide for Glycaemic Control in Type 1 Diabetic Cases) was started in December 2016 and completed in June 2019 (10). Prior to the start of MAG1C, only small benefits had

been shown by adding short-acting exenatide to insulin in T1DM in the two studies undertaken. The first trial was an open-label crossover study of a small number of subjects (20 subjects) with long-standing T1DM, 17 of the subjects had some remaining pancreatic β-cell function and the potential to secrete insulin. ln these subjects, treatment with exenatide for four months led to a reduction in body weight (4.1 kg) and decreased the use of injected insulin without increasing β-cell function/insulin secretion. In this study, exenatide also delayed gastric emptying, but had no effect on fasting glucagon levels. This combination of effects with exenatide led to a maintenance of glucose control with an HbA1c of 6.5% (11). The second trial was an open-label study in 18 subjects with new-onset T1DM and investigated the effect of exenatide, sitagliptin, or no addition to insulin on β-cell function. This was a pre- post- study, and after one year, it showed that exenatide added to injected insulin in six of the subjects, prevented insulin-induced weight gain and reduced the daily dose of insulin, without altering insulin secretion/β-cell function. However, the reduction in HbA1c was the same in the insulin-treated group and the insulin plus exenatide group. In this trial, exenatide did not change the incidence of severe hypoglycaemia and there was no ketosis (12).

MAG1C was a randomised, double-blind, placebo-controlled clinical trial of mealtime exenatide in T1DM subjects taking insulin. Eighty-five percent of the funding came from AstraZeneca, the producer of the short-acting exenatide. To be enrolled subjects also had to have a BMI >22 kg/m^2 and HbA1c in the range 7.5–10%. Exclusions included hypoglycemic unawareness, diabetic gastroparesis and impaired kidney function. Many of the assessed subjects (498 of 654) declined the invitation or did not answer, leaving only a small number of participants (108 participants), and three of these were excluded from analysis as they probably had T2DM. The participants had a mean age of ~50 years, HbA1c of ~8.3% and BMI of ~28.3 kg/m^2. Participants were randomized to short-acting exenatide (5 μg escalated to 10 μg after 2 weeks, subcutaneously) or placebo before breakfast, lunch and dinner. Side effects caused 10 of the subjects taking exenatide to discontinue its use, compared to none in the placebo group (13).

The primary endpoint of MAG1C was the between-group differences in HbA1c levels, and at 26 weeks, this was small at –0.1% between the exenatide and placebo group, and not significantly different. Secondary endpoints included measures related to glucose levels (e.g., fasting glucose, postprandial glycemic excursions, time in

hyperglycemia) and showed no difference between groups at 26 weeks. Exenatide significantly reduced body weight by 4.4 kg, and total insulin requirements by 9.0 units/day. This reduction in insulin was due to reductions in prandial insulin dose, with no change in baseline insulin doses. Exenatide treatment had no effect on glucagon levels. The incidence of gastrointestinal adverse effects (nausea, vomiting, and acid reflux or heartburn) was higher with exenatide than placebo (13).

The authors concluded from MAG1C that short-acting exenatide did not seem to have a future as a standard add-on treatment to insulin therapy in T1DM, mainly because it did not decrease HbA1c (13). It seems to me, that the GLP-1R agonists had no future in T1DM, could have been a possible conclusion before and during the MAG1C trial (9). Thus, prior to MAG1C, it was known that despite exenatide reducing body weight and the dose of insulin required in T1DM, but there was no evidence that this improved glucose control, and the results of MAG1C do not change these findings. Also, prior to MAG1C, there was no conclusive evidence that exenatide suppressed glucagon levels, and this was confirmed in MAG1C. Probably, the most significant new finding of MAG1C was that the gastrointestinal adverse effects of exenatide led to high levels of discontinuation.

Does the finding of no future with exenatide extend to other GLP-1R agonists? Probably. The GLP-1R agonist liraglutide has also been studied in T1DM. Small clinical trials of liraglutide in obese subjects with T1DM have shown reductions in HbA1c and body weight (14,15). However, in larger phase 3 clinical trials, ADJUNCT ONE and ADJUNCT TWO, in addition to decreasing HbA1c and body weight, liraglutide also increased symptomatic hypoglycaemia and hypoglycemia with ketosis (16,17). Due to these findings, Novo Nordisk decided not to apply to expand the use of liraglutide to T1DM (9). Other GLP-1R agonists include albiglutide, dulaglutide and semaglutide. Albiglutide has been compared to placebo in a phase 2 trial of 89 subjects with newly diagnosed T1DM. After 52 weeks of treatment with albiglutide, there was no change in body weight, insulin use, or HbA1c, but there was an excess of gastrointestinal adverse effects (18). Although a small trial has shown that dulaglutide decreased HbA1c and BMI in T1DM, it also increased gastrointestinal adverse effects (19). Thus, albiglutide and dulaglutide are also GLP-1R agonists not likely to be useful in T1DM. To my knowledge, the GLP-1R agonist semaglutide has not been tested in T1DM to date and given the disappointing results with the other

GLP-1R, such testing seems inappropriate. In conclusion, in T1DM, exenatide and other GLP-1R agonists may improve some aspects of glycaemic control (e.g., HbA1c and body weight), but they may also have detrimental effects on other aspects of glycaemic control (hypoglycaemia, hyperglycemia with ketosis), and they all have adverse effects on the gastrointestinal tract. Consequently, GLP-1R agonists should probably no longer be considered for T1DM.

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Footnote

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