Commencing insulin in the obese person with type 2 diabetes and how to limit weight gain

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Treating type 2 diabetes is becoming ever increasingly complex with multiple factors to consider when individualising care. The weight of the individual and the impact of potential weight gain from commencing insulin is one of those considerations. This makes the decision to commence insulin when diabetes is complicated with obesity a difficult one. Starting insulin in this situation is often associated with a steady and continual weight gain, with the achievement of adequate blood glucose levels often illusive (UK Prospective Diabetes Study Research Group, 1998).

All too often, both the healthcare professional and the patient become disillusioned and frustrated with a lack of progress towards target blood glucose levels accompanied by increasing weight. Insulin itself drives hunger and the storage of fat, and, once insulin treatment has been started, treating hypos or eating to avoid hypos may also cause weight gain in a person who fears them. Steady weight gain leads to increasing insulin resistance, and this in turn leads to further insulin need and further weight gain. It is not surprising, therefore, that starting insulin in the obese individual is often delayed or avoided for many years by both patients and healthcare professionals alike. The aim of treatment, therefore, must be to target both insulin deficiency and insulin resistance together.

In addition to the continual reinforcement of diet and lifestyle issues, which cannot be underestimated at the point of insulin initiation, there is an ever-increasing choice of medications for type 2 diabetes. We need to consider how to use these medicines to their best advantage, to delay the need for insulin or to limit the total daily insulin need, thereby, limiting or preventing weight gain when starting insulin in these complex individuals. The potential benefits of using combination therapy to improve the multifaceted face of type 2 diabetes and obesity allows us to use the minimum amount of insulin necessary to achieve target glucose levels.

Choosing the insulin regimen

When deciding on an insulin regimen, thought has to be given to the action profiles of different insulin options. It is common practice in insulin-naive people to start with an intermediate-acting insulin such as Insulatard®, Humulin® I or Insuman® Basal in addition to oral therapies. In some cases where the individual has an HbA_{1c} ≥9% (75 mmol/mol [NICE, 2009]), a "pre-mixed" insulin can be started (e.g. Humulin® M3, Insuman® Comb 15, Insuman® Comb 25 and Insuman® Comb 50). Pre-mixed insulins have a defined peak or peaks in their action profile and often require a snack to be eaten prior to bed or even between meals. The need for additional snacking for insulin-naive individuals is clearly disadvantageous and leads to unnecessary weight gain when commencing insulin therapy; this is obviously not desirable for those for whom obesity is an issue.

Newer background insulins (e.g. Lantus® [insulin glargine]; Levemir® [insulin determir] and Tresiba® [insulin degludec]) have flatter action profiles, which minimise the need to supplement with snacks, and there is evidence of a reduced incidence of hypoglycaemia and limited weight gain (Meneghini et al, 2007; Ratner et al, 2013). It could, therefore, be argued that choosing insulins that offer a reduced need for snacks and have a reduced hypoglycaemia risk should be the first consideration for individuals who are obese. The use of these insulins in addition to therapies that target insulin resistance and have either insulin-sparing or weight-loss properties has to be the therapeutic goal for obese people with type 2 diabetes.

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Anti-diabetes medicines

Metformin is well recognised as the first-line treatment for type 2 diabetes. It targets insulin resistance, is weight neutral and does not induce hypoglycaemia. Therefore, it would be continued as a therapy when insulin is added to the regimen. If renal function is declining, the dose of metformin becomes a consideration: it is recommended that metformin be stopped if estimated glomerular filtration rate (eGFR) reduces to less than 30 mL/min/1.73 m^2 (NICE, 2009).

Dipeptidyl peptidase-4 inhibitors

The dipeptidyl peptidase-4 (DPP-4) inhibitor drug class (which includes alogliptin, linagliptin, saxagliptin, sitagliptin and vildagliptin) inhibits the breakdown of endogenous incretin hormones such as glucagon-like peptide-1 (GLP-1). In inhibiting its breakdown, the benefits of GLP-1 last for longer (potentiating insulin secretion and reducing glucagon secretion in a glucose-dependent manner [Day and Bailey, 2015]). Although the DPP-4 inhibitor class is associated with weight neutrality, there is evidence that it can delay the need for insulin therapy for up to 2 years (Blonde et al, 2014). As such, commencing this class early in the treatment pathway for people with both type 2 diabetes and obesity must be a consideration with the long-term view of delaying the need for insulin.

This class of medication is also associated with insulin-sparing properties (Vora, 2013). By limiting the total amount of insulin needed, weight gain can be limited or eliminated altogether. This is an important factor to be considered when adding insulin to the medication regimens of obese people. All too often, in my clinical experience, this medication is stopped when insulin is added to a regimen and the benefits it offers are lost.

GLP-1 receptor agonists

The use of a GLP-1 receptor agonist with insulin is another useful combination. GLP-1 receptor agonists reduce HbA_{1c} with the additional benefit of weight loss. In this class, exenatide twice daily, liraglutide, lixisenatide, albiglutide and dulaglutide have a licence for combination with insulin (electronic Medicines Compendium [eMC], 2015a; eMC, 2015b; eMC, 2014a; eMC, 2014b; European Medicines Agency, 2014; eMC, 2015c; respectively). These injectable agents work in multiple ways: firstly, slowing gastric motility, thereby increasing the feeling of fullness; secondly, stimulating insulin release in a glucose-dependent fashion; thirdly, decreasing glucagon release and, thereby, decreasing glucose release from the liver; and, finally, acting directly on the satiety centre in the brain. This direct effect on satiety leads to the weight-loss properties of this class of medication (Drucker and Nauck, 2006). The combination of a GLP-1 receptor agonist with insulin is a powerful approach to achieving both a reduction in glucose levels and weight in people with type 2 diabetes (Holst and Vilsbøll, 2013). Recently, a single-injection combination of basal insulin and a GLP-1 receptor agonist (IDegLira) has been launched in the UK (eMC, 2014c), and more insulin–GLP-1 receptor agonist combinations are in development (e.g. insulin glargine with lixisenatide – LixiLan [Rosenstock et al, 2014a]). These fixed-dose combinations offer the convenience of combining two injections into one, and this has to be a consideration for individuals who are often on multiple therapies and for whom adherence is an issue (García-Pérez et al, 2013).

Sodium–glucose cotransporter 2 inhibitors

The latest oral therapy class for type 2 diabetes is the sodium–glucose cotransporter 2 (SGLT2) inhibitors. There are currently three medications in this class (canagliflozin, dapagliflozin and empagliflozin) with more to be launched in the near future. The SGLT2 inhibitor works directly on the kidney to inhibit glucose reabsorption, which causes glucose, and thus calories, to be eliminated from the body through the urine.

This glucose loss results in a weight loss of around 2–3 kg (Day and Bailey, 2015). For optimal efficacy, adequate kidney function is paramount, and so commencement at maximal dosage requires eGFR to be greater than 60 mL/min/1.73m^2 (Lee et al, 2007). With their mode of action being completely insulin independent, the SGLT2 inhibitors have demonstrated good efficacy across all combinations of drug class: from use as an add-on to metformin, to use in combination with insulin. Studies have shown that SGLT2 inhibitors in combination with insulin can reduce weight gain (Wilding et al, 2012; Rosenstock et

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al, 2014b; Neal et al, 2015) and stabilise insulin dosage (Wilding et al, 2012).

The priority

Newer therapies with weight neutral or weight loss properties offer an additional dimension in primary care to tackle the issue of weight gain in obese individuals who require insulin therapy. Treating both an insulin deficit and insulin resistance has to be the primary consideration when commencing insulin, and in essence, early use of therapies that have an evidence base for delaying insulin initiation must, in my view, be a priority. When initiating insulin therapy in people who are obese, a combination of therapies to limit or negate weight gain or, indeed, effect weight reduction is a major advantage available in today's clinical practice. ■

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