Hypoglycaemia and obesity: Coexistent complications or causal link

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Insulin and sulphonylurea therapies for type 2 diabetes are very effective and well established in the management of hyperglycaemia; however, their use is complicated by the side effects of hypoglycaemia and weight gain. While not affecting everyone, these side effects tend to coexist in many individuals suggesting there may be a codependency or even a shared aetiopathogenic mechanism. The potential mechanisms associating these two very common side effects of traditional diabetes treatments will be reviewed.

Traditional insulin-based therapies are well-established in the management of diabetic hyperglycaemia in type 2 diabetes. However, two major side effects limit acceptance of, and compliance with, such therapies: an increased incidence of hypoglycaemia and frequent weight gain that continues over several years. Weight gain as a result of insulin therapy is a consistent finding of major trials (The Diabetes Control and Complications Trial Research Group, 1993; UK Prospective Diabetes Study Group, 1998) and is often greater than that seen with other treatment regimens. Such weight gain may not only act as a barrier to patient compliance but may, to some extent, also oppose the beneficial health consequences of improved glycaemic control. Indeed, every BMI unit increase is associated with an increased cardiovascular risk of 9.1% for men and 15.6% for women (Anderson and Konz, 2001).

Several explanations for the mechanism by which insulin and sulphonylureas cause weight gain have been suggested, including alteration of physical activity level, the anabolic and/or lipogenic actions of insulin, decreased glycosuria or the absence of hepatic suppression of glucose production due to relatively low insulin in the portal system, and chronic and postprandial elevations in glucagon-stimulated hepatic gluconeogenesis (Torbay et al, 1985; Carlson and Campbell, 1993; The Diabetes Control and Complications Trial Research Group, 1993; Bagg et al, 2001; Heller, 2008). Moreover, the link between insulin therapy and increased weight appears somewhat paradoxical given the well-established anorectic action of insulin on hypothalamically mediated feeding responses. Recently, however, there has been an increasing focus on the observed intra-individual association between frequency of hypoglycaemia and weight gain. The ACCORD (Action to Control Cardiovascular Risk in Diabetes [2008]) study demonstrated an association between weight gain and hypoglycaemia, such that those at highest risk of developing hypoglycaemia also put on the most weight. This may simply be confounding of those who required the greatest doses of insulin, sulphonylurea therapy and glinides in order to achieve the tight glycaemic targets set; however, there are several potential mechanisms that could explain or suggest a direct causal association.

Fear of hypoglycaemia

Hypoglycaemia is one of the most feared side effects of the management of diabetes. Although many clinical trials use strict biochemical criteria for the diagnosis of hypoglycaemia, health-related quality of life (HRQoL) is not significantly associated with objectively determined hypoglycaemia but is substantially attenuated with subjective reporting of hypoglycaemia (Gilet et al, 2012). Indeed, this association between subjectively reported symptoms and reduced quality of life, results in severe hypoglycaemia being feared more than the risk of going blind, and minor hypoglycaemia being feared as much as renal failure (Pramming et al, 1991). This is, in part, due to the tangibility of experiencing hypoglycaemia; once a person has experienced the lack of control associated with a severe or even minor attack, they will take any steps to avoid further hypoglycaemia leading to excessive "prophylactic" calorie intake, termed defensive eating. The behaviour adjustment in some cases

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produces a permanent lifestyle modification that drives weight gain associated with hypoglycaemia (Cryer et al, 2003).

Learned versus physiological response

The learned response to hypoglycaemia

A murine model comparing insulin-treated animals with diabetes with and without recurrent hypoglycaemia, however, suggests that the mechanism of weight gain after recurrent hypoglycaemia still occurs without any significant changes in dietary intake (McNay et al, 2013). Indeed, the hyperphagia, which is well documented after a single hypoglycaemic event, becomes attenuated after recurrent hypoglycaemia, with anorexia being observed in these animals. Clearly these animals do not exhibit the learned behavioural avoidance adaptations; however, this does support the hypothesis that the hyperphagia associated with recurrent hypoglycaemia in humans is a learned response rather than a physiological response. Thus hyperphagia can be rectified with education, and particularly with removing or reducing the hypo-stimulating medication.

The physiological response to hypoglycaemia

The physiological responses to hypoglycaemia may account for some of the weight gain. Hypoglycaemia triggers increased sympathetic, adrenal and parasympathetic outflow from the central nervous system. It subsequently increases adenohypophyseal growth hormone and adrenocorticotropin (and thus cortisol) secretion, among other pituitary hormone responses. Finally, through mechanisms that include (but are not limited to) increased autonomic activity, hypoglycaemia causes reduced pancreatic beta-cell insulin secretion and increased pancreatic beta-cell glucagon secretion. The net result of reduced insulin secretion, elevated glucagon secretion and the autonomic and pituitary activations is an increase in endogenous glucose production, and glucose utilisation by tissues other than the brain is limited, resulting in hyperphagia and calorie retention (Cryer et al, 2003). These responses can, however, only account for a small proportion of the hypoglycaemia-associated weight gain.

It has proven difficult to establish the mechanisms underlying weight gain associated with hypoglycaemia in human studies. This is due to the complex nature of potential mechanisms, the difficulty in achieving optimal experimental glycaemic control and detection of hypoglycaemia, difficulty in accurately recording food intake and motor activity, and the ethical issues in constructing control groups with potentially sub-optimal treatment regimens. The overall conclusion has been that the causes of weight gain associated with diabetes treatments and hypoglycaemia remain unclear (Heller, 2004). Until these are better understood, in my view, treatment strategies must focus on avoiding hypoglycaemia. This is apparent in the most recent guidelines, such as those from the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE), which have recommended the use of sulphonylureas and glinides only with caution, and given preference to the use of metformin, glucagon-like peptide-1 receptor agonists, dipeptidyl peptidase-4 inhibitors and sodium–glucose cotransporter 2 inhibitors, which are associated with low rates of hypoglycaemia and weight neutrality or weight loss (Garber et al, 2015).

In summary, there is a clear association between hypoglycaemia and weight gain. The exact aetiopathogenic mechanism is not clear and is likely to be multifactorial. For logistic and ethical reasons, this is unlikely to ever be fully elucidated and, therefore, the emphasis remains on avoidance of hypoglycaemia with concomitant weight neutrality. ■

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