Insulin therapy for the diabese population: How can we use it most effectively?

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Never before have we faced such an enormous health and economic problem in managing obesity and diabetes in the UK and worldwide. As weight management is now thought to be equally as important as glycaemic control for the care of people with diabetes, several new classes of drugs are now in use and in development to induce weight loss and improve glycaemic control. However, there will always be a significant proportion of our patients with diabetes who will need insulin to improve their glycaemic control. Both healthcare professionals and patients alike are known to delay initiation of insulin, and one of the reasons for this is the concern about weight gain.

Type 2 diabetes is a progressive condition and is characterised by a relentless decline in beta-cell function and a worsening of insulin resistance (Fonseca, 2009). At some stage in the natural history of type 2 diabetes, insulin secretion from beta cells will become inadequate, and people with diabetes who have poor beta-cell reserve will need insulin to improve their glycaemic control.

Insulin physiology

Insulin is an anabolic hormone produced by the beta-cells of the pancreas and is secreted into the portal vein. Insulin secretion varies whether the body is in a fed state or a fasting state. In the fed state, consumed carbohydrates increase plasma glucose and promote insulin secretion from the beta-cells of the pancreas. Following secretion in the fed state, insulin promotes glycogen synthesis in skeletal muscle and liver, promotes lipogenesis in the liver and adipose tissue and suppresses the breakdown of fat (lipolysis) in the adipose tissue. In the fasted state, insulin secretion is decreased, and as a result there is increased liver glucose production. There is also reduced lipid production in the liver and increased breakdown of lipids in adipose tissue (Samuel and Shulman, 2012).

Insulin release from the beta-cells of the pancreas is a biphasic process (Curry et al, 1968). The first phase of insulin secretion is released upon food consumption and is dependent on the amount of insulin in store. The first phase insulin secretion lasts for about 13 minutes (Del Prato, 2003). Once the initial insulin stores are depleted, a second phase of insulin release is initiated, which results in a plateau over the subsequent 2–3 hours (Gerich, 2002). The second phase compared to the first phase is longer as insulin needs to be synthesised, processed and secreted for the duration of increased blood glucose (Cartailler, 2015).

Approximately, 50% of the insulin secreted by the pancreas into the portal system is removed during its initial passage through the liver, which leads to approximately three times greater a concentration of insulin in the portal vein compared with a peripheral vein (Scheen, 2004). In people without diabetes or metabolic syndrome, pancreatic insulin secretion in the fasting (or basal) state varies from 0.25 to 1.5 units per hour, and this basal secretion accounts for over 50% of the total insulin secretion over 24 hours (Wilcox, 2005). Basal insulin secretion is, therefore, crucial for blood glucose control (Pørksen, 2002).

Now that we know how insulin is secreted and how it acts on various organs and alters metabolism in the fasted and fed state, do we have an insulin or delivery system which can mimic this? Currently we have not yet mastered the technique of delivering insulin to produce optimal benefits, while at the same time ensuring that excessive insulin is not administered.

Insulin and weight gain

Weight gain appears unavoidable when people with type 2 diabetes are commenced on insulin. During the first year of insulin therapy, there is on average a 5 kg gain in body weight for every 5 mmol/L decrease in fasting glucose or 2.5% (27.3 mmol/mol) drop in HbA_{1c}

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(Makimattila et al, 1999). In fact, research from the UKPDS (UK Prospective Diabetes Study) showed that the average person with type 2 diabetes gains about 4 kg in their first 3 years of insulin use (UKPDS Research Group, 1998). Weight gain mainly represents an increase in fat mass, which enhances insulin resistance and increases the risk of obesity-related complications. There are also several other causes of weight gain associated with insulin use:

- Reduced glycosuria (Russell-Jones and Khan, 2007).
- Anabolic action of insulin (Russell-Jones and Khan, 2007).
- Fluid retention (Dorkhan et al, 2009).
- Hypoglycaemia and increased calorie consumption in defensive eating from the fear of hypoglycaemia (Russell-Jones and Khan, 2007).
- Excess insulin administration (Russell-Jones and Khan, 2007).
- Combination of obesity and muscle impairment – "sarcopenic obesity" (Srikanthan et al, 2010).

Excessive weight gain with insulin therapy should be avoided, and there are several ways this can be achieved:

- Change in lifestyle.
- Education and prevention of hypoglycaemia.
- Ensuring optimal use of newer medications for diabetes.

There are three articles in this issue of *Diabesity in Practice* that further explain the details of the management of diabesity in relation to insulin use. On page 47, Su Down explains the importance of selecting the most appropriate insulin at initiation. She stresses that, in addition to the use of appropriate insulins, therapies that target insulin resistance and have either insulin-sparing or weight-loss properties should be incorporated in the management of obese people with type 2 diabetes. On page 51, David Strain discusses the association between hypoglycaemia and weight gain. Interestingly, in this article they discuss the relationship between hyperphagia following a single episode of hypoglycaemia and the effect of eating following recurrent hypoglycaemia.

Finally on page 55, Billy Law's article reviews evidence related to weight outcomes in obese adults with type 2 diabetes on insulin therapy. From the available evidence, suggestions are made for mitigating weight gain, and even inducing weight loss, in this ever-growing population.

One of the major barriers to insulin initiation and therapy for people with type 2 diabetes is the fear of weight gain among both healthcare professionals and patients. Current insulin regimens and delivery devices do not mimic natural insulin secretion and action. We need to wait and see if closed-loop insulin pumps, oral insulins or insulin patches can mimic natural insulin secretion and action. Until then, we will need to adopt the measures elicited in the comment and article published in this issue of the journal. ■

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