Hypoglycaemia in Type 2 Diabetes – Clinical Consequences and Impact on Treatment

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Abstract

For patients with diabetes, hypoglycaemia can present a number of risks ranging from mild to life-threatening in severity. Frequently occurring hypoglycaemia is associated with increased morbidity and mortality. Recent studies have found associations between intensive glycaemia treatment and an increased incidence of hypoglycaemia, prompting much discussion concerning the clinical significance of hypoglycaemia in the treatment of diabetes, especially considering that many hypoglycaemic episodes are subclinical and unrecognised. Hypoglycaemia has also been linked to an increased probability of developing dementia and, not surprisingly, poor quality of life as well. It may be helpful to try to prevent hypoglycaemic episodes through careful monitoring of patients with risk factors that predispose them to hypoglycaemia, while also selecting therapies that can minimise the incidence of hypoglycaemic episodes.

Keywords

Hypoglycaemia, type 2 diabetes, cardiovascular disease, insulin, sulphonylurea, metformin, thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors

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Hypoglycaemia is a common problem for many patients with diabetes and the risks and consequences need to be considered when prescribing therapy. Mild episodes can cause unpleasant symptoms and disrupt daily activities, while severe hypoglycaemia can result in disorientation and unusual behaviour, and may be life-threatening. Frequent hypoglycaemia, as a complication of treatment, is associated with increased morbidity and mortality, making it a limiting factor in achieving adequate glycaemic control.[1–6] In type 1 diabetes, hypoglycaemia has been recognised as a major hurdle for optimal glycaemic control for many years, with the Diabetes Control and Complications Trial (DCCT) clearly indicating an inverse relationship between lowering glycated haemoglobin (HbA_{1c}) and the occurrence of severe hypoglycaemia.[7] Therefore, the most important beneficial consequence of the introduction of insulin analogues in the treatment of patients with type 1 diabetes is not a major improvement in HbA_{1c}, but rather a reduction in occurrence of hypoglycaemia.[8]

Although less frequent, many glucose-lowering therapies used in patients with type 2 diabetes can also cause hypoglycaemia, particularly sulphonylureas and insulin. Recent results from trials including the Action to Control Cardiovascular Risk in Diabetes (ACCORD) and the Veterans Affairs Diabetes Trial (VADT) have stimulated discussion of the potential long-term cardiovascular (CV) risk of hypoglycaemic events in patients with type 2 diabetes. The importance of avoiding hypoglycaemia is becoming increasingly considered in terms of diabetes care in both type 1 and 2 diabetes.

The true incidence of hypoglycaemia is unknown. Many episodes are subclinical and go unnoticed by both the physician and the patient. The frequency is likely to be significantly underestimated. The objective of this article is to discuss the impact and clinical implications of hypoglycaemia, with particular attention to people with type 2 diabetes.

Definition of Hypoglycaemia

Hypoglycaemia has been defined as a plasma glucose level of <70mg/dl (<3.9mmol/l), as once levels go below this threshold, activation of the anti-insulin neuroendocrine counter-regulatory response normally occurs.[1,2] However, the definition of hypoglycaemia used in clinical trials often varies between investigators and the threshold may range from 55 to 70mg/dl (3 to 3.9mmol/l), leading to different estimations of its incidence.[9,10] By contrast, more descriptive definitions have also been employed where the authors manually review and classify subjects into 'mild' (not requiring third-party help) or 'severe' (if the patient requires help).[11] These different approaches to defining hypoglycaemia make it difficult to pinpoint its exact incidence.

Frequency of Hypoglycaemia

Although the true frequency of hypoglycaemia is hard to determine, in an analysis of 50,048 patients with type 2 diabetes, 4.1% suffered an episode of hypoglycaemia while on treatment with oral antidiabetes agents (OADs). In the same analysis, use of insulin was found to be a significant risk factor for hypoglycaemia, as was sulphonylurea (SU)

Table 1: Frequency of Hypoglycaemia from Observational Studies in Outpatient Settings

Study	Number	Frequency of Hypoglycaemia	
		Type 1	Type 2
Jennings et al., 1989[a]	219		20% of those taking SU
Miller et al., 2000[b]	1,055		16% with OADs 30% with insulin
Shorr et al., 1997[c]	19,932		1.23 severe episodes/100 person-years with SUs 2.76 severe episodes/100 person-years with insulin
Gurlek et al., 1999[d]	165	0.15 severe episodes/patient/year with insulin	0.15 severe episodes/patient/year with insulin
Leese et al., 2003[e]	160	7.1% requiring emergency treatment	7.3% requiring emergency treatment
Donnelly et al., 2005[f]	267	42.9 per patient/year	16.4 per patient/year
Henderson et al., 2003[g]	215		0.28 severe episodes/patient/year
MacLeod et al., 1993[h]	600	1.7 episodes/patient/year	0.73 episodes/patient/year
Hepburn et al., 1993[i]	172		82.7% with insulin

OADs = oral antidiabetes agents; SU = sulphonylurea.

a. *Jennings AM, Wilson RM, Ward JD, Symptomatic hypoglycaemia in NIDDM patients treated with oral hypoglycaemic agents,* Diabetes Care*, 1989;12:203–8.*
b. *Miller CD, Phillips LS, Ziemer DC, et al., Hypoglycaemia in patients with type 2 diabetes mellitus,* Arch Intern Med*, 2001;161:1653–9.*
c. *Shorr RI, Ray WA, Daugherty JR, et al., Incidence and risk factors for serious hypoglycaemia in older persons using insulin or sulfonylureas,* Arch Intern Med*, 1997;157:1681–6.*
d. *Gurlek A, Erbas T, Gedik O, Frequency of severe hypoglycaemia in type 1 and type 2 diabetes during conventional insulin therapy,* Exp Clin Endocrinol Diabetes*, 1999;107:220–24.*
e. *Leese GP, Wang J, Broomhall J, et al., Frequency of severe hypoglycaemia requiring emergency treatment in type 1 and type 2 diabetes: a population-based study of health service resource use,* Diabetes Care*, 2003;26:1176–80.*
f. *Donnelly LA, Morris AD, Frier BM, et al., Frequency and predictors of hypoglycaemia in Type 1 and insulin-treated Type 2 diabetes: a population-based study,* Diabet Med*, 2005;22:749–55.*
g. *Henderson JN, Allen KV, Deary IJ, et al., Hypoglycaemia in insulin-treated Type 2 diabetes: frequency, symptoms and impaired awareness,* Diabet Med*, 2003;20:1016–21.*
h. *MacLeod KM, Hepburn DA, Frier BM, Frequency and morbidity of severe hypoglycaemia in insulin-treated diabetic patients,* Diabet Med*, 1993;10:238–45.*
i. *Hepburn DA, MacLeod KM, Pell AC, et al., Frequency and symptoms of hypoglycaemia experienced by patients with type 2 diabetes treated with insulin,* Diabet Med*, 1993;10:231–7.*

(adjusted odds ratio [OR] 3.73).[11] By contrast, use of metformin was associated with a comparatively low risk (OR 1.42) – i.e. hypoglycaemia was nearly three times more common with SU than with metformin treatment in the absence of insulin. The recorded frequencies of hypoglycaemia in selected trials are listed in *Table 1*.

Causes of Hypoglycaemia

In patients with diabetes, causes of hypoglycaemia include missed or delayed food intake, a meal or snack that is too small, vigorous exercise without adequate carbohydrate compensation and alcohol consumption.[1] A major cause of hypoglycaemia in patients is the medicine used to control glycaemia.[12] Relative or absolute insulin excess from therapy in combination with compromised physiological defences against falling plasma glucose concentrations can lead to hypoglycaemia.[3,4] Insulin excess occurs because of an inadequate action profile of the drug when placed in the context of factors such as food intake, exercise, drug interactions and insulin clearance.[1] Meanwhile, in type 1 and more advanced type 2 diabetes, there is impairment of all three physiological defences that would normally correct hypoglycaemia: there is no decrease in insulin levels, no increase in glucagon levels and the increase in epinephrine (adrenaline) levels may be attenuated, resulting in a higher hypoglycaemia risk with insulin use.[11,13,14]

The potential of a specific OAD to cause hypoglycaemia is dependent on its mechanism of action. For example, SUs are insulin secretagogues and work by increasing insulin secretion regardless of blood glucose levels, effectively uncoupling the glucose sensitivity of pancreatic islet beta-cells and insulin secretion, thus increasing the risk of hypoglycaemia.[15,16] By contrast, metformin does not directly stimulate insulin secretion and therefore the risk of hypoglycaemia is low.[11]

Impaired Awareness of Hypoglycaemia

The initial symptoms of hypoglycaemia are largely triggered by increased levels of epinephrine (adrenaline), one of the counter-regulatory responses normally associated with low blood glucose.[3,4] However, in many patients with type 1 and 2 diabetes of longer duration, counter-regulatory responses are blunted – a phenomenon known as hypoglycaemia-associated autonomic failure (HAAF).[4,17,18] This syndrome not only involves reduced neuroendocrine counter-regulatory responses to lowered blood glucose, but also lowered glycaemic thresholds for activation of defences against hypoglycaemia. This latter can lead to hypoglycaemia unawareness, which is the inability to perceive the normal (early) warning symptoms of hypoglycaemia.

Studies suggest that even one prolonged, moderate episode of hypoglycaemia may be sufficient to significantly reduce counter-regulatory responses.[19,20] Without the warning signs, episodes become difficult to detect. Accordingly, the incidence of subclinical hypoglycaemia cannot be determined accurately, although episodes are common in insulin-treated patients.[1] Indeed, the prevalence has been estimated as high as 19.5% in patients with type 1 diabetes.[21] The major risk associated with episodes of subclinical hypoglycaemia is the potential for reduced awareness of the onset of a severe episode because the glycaemic threshold has been substantially lowered. In turn, a bout of recurrent episodes can lead to a vicious cycle of hypoglycaemia, inducing further hypoglycaemia.[17,18,22] Indeed, subclinical hypoglycaemia (not surprisingly) is associated with a six-fold increased risk of severe hypoglycaemia.[21,23] In insulin-treated patients with type 2 diabetes, the prevalence of impaired awareness of hypoglycaemia has been estimated to be around 10%. Impaired awareness of hypoglycaemia in this cohort was associated with a five-fold higher incidence of hypoglycaemia and a 17-fold higher incidence of severe episodes.[10] On the other hand, studies suggest that several weeks of stringent avoidance of hypoglycaemia can reverse hypoglycaemia unawareness in the majority of patients.[1,24–26]

Hypoglycaemia and Long-term Cardiovascular Morbidity and Mortality

In addition to the immediate consequences of hypoglycaemia, episodes may also lead to other longer-term health consequences. Three recently published studies have examined the effects of intensive versus standard glycaemia treatment on CV risk in

Table 2: Comparison of the Three Trials of Intensive Glycaemic Control and Cardiovascular Disease Outcomes

	ACCORD	ADVANCE	VADT
Participant Characteristics			
Number	10,251	11,140	1,791
Mean age (years)	62	66	60
Duration of diabetes (years)	10	8	11.5
Sex (% male/female)	39/61	42/58	97/3
History of CVD (%)	35	32	40
BMI (kg/m^2)	32	28	31
Median baseline HbA_{1c} (%)	8.1	7.2	9.4
On insulin at baseline (%)	35	1.5	52
Protocol Characteristics			
HbA_{1c} goals (%) (I versus S)*	<6.0 versus 7.0–7.9	≤6.5 versus 'based on local guidelines'	<6.0 (action if >6.5) versus planned separation of 1.5
Protocol for glycemic control (I versus S)*	Multiple drugs in both arms	Multiple drugs added to gliclizide versus multiple drugs with no gliclizide	Multiple drugs in both arms
Management of other risk factors	Embedded blood pressure and lipid trials	Embedded blood pressure trial	Protocol for intensive treatment in both arms
On-study Characteristics			
Weight changes (kg):			
Intensive glycaemic control arm	+3.5	-0.1	+7.8
Standard glycaemic control arm	+0.4	-1.0	+3.4
Severe hypoglycaemia (participants with one or more episodes during study) (%):			
Intensive glycaemic control arm	16.2	2.7	21.2
Standard glycaemic control arm	5.1	1.5	9.9
Outcomes			
Definition of primary outcome	Non-fatal MI, non-fatal stroke, CVD death	Microvascular plus macrovascular (non-fatal MI, non-fatal stroke, CVD death) outcomes	Non-fatal MI, non-fatal stroke, CVD death, hospitalisation for heart failure, revascularisation
HR for primary outcome (95% CI)	0.90 (0.78–1.04)	0.9 (0.82–0.98); macrovascular 0.94 (0.84–1.06)	0.88 (0.74–1.05)
HR for mortality findings (95% CI)	1.22 (1.01–1.46)	0.93 (0.83–1.06)	1.07 (0.81–1.42)

*ACCORD = Action to Control Cardiovascular Risk in Diabetes; ADVANCE = Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; VADT = Veterans Affairs Diabetes Trial; CVD = cardiovascular disease; I = intensive glycaemic control; S = standard glycaemic control; CI = confidence interval; HR = hazard ratio; MI = myocardial infarction. *Medication rates for ACCORD are for any use during the study.*

patients with type 2 diabetes (see *Table 2*).[27–29] In the three studies, the incidence of hypoglycaemia was significantly higher in the intensive therapy group. None found that near-normal glycaemic control (median HbA_{1c} of 6.4% at study end in the intensive group) significantly reduced the incidence of CV events within a 3.5–5-year time-frame.[27–29]

By contrast, the ACCORD trial found that overall mortality was greater in the intensive therapy group.[27–29] In 19 of the 41 unexpected excess deaths from CV causes in the ACCORD study, 'unexpected or presumed CV disease' was possibly related to, or precipitated by, severe hypoglycaemia.[27–29] Interestingly, in the ACCORD study, previous occurrence of severe hypoglycaemia was one of the strongest predictors of a primary CV event regardless of the treatment arm. In addition, while hypoglycaemic events were more frequent in the intensive therapy group, this arm also saw a greater increase in weight gain of more than 10kg. These factors, as well as the differences in number of drugs and regimens, could have contributed to the final mortality rates.

In VADT, hypoglycaemia was one of the strongest predictors of CV death (hazard ratio [HR] 4.042, 95% confidence interval [CI] 1.449–11.276; p=0.01); other predictors were prior event and age.[30]

CV risk may also be increased by recurrent subclinical hypoglycaemic episodes as a low blood glucose level stimulates sympathetic neural activation and catecholamine secretion, which can lead to arrhythmia and increased heart rate, blood pressure and overall workload of the heart.[31] These haemodynamic changes can result in stress in the arterial wall and may contribute to destabilisation of atherosclerotic plaques, potentially precipitating an atherothrombotic event. Furthermore, acute hypoglycaemia causes physiological changes that affect the CV system and several haematological parameters, largely as a result of sympatho-adrenal activation and counter-regulatory hormonal secretion.[32]

A study using healthy subjects found that antecedent hypoglycaemia led to impaired autonomic function, which could potentially contribute directly to mortality in diabetes and CV disease.[33] By contrast, a study focusing on patients hospitalised with acute myocardial infarction (AMI) reported that hypoglycaemia only increased mortality when episodes occurred spontaneously without insulin treatment (18.4% mortality rate in patients with hypoglycaemia versus 9.2% in those without).[34] When hypoglycaemia was induced by insulin therapy, there was no significant difference in mortality between patients who suffered hypoglycaemia and those who did not (10.4 versus 10.2%). Regardless of insulin treatment, the patients with hypoglycaemia were older and had more co-morbidities.[34] Finally, the data also suggest that

Table 3: Contributors to Increased Risk of Severe Hypoglycaemia

Loss of Endogenous Insulin Secretion
Inability to reduce circulating insulin concentrations
Loss of signal to alpha-cells to increase glucagon secretion
Possible loss of C-peptide or amylin effects
Primary Failure of Hormones that Raise Blood Glucose Concentrations
Hypopituitarism
Adrenal cortical failure
Isolated growth hormone deficiency
Defective Glucose Counter-regulation
Loss of glucagon response to hypoglycaemia
Delayed onset of counter-regulatory response secondary to antecedent hypoglycaemia
Prolongation of Insulin Effect
Exogenous insulin injection
Insulin secretagogues
Renal impairment
Hyperthyroidism
High levels of insulin-binding antibodies
Liver failure
Exaggerated Mismatch Between Insulin and Nutrient Absorption
Primary gastrointestinal disease with malabsorption (coeliac disease)
Delayed insulin administration
Lifestyle Contributors to Individual Episodes of Severe Hypoglycaemia
Acute increase in muscle glucose uptake during exercise
Depletion of liver and muscle glycogen by vigorous/prolonged exercise
Suppression of gluconeogenesis by alcohol
Use of drugs enhancing effects of insulin secretagogues

hypoglycaemia during hospitalisation for AMI was a marker for more severe illness and not necessarily a direct cause of it, providing some reassurance to physicians in their efforts for glycaemic control in patients. However, the question remains whether hypoglycaemia resulting from certain drugs is harmful to patients.

Analyses of ACCORD do not show any definitive relationship between the increased CV mortality in the intensive treatment arm and any combination of drugs used. However, the combination of an SU and metformin in ACCORD has previously been shown to be associated with a significantly higher rate of CV events and trends towards a higher rate of total mortality compared with SU or metformin monotherapy treatment in the United Kingdom Prospective Diabetes Study (UKPDS).[35–37] Furthermore, a recent meta-analysis suggests that the combination of an SU plus metformin in patients with type 2 diabetes, while having no significant effects on either CV disease mortality or all-cause mortality alone, may increase the relative risk of the composite end-point of CV hospitalisation or mortality (fatal and non-fatal events). The authors presented several possible explanations for their observation, one of which is the tendency of SUs to cause hypoglycaemia, which may be further aggravated by the metformin causing decreased hepatic glucose production, possibly impairing the recovery from hypoglycaemia. However, the authors highlight the limitations that exist in their meta-analysis and stress the need for larger-scale studies to further characterise the results.[38] Glyburide (glibenclamide), the most widely used SU, was linked to a 52% greater risk of experiencing at least one hypoglycaemic episode compared with other secretagogues and an 83% greater risk compared with other SUs;[39] however, it was not associated with a higher risk of CV events.

These studies suggest a possible association between hypoglycaemia and CV risk, leading to a need to find treatment options that have a lower risk of hypoglycaemic events to prevent potential long-term CV morbidity and mortality.

Hypoglycaemia and Other Co-morbidities

In addition to CV risk, hypoglycaemia may have an effect on risk of dementia in older patients with type 2 diabetes.[40] A longitudinal cohort study was performed from 1980 to 2007 with 16,667 patients with a mean age of 65 years with type 2 diabetes. Severe hypoglycaemic episodes requiring hospitalisation significantly increased a patient's probability of developing dementia, with the risk increasing with more episodes.[40] Further research is required to determine the association between minor episodes and risk of dementia. These results support the need for caution specifically in treating older patients with diabetes in order to limit the risk of dementia. They also illustrate the complexities connected with diabetes treatment, as any hypoglycaemia – caused by drugs or otherwise – may lead to a number of unknown consequences for the patient.

Hypoglycaemia and Quality of Life

Hypoglycaemia and its symptoms may cause fear in patients with diabetes and clinicians alike and can potentially lead to stress and an impaired quality of life for patients and clinical inertia within the medical community. Hypoglycaemic episodes have both short- and long-term consequences on health-related quality of life (HRQoL). The short-term consequences refer to the symptoms associated with the actual event. While hypoglycaemic episodes may be relatively harmless, episodes can result in unconsciousness or impaired cognition and thus situations may arise that can be detrimental for both the patient and surrounding individuals.[41] The long-term consequences relate to changes in patient behaviour and their fear of future episodes, resulting in negative social and emotional states.[41,42] Fear of hypoglycaemia is one of the most problematic long-term consequences.[42] Patients who suffer hypoglycaemic episodes, even non-severe episodes, are more likely to experience anxiety and panic attacks that in turn can increase the number of episodes.[41] An important clinical implication resulting from a fear of hypoglycaemia is reluctance by the patient and physician to intensify antidiabetes therapy that may lead to a negative impact on diabetes management, metabolic control and subsequent health outcomes.[41,43] This clinical inertia, which has been summarised as "the failure to initiate or intensify therapy in a defined time among patients who have not attained clinical goals and whom intensification is likely to benefit",[44] is a limiting factor in diabetes treatment. Moreover, in an attempt to avoid hypoglycaemia, some patients may alter treatment intensity and overeat to elevate blood glucose levels.[41] However, it has been shown that blood glucose awareness training can reduce fear in patients.[42]

Individuals at High Risk and Clinical Implications of Hypoglycaemia

Although many patients with diabetes are at risk of experiencing hypoglycaemic episodes, there are factors that predispose certain individuals to a greater risk. In older patients in particular, factors such as a restricted carbohydrate intake, renal and hepatic dysfunction and the effects of alcohol and medications in common use may increase the risk of hypoglycaemia (see *Table 3*).[45,46] These aspects, in combination with SU or exogenous insulin therapy, make it more likely that a patient will experience hypoglycaemia.[46] An inadequate glucagon response arising with long-standing diabetes, in particular in

type 1 diabetes, puts patients with diabetes at greater risk as defences against hypoglycaemia are largely reduced.[1] However, patients with long-standing type 2 diabetes with endogenous insulin deficiency who have been on insulin therapy for many years are also at increased risk of severe hypoglycaemia.[47] Patients with a history of repetitive hypoglycaemia, in particular in combination with hypoglycaemia unawareness, are at particular risk of severe hypoglycaemic attacks. Furthermore, too aggressive glycaemic therapy resulting in lower glycaemic goals, lower HbA_{1c} levels or both can have also an effect on future hypoglycaemic episodes.[1]

Finally, special attention should be given to those patients in whom even mild hypoglycaemic attacks may have major consequences, e.g. people in certain occupations (those working at heights or with heavy machinery and occupational drivers) and people living alone. In these circumstances, great care should be taken to avoid hypoglycaemia altogether.

Given the potential severity of hypoglycaemic events and their effect on the health of patients, it is important to minimise their incidence. This can be accomplished by treating diabetes with drugs that have a lower risk of hypoglycaemia, such as metformin, thiazolidinediones and dipeptidyl peptidase-4 (DPP-4) inhibitors. The inhibition of the DPP-4 enzyme by this latter new class of drugs enhances the action of glucagon-like peptide-1 (GLP-1). As GLP-1 causes insulin secretion to increase only when glucose levels are elevated, hypoglycaemia is less likely to occur.[48] In fact, the UK's National Institute for Health and Clinical Excellence (NICE) has recently recommended that DPP-4 inhibitors be used as a second-line therapy for patients with type 2 diabetes if the person is at significant risk of hypoglycaemia or its consequences. A recent meta-analysis of randomised clinical trials studied the role of DPP-4 inhibitors in the treatment of type 2 diabetes and found that DPP-4 inhibitors lowered HbA_{1c} with little or no weight gain or hypoglycaemia risk. However, further study is needed to determine the long-term safety profiles of this class of drug.[49] Glitazones are another class of type 2 diabetes therapy that have been studied as a potential treatment with a low hypoglycaemia risk. These agents work by helping the body use its available amounts of insulin more effectively, thereby improving the patient's insulin sensitivity. As a result, glitazones are associated with a low incidence of hypoglycaemia.[50] However, when either drug class is used in combination with SUs or insulin, the combination can still lead to blood glucose levels dropping below normal.

Summary and Conclusions

Hypoglycaemia and its potentially serious consequences are a major concern when managing patients with diabetes.[22] Recurrent episodes of hypoglycaemia, especially severe events, can lead to poor treatment adherence in patients and a reluctance to intensify treatment by health professionals, as well as having a negative impact on patient quality of life. Hypoglycaemia was a predictor of CV events in both ACCORD and VADT (although a causal relationship was not definitely established) and might precipitate other morbidities, such as dementia. It would seem prudent to use therapies that are associated with a lower risk of hypoglycaemia (particularly in high-risk subjects) in an attempt to achieve optimal and early glycaemic control in patients with type 2 diabetes, while minimising the risk of adverse consequences. ■

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