Profound weight reduction with GLP-1 agonist therapy: a delayed hyper-response

Obesity is a major driver of type 2 diabetes and is therefore a key therapeutic target.[1] The weight loss effects of glucagon-like peptide 1 (GLP-1) receptor agonists are well recognised. A meta-analysis of clinical trials demonstrated an average weight loss of 2.9kg compared with controls over an observation period of 20–52 weeks.[2] We report a case of 24.4kg (26%) weight loss in a patient with type 2 diabetes associated with exenatide, a twice-daily GLP-1 receptor agonist.

The patient was a 66-year-old woman with type 2 diabetes diagnosed in 1998. Her past medical history included rheumatoid arthritis (RA), hypothyroidism, hypercholesterolaemia and asthma. At initial assessment, in 2004, treatment comprised metformin 850mg twice daily, methotrexate 10mg weekly, folic acid 5mg weekly, hydroxychloroquine 200mg twice daily, celecoxib 100mg twice daily, levothyroxine 100µg daily, atorvastatin 30mg daily, a salbutamol inhaler as required, and co-proxamol as required. Her hypothyroidism and RA were well controlled.

During the first four years of management the patient's weight increased slowly to a maximum of 94.3kg (BMI 35.5kg/m^2) in 2008. Her HbA$_{1c}$ measurements rose to a plateau level of 72.7mmol/mol (8.8%). During this period her metformin dose was increased to 500mg four times daily and gliclazide 80mg twice daily was initiated. As a result of ongoing poor glycaemic control exenatide 5µg by subcutaneous injection twice daily was started in February 2008 and increased to 10µg twice daily after one month.

Over the first year following initiation of exenatide there was a reduction in HbA$_{1c}$ to 50mmol/mol (6.7%) with slight weight reduction (-1.9kg; -2%). Subsequently there was substantial weight loss (-24.4kg; -26%) to a BMI of 26.3kg/m^2 and the patient achieved normoglycaemia. Exenatide was discontinued in May 2011 although she remained on metformin and gliclazide. She has experienced a gradual weight increase since, but still remains considerably lower than her pre-treatment weight (Figure 1). Additionally, she did not require further anti-inflammatory drugs for her arthritis. No other cause of her observed weight loss was identified. The patient reported reduced appetite while on exenatide which returned following cessation of treatment.

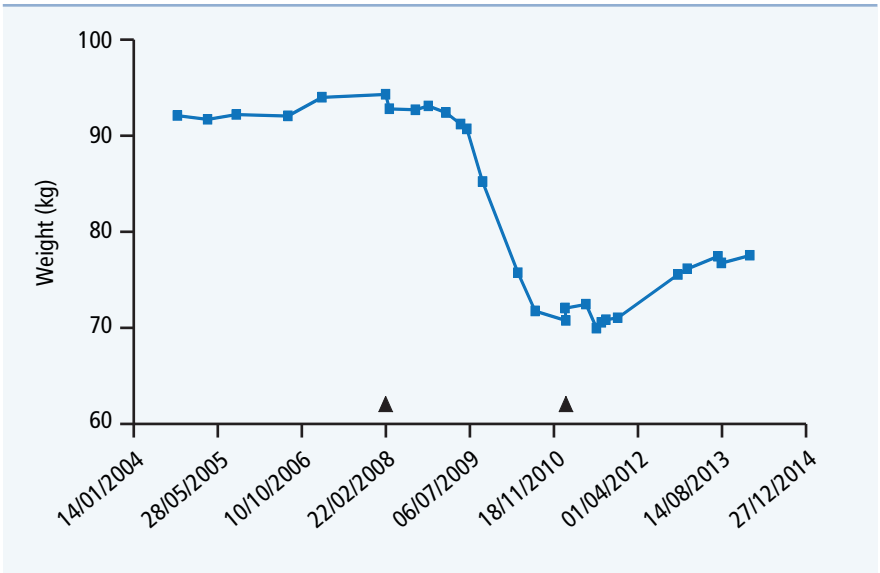

Figure 1. The measured weights over time of a patient treated with exenatide. The start and stop dates of exenatide are indicated with black triangles

This profound weight loss is substantially greater than reported in clinical trials of GLP-1 receptor agonists and is comparable to that achieved with bariatric surgery.[3] Only a few similar cases have been reported;[4,5] however, weight loss was immediate in these cases. We suggest there is a therapeutic subgroup of patients who are hyper-responsive to GLP-1 receptor agonists. Some guidelines recommend a minimum six-month trial of non-surgical interventions prior to recommending surgical treatment.[6] The delayed response seen in our patient might also indicate that a longer trial period of medical management is suitable in some instances.

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