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Longstanding insulin dependent diabetics may not require insulin after the introduction of GLP-1 analogues

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Abstract

Glucagon like peptide (GLP-1) analogues are a relatively novel medication developed primarily for the treatment of type 2 diabetes since 2005. Although GLP-1 analogues have been shown to be more effective in the first few years of diagnosis in type 2 diabetes, we report a case of a patient with longstanding insulin-dependent diabetes started on a GLP-1 analogue, liraglutide, who now has controlled blood sugars without the need of insulin.

Keywords

Obesity, type 2 diabetes, GLP-1 analogues, GLP-1, insulin-dependent diabetes

Case report

A 41-year–old female with insulin-dependent diabetes since 1993 was seen in a tertiary diabetes clinic in 2009 for increasing weight gain and poor glycaemic control. She was diagnosed with type 1 diabetes in 1993 aged 23 after presenting to hospital with symptoms of polyuria and polydipsia. From the clinic letters she was initially commenced on glibenclamide (sulphonylurea) for a few months, unsuccessfully, before being switched to insulin; however, according to the patient she was commenced on insulin straight away. She was diagnosed with a suprasellar teratoma in 1978 requiring surgical removal followed by 40 fractions of radiotherapy leaving her with pan-hypopituitarism. Her other co-morbidities included inflammatory bowel disease, renal amyloidosis and hepatic adenoma. Her medications included lisinopril, desmopressin, hydrocortisone, oral contraceptive pills, levothyroxine and growth hormone.

In the clinic, she weighed 129 kg with a BMI of 45 kg/m^2 and HbA1c of 9.7% (83 mmol/mol). *She had no obvious signs of insulin resistance such as acanthosis nigricans*. She was on humalog, 16 units three times a day, and glargine 10 units nocte. The main reason for the referral was weight gain. Her options of treatment were limited. Previously, the patient had responded well to rimonobant but this was subsequently suspended by the European Medicines Agency. Orlistat was contraindicated due to inflammatory bowel disease. Sibutramine was also contraindicated due to a history of proteinuria and hypertension and it was also withdrawn from the market due to safety concerns. In light of the published evidence, liraglutide was considered an option for weight management but it was felt that it may not influence her diabetes due to the longstanding history which also highly suggests she has type 1 diabetes. Bariatric surgery was discussed but the patient was not keen on this option. With the patient understanding the implications and the side effects of liraglutide outside its license indication, she was initiated on a combination of insulin and liraglutide.

Four months after treatment, she showed a dramatic improvement with weight loss of 11 kg and HbA1c dropping to 7% (53 mmol/mol). Humalog was stopped completely and the dose of glargine was gradually reduced to four units once a day. One year after starting liraglutide, her HbA1c dropped further to 6.7% (50 mmol/mol) and in view of her history of recurrent hypoglycaemia, glargine was stopped completely. Her latest review has shown a good therapeutic response to a liraglutide-only regime with her weight reduced to

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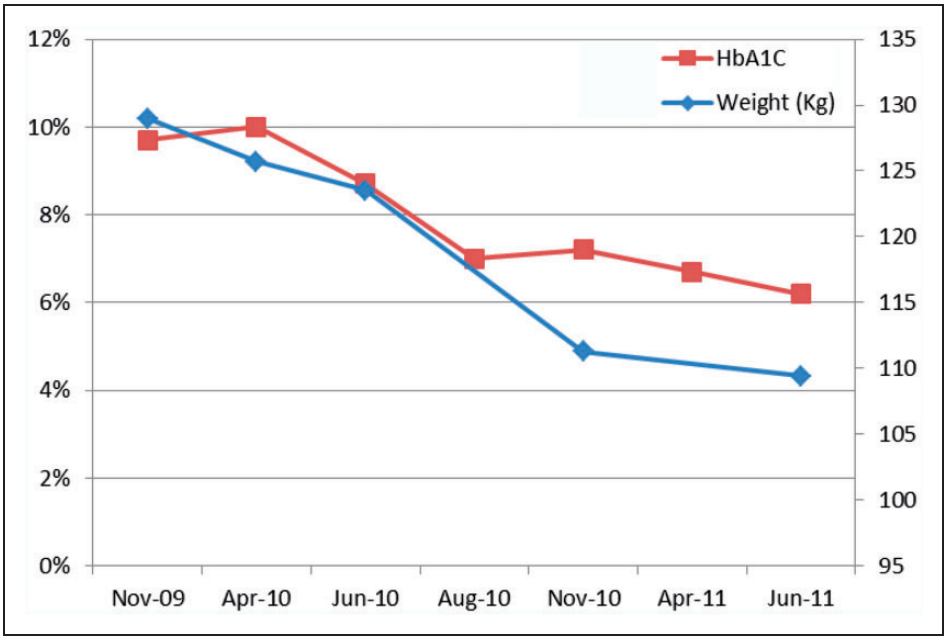

Figure 1. Graph showing improvement in HbA1c and weight with introduction of liraglutide.

109.4 kg (BMI 37 kg/m^2) and HbA1c of 6.2% (44 mmol/mol) (Figure 1).

Discussion

The current role of GLP-1 analogues is as a third add-on therapy in type 2 diabetes patients in whom insulin would have occupational implications and with a BMI $\geq$ 35.[1,2]

GLP-1 analogues work by stimulating beta cells in the pancreas to secrete insulin whilst simultaneously inhibiting glucagon secretion leading to a reduction in postprandial glucose excursion. Inhibition of glucagon secretion is both through the paracrine action of insulin as well as direct inhibition of glucagon secreting alpha cells.[3] In addition, GLP-1 analogues have been shown to cause weight loss by delaying gastric emptying and promoting satiety as well as by acting centrally on the hypothalamus appetite centre.[4]

Only in the last few years has it been suggested that liraglutide can be used as a combination therapy with insulin in type 2 diabetes. At the World Diabetes Congress 2013, a multinational randomised controlled trial showed that a fixed-ration combination of liraglutide and insulin degludec improves glycaemic control in type 2 diabetes patient inadequately controlled on basal insulin.[5] Another observational study in Japan (2013) found that type 2 diabetes patients who switched from insulin to liraglutide achieved improvement in HbA1c levels albeit less significant compared to drug naïve patients or those previously on oral hypoglycaemic agents. It also characterised insulin-dependent type 2 diabetes patients who responded to liraglutide, had higher C-peptide immunoreactivity levels, younger age and lower daily insulin requirement.[6] Indeed, there are a number of studies now that have illustrated benefit in treating type 2 diabetes or even to delay insulin use.[7]

However, to date, only one published observational study shows that the usage of liraglutide as an additional therapy for type 1 diabetic patients helps improve glycaemic control, reduction in insulin requirement and weight loss at 24 weeks[8]—but this study sample had well controlled type 1 diabetes.[8] There are also some studies of varying methodological quality illustrating GLP-1 analogues more generally leading to significant changes in insulin dose, reduction of blood glucose variations and a reduction in glucagon—but based on the current data, there is a need to carry out large randomised-controlled trials.[9] Indeed to this end, a randomised, double-blind, placebo controlled trial is currently underway in Denmark to look at the effect of liraglutide as an additional treatment to insulin on HbA1c, weight and hypoglycaemia in poorly controlled type 1 diabetes. It is due to finish in 2015.[10]

Although according to the clinical letters, our patient was diagnosed with type 1 diabetes, there was no confirmation with autoantibody tests. Nevertheless, the history of early initiation of insulin highly suggests that her diabetes is of type 1. Our case is the first to demonstrate that liraglutide, initially as a combination therapy with insulin, at one year has not only helped achieve 20 kg weight loss but it has also achieved optimal glycaemic control to the extent that a patient who

was previously on insulin for more than 20 years does not need any insulin now. We thus look in earnest to future developments in this regard.

Ethical approval

None

Guarantor

WH is the guarantor for this paper

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Declaration of Conflicting Interests

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Contributorship

All authors contributed equally

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