

Combining SGLT2 inhibitor and GLP-1 agonist: exaggerated weight loss in a morbidly obese patient with type 2 diabetes

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Introduction

Obesity and type 2 diabetes are commonly seen together in current clinical practice. Morbid obesity and poorly controlled diabetes is often a therapeutic challenge. Management ideally needs to target insulin resistance and hormonal control mechanisms. When subcutaneous insulin is used in patients with obesity and type 2 diabetes, it exacerbates weight gain and thus a vicious cycle of worsening insulin resistance requires additional management strategies.

We report a case of exaggerated weight reduction with combination therapy of liraglutide and dapagliflozin. The patient achieved a loss in excess body weight (EBW) of 73.5 kg or 40.3% and a reduction in HbA_{1c} from 83 mmol/mol (9.7%) to 36 mmol/mol (5.4%) in response to the combination therapy of oral dapagliflozin with subcutaneous liraglutide and concurrent discontinuation of subcutaneous insulin.

Key words: morbidly obese, weight reduction, SGLT2 inhibitor, GLP-1 agonist

Background

To date there are limited published data on the effectiveness of a combination of an SGLT2 inhibitor with GLP-1 agonist therapy in glucose lowering and weight reduction in type 2 diabetes.¹ Both SGLT2 inhibitors and GLP-1 agonists have marked heterogeneity of response for both glucose and weight reduction, with some patients exhibiting a hyper-responder response.² This case highlights the potential benefit of this combination in patients with type 2 diabetes and morbid obesity and suggests a new strategy for medical therapy to achieve marked weight loss and improve glycaemic control.

Case report

A 52-year-old man was referred for specialist opinion on man-

Table 1 Improvements in clinical parameters over 1 year

Clinical parameter	Baseline	Changes at 1 year
Weight, kg	209.5	-73.5
BMI, kg/m ²	61.2	-21.5
EBW, kg	124	-50 (loss of 40.3% EBW)
Blood pressure, mmHg	225/110	-34/19
HbA _{1c} , mmol/mol (%)	83 (9.7%)	-47 (-4.3%)
Obstructive sleep apnoea symptoms	Present	Absent

BMI, body mass index; EBW, excess body weight.

aging insulin-dependent diabetes. Diabetes was diagnosed 20 years previously following an episode of possible ketoacidosis and significant weight loss and treated with subcutaneous insulin. He weighed 209.5 kg (124 kg EBW) with a body mass index (BMI) of 61.2 kg/m². He reported lifelong problems with being overweight, which was exacerbated by insulin therapy. Despite biphasic isophane insulin 50 units twice daily and metformin, he had poor glycaemic control with HbA_{1c} of 83 mmol/mol (9.7%) and complications of pre-proliferative retinopathy and peripheral neuropathy. His urine ketones were negative, as were anti-GAD and anti-islet cell antibodies. His C-peptide level was normal at 3.17 µg/L. He had normal renal biochemistry with serum creatinine of 71 mmol/L. Severe hypertension was evident at 225/110 mmHg, and clinical evidence of obstructive sleep apnoea and clinical signs of insulin resistance including skin tags at the posterior neck were observed.

In the presence of a clinical and biochemical phenotype of type 2 diabetes rather than type 1, his insulin was initially reduced to 30 units. Due to gastrointestinal side-effects, immediate release metformin was switched to modified release metformin and over a period of months the insulin was withdrawn. Dapagliflozin 10 mg once daily with subcutaneous liraglutide titrated up to 1.8 mg once daily were commenced in addition to antihypertensive drugs.

Glycaemic control markedly improved to an HbA_{1c} value of 54 mmol/mol (8.7%) at 3 months, 43 mmol/mol (7.1%) at 6 months and 36 mmol/mol (5.4%) after 1 year. Most strikingly, a

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remarkable 73.5 kg (40.3% EBW) weight loss was observed within 1 year of treatment, achieving a nadir of 136 kg (BMI –39.7 kg/m²) along with improvements in his blood pressure and resolution of obstructive sleep apnoea symptoms, despite his diet and physical exercise being unchanged throughout (Table 1).

Discussion

This case demonstrates the potential for inducing marked weight loss with improvements in glycaemic control through the combination of liraglutide, dapagliflozin and metformin. Our patient lost 73.5 kg of his weight or 40.3% EBW loss with the changes in medication without a significant change in his lifestyle. This degree of weight loss is usually seen following bariatric procedures. Currently available weight loss medications achieve on average a 5% EBW loss. Liraglutide is well known for weight loss benefits and weight loss maintenance.^{3–5} Clinical trials demonstrated a weight loss of 3.7–8 kg after a 2-year period of liraglutide 3 mg per day and a weight loss of 1.3–4.7 kg using 2.4 or 3.0 mg daily in respective studies.³ Weight loss benefits were evident when liraglutide was combined with metformin and a sulphonylurea.^{6,7} Dapagliflozin also aided weight loss when added to metformin in patients with poorly controlled type 2 diabetes,^{8,9} with a small cohort exhibiting excessive weight loss.¹

To our knowledge, this is the first reported case in a morbidly obese individual where the combination of GLP-1 agonists and SGLT2 was associated with marked weight loss and dramatic improvements in glycaemic control, comparable to surgical intervention.

There are limited reported data on the combination of SGLT2 inhibitors and GLP-1 agonists.¹ One report on the combination of a SGLT inhibitor with other therapies in type 2 diabetes mellitus demonstrated an improvement in weight and glycaemic control and resulted in either dose reduction or cessation of other diabetes therapies in the treated cohort.¹ Avoidance of pharmacokinetic interactions causing negligible effects on each other's plasma concentrations has been observed when SGLT2 inhibitors and other oral hypoglycaemic drugs are co-administered.¹⁰ In the absence of pharmacodynamic data on the interaction between SGLT2 inhibitors and GLP-1 agonists, we hypothesise that the two drugs may potentiate the weight loss effect when used synergistically.

Individual variations in weight loss response are known to occur with liraglutide, and genetic differences in GLP-1 receptors are considered to be associated with these responder differences.¹¹ Our patient's heightened weight loss may be partly due to individual variation in response to either of the medications as a 'hyper-responder'. However, this patient's weight loss was maximised by the discontinuation of insulin.

In the management of patients with type 2 diabetes and morbid obesity, the combination of an SGLT2 inhibitor and GLP-1 agonist provides a pharmacological option to achieve improved clinical effect and possibly avoid the need for subcutaneous insulin.

Conflict of interest None

Funding sources None.



Key messages

- Management of type 2 diabetes with morbid obesity is complex
- Combination of SGLT2 inhibitor and GLP-1 agonist in diabetes management may assist marked glucose and weight reduction in certain individuals
- Pharmacological "hyper-responders" may avoid bariatric procedures

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