Hypoglycaemia in Type 2 Diabetes

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Abstract
Rates of hypoglycaemia in those with Type 2 diabetes newly started on insulin are less than in Type 1 diabetes but rise with time. As insulin secretion declines, the ability to release glucagon is diminished. Adrenaline release partially compensates for deficient glucagon secretion but is vulnerable to repeated hypoglycaemia leading to diminished sympathoadrenal activation. Thus the inevitable decline in endogenous insulin, eventually produces a similar failure of physiological protection to hypoglycaemia as in Type 1 diabetes.

Introduction
Since the publication of the DCCT [1] and then the UKPDS [2] there has been pressure to achieve ever more tighter glycaemic targets in people with Type 2 diabetes. This pressure has increased further since the UKPDS published epidemiological evidence which hinted that the incidence of cardiovascular disease might also be reduced if glucose concentrations were lowered to near normal levels.[3] However, the potential risk of severe hypoglycaemia has been an important limitation preventing many patients from achieving tight glycaemic targets. Recently the ACCORD study in which the intensive group was being treated aggressively with insulin and other agents to reach an HbA1c target of 6%, was terminated prematurely because fatal events were more common compared to those receiving standard therapy. It is too early to conclude as to whether increased rates of hypoglycaemia contributed to these events but it does indicate how important it is to assess the contribution of hypoglycaemia to morbidity and perhaps mortality in people with Type 2 diabetes.

Epidemiology of hypoglycaemia in Type 2 diabetes
Clinical trials have generally reported rates of hypoglycaemia in subjects with Type 2 diabetes which are lower than in trials of those with Type 1 diabetes with comparable levels of glycaemic control. In the UKPDS [2] around 2% of patients experienced severe hypoglycaemia compared to around 30% in the DCCT. However, if patients are matched for duration of insulin treatment then rates are not very different.[4] This suggests that increasing duration of diabetes is associated with an increased risk of severe hypoglycaemia perhaps due to a progressive failure of endogenous insulin secretion. This hypothesis is supported in a recent study in which we compared rates of self reported and biochemical hypoglycaemia in different groups of patients with diabetes. We showed that patients with Type 2 diabetes recently started on insulin had rates of hypoglycaemia (both biochemical and symptomatic) which were similar to those patients who were taking sulphonylureas.[5] However, individuals with Type 2 diabetes who had been treated with insulin for over 5 years and whose endogenous insulin production as measured by stimulated C-peptide was lower, had significantly higher rates of hypoglycaemia including severe episodes. Population based studies have also indicated that severe hypoglycaemic episodes occur at rates comparable to those in Type 1 diabetes.[6] Since Type 2 diabetes is much more common than Type 1 diabetes, it is clear that in terms of absolute numbers of episodes, hypoglycaemia in Type 2 diabetes presents the clinician with a larger clinical problem.

Experimental studies of counterregulation in Type 2 diabetes
Many investigators have explored how Type 2 diabetes modifies the protective responses to hypoglycaemia that determine an individual's risk of experiencing severe episodes

during treatment. Early studies were difficult to interpret since other factors can modulate the physiological response to hypoglycaemia including age, duration of diabetes and beta-cell reserve. Meneilly et al have reported glucose thresholds for glucagon and adrenaline counterregulatory responses of 2.8mmol/l in elderly non-diabetic patients, significantly lower than a younger group where the threshold was 3.2mmol/l.[7] The same investigators have also examined adrenaline responses in elderly subjects with Type 2 diabetes and showed that adrenaline was released at a higher glycaemic threshold in elderly subjects with Type 2 diabetes compared to a non-diabetic control group of similar age.[8]
The use of different experimental models has also made it difficult to compare studies.[9] Nevertheless early work generally indicated that glucagon responses were relatively preserved in individuals with Type 2 diabetes. [10] [11] [12] This contrasted with the situation in Type 1 diabetes where glucagon responses to hypoglycaemia are diminished early after diagnosis.[13]

However, not all studies demonstrated normal responses to hypoglycaemia Bolli et al[14] explored physiological defences to hypoglycaemia using subcutaneous injections of regular insulin and reported a significant reduction in the glucagon response (although rises in adrenaline were comparable to non-diabetic individuals). More recently, Segel et al have reported that patients with insulin treated Type 2 diabetes and diminished endogenous insulin secretion had reduced glucagon responses when compared to patients on oral agents or non-diabetic controls.[15]

Endogenous insulin secretion and release of glucagon

This confirms the impression from epidemiological studies that duration of diabetes and its effect on the integrity of counterregulatory responses to hypoglycaemia may reflect a failure of endogenous insulin secretion. A number of studies have indicated that the glucagon response to hypoglycaemia is mediated by paracrine cross-talk between pancreatic alpha and beta cells.[16-19] The release of glucagon is prevented by tonic inhibition of alpha cells by local release of insulin from adjacent beta cells. During hypoglycaemia, endogenous insulin release shuts down below a glucose of 4mmol/l[20] and the fall of insulin levels within the islet leads to loss of inhibition and an appropriate secretion of glucagon. With the progressive loss of beta cells and the resulting disruption of the normal islet architecture, the release of glucagon during hypoglycaemia does not occur. Thus, the inability to secrete insulin leads to impairment of a crucial hormonal defence to hypoglycaemia.

In patients with Type 1 diabetes, reduced endogenous insulin release is associated with more erratic free insulin profiles and an increased dependence on sympathoadrenal activation as a defence against hypoglycaemia. It appears that the same pathogenic mechanisms may also develop in individuals with Type 2 diabetes.

Effect of antecedent hypoglycaemia in Type 2 diabetes

The effect of antecedent hypoglycaemia on counterregulatory responses in those with Type 2 diabetes was first reported by Peacey et al who found that one episode of hypoglycaemia appeared to have little effect on adrenaline and symptomatic responses to subsequent hypoglycaemic episodes.[21] However, other work has not confirmed these initial observations. Davis et al reported equivalent reductions in adrenaline and

symptomatic responses following antecedent hypoglycaemia as those seen in Type 1 diabetes.[22]

Korzon-Borakowska et al[23] measured physiological responses before and after a period of tightening glycaemic control and demonstrated a lowering of the glycaemic thresholds for adrenaline and symptoms and a reduced adrenaline response. It therefore seems likely that tightening control might lead to a re-setting of protective physiological responses at a lower blood glucose. Spyer et al[24] measured glucose thresholds for the physiological and symptomatic response to hypoglycaemia and demonstrated release of adrenaline and onset of symptoms at higher concentrations than non-diabetic controls.

These studies all provide evidence indicating that glycaemic thresholds for physiological defences to hypoglycaemia can vary in people with Type 2 diabetes as has also been demonstrated in Type 1 diabetes. Indeed the data show that many patients with Type 2 diabetes exhibit counterregulatory responses at glucose concentrations above 4mmol/l.. Thus it appears that the same factors which contribute to what Cryer has termed Hypoglycaemia Associated Autonomic Failure (HAAF)[25] in Type 1 diabetes also operate in Type 2 diabetes. The apparently normal physiological defences to hypoglycaemia and low risk of hypoglycaemia early after diagnosis may simply be due to relatively preserved beta cell function.

Effect of treatment on physiological responses to hypoglycaemia

The choice of treatment in Type 2 diabetes might also influence the risk of hypoglycaemia. In the UKPDS, rates of hypoglycaemia were 3 times higher in those assigned to insulin treatment compared to those taking sulphonylureas.[2] This might be solely due to direct effects of treatment with insulin therapy producing inappropriate hyperinsulinaemia and resulting hypoglycaemia. Alternatively, the treatment itself might induce differences in physiological defences to hypoglycaemia. We have tested physiological responses to hypoglycaemia during a hypoglycaemic clamp in a subset of patients with Type 2 diabetes who participated in the UKPDS and compared insulin and sulphonylurea treated groups.[26] We showed that although sweating responses were lower in those treated with insulin, there were no other significant differences in counterregulatory or symptomatic responses or glycaemic thresholds. Other experimental studies have also reported similar physiological responses to hypoglycaemia in patients taking different therapies for Type 2 diabetes.[14] In more recent work we found that patients taking sulphonylureas had a glycaemic threshold for the increase in symptoms which was set at a higher glucose level than a group of patients treated with insulin or non-diabetic controls although the glycaemic threshold for the release of adrenaline was no different.[27] There were no clear differences in rates of hypoglycaemia between the 2 groups, particularly in the day or two before these responses were tested suggesting that this difference might have been due to a specific effect of sulphonylureas. However, more work in this area is needed.

Conclusion

Patients with Type 2 diabetes are relatively protected from severe hypoglycaemia and hypoglycaemia unawareness when compared to Type 1 diabetes. These differences are most marked in those with a relatively short duration of disease. However rates of hypoglycaemia increase with increasing duration and are associated with deficiencies in

symptomatic and counterregulatory protective mechanisms. It seems likely that the inevitable decline in endogenous insulin secretion that accompanies Type 2 diabetes, eventually produces a similar vulnerability to the pathogenetic mechanisms of hypoglycaemia as those in Type 1 diabetes.

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