33 Hypoglycemia in Diabetes

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Keypoints

- Iatrogenic hypoglycemia is the limiting factor in the glycemic management of diabetes. It occurs during treatment with an insulin secretagogue or with insulin.
- The key physiologic defenses against falling plasma glucose concentrations are decrements in insulin and increments in glucagon and epinephrine. The behavioral defense is carbohydrate ingestion prompted by symptoms that are largely the result of sympathetic neural activation.
- Hypoglycemia in diabetes is the result of therapeutic hyperinsulinemia. As glucose levels fall, decrements in insulin and increments in glucagon are lost, because of β-cell failure, in type 1 diabetes mellitus (T1DM) and advanced type 2 diabetes mellitus (T2DM). In that setting, attenuated increments in epinephrine cause the syndrome of defective glucose counter-regulation. Attenuated increments in sympathetic neural activity largely bring about the syndrome of hypoglycemia unawareness.
- The concept of hypoglycemia-associated autonomic failure (HAAF) in diabetes posits that recent antecedent hypoglycemia, as well as prior exercise or sleep, causes both defective glucose counter-regulation and hypoglycemia unawareness by attenuating the sympathoadrenal response to subsequent hypoglycemia.
- Hypoglycemia unawareness and, in part, the reduced epinephrine component of defective glucose counter-regulation are reversible in 2–3 weeks with scrupulous avoidance of hypoglycemia in most affected patients.
- The risk factors for hypoglycemia, based on this pathophysiology, include relative as well as absolute therapeutic insulin excess, and factors indicative of HAAF which include absolute endogenous insulin deficiency, a history of severe hypoglycemia, hypoglycemia unawareness, or both as well as prior exercise or sleep, and aggressive glycemic therapy per se.
- This pathophysiology explains why the incidence of iatrogenic hypoglycemia increases over time in T2DM, approaching that in T1DM. Most episodes of hypoglycemia occur in people with T2DM.
- Minimizing the risk of iatrogenic hypoglycemia requires acknowledging the problem, applying the principles of aggressive glycemic therapy and considering the risk factors for relative as well as absolute therapeutic insulin excess and for HAAF.
- Maintenance of the greatest degree of glycemic control that can be accomplished safely in a given patient at a given stage of that individual's diabetes is in the patient's best interest. Concerns about hypoglycemia should not be an excuse for poor glycemic control.

Overview of the clinical problem

Iatrogenic hypoglycemia is the most important limiting factor in the glycemic management of diabetes [1,2]. It causes recurrent morbidity in most people with type 1 diabetes mellitus (T1DM) and many with advanced type 2 diabetes mellitus (T2DM), and is sometimes fatal. It compromises physiologic and behavioral defenses against subsequent falling plasma glucose concentrations and thus causes a vicious cycle of recurrent hypoglycemia. It precludes maintenance of euglycemia over a lifetime of diabetes and thus full realization of the vascular benefits of glycemic control.

Hypoglycemia in diabetes is fundamentally iatrogenic, the result of pharmacokinetically imperfect treatments with an insulin secretagogue (e.g. a sulfonylurea or a glinide) or with exogenous insulin that results in episodes of hyperinsulinemia. Nonetheless, hypoglycemia is typically the result of the interplay of relative or absolute therapeutic insulin excess and comprised physiologic and behavioral defenses against falling plasma glucose concentrations [1,2].

The problem of hypoglycemia in diabetes has been summarized [1] and reviewed in detail [2]. My premise is that understanding of the pathophysiology of glucose counter-regulation, the mechanisms that normally prevent or rapidly correct hypoglycemia, leads to insight into the frequency of, risk factors for and prevention of iatrogenic hypoglycemia. Therefore, the physiology of glucose counter-regulation and its pathophysiology in diabetes are addressed first, followed by a summary of the magnitude of the clinical problem. With that background, a clinical approach to the prevention of iatrogenic hypoglycemia, and if necessary its treatment, is discussed.

Physiology of glucose counter-regulation

Hypoglycemia and the brain

Glucose is an obligate oxidative fuel for the brain under physiologic conditions [1–4]. The brain accounts for more than 50% of whole body glucose utilization. Because it cannot synthesize glucose, utilize physiologic concentrations of circulating nonglucose fuels effectively or store more than a few minutes supply as glycogen [1,2], the brain requires a virtually continuous supply of glucose from the circulation. Because facilitated blood–brain glucose transport is a direct function of the arterial plasma glucose concentration, that requires maintenance of the physiologic plasma glucose concentration. Hypoglycemia causes functional brain failure, which is typically reversed after the plasma glucose concentration is raised [4]. Rarely, profound prolonged hypoglycemic causes brain death [4].

Responses to hypoglycemia

Falling plasma glucose concentrations cause a sequence of responses in individuals without diabetes (Table 33.1) [1,5–8]. The first physiologic response, which occurs as plasma glucose concentrations decline within the postabsorptive plasma glucose concentration range, is a decrease in insulin secretion. The secretion of glucose counter-regulatory (plasma glucose raising) hormones, including glucagon and epinephrine, increases as plasma glucose concentrations fall just below the physiologic range. Lower plasma glucose levels cause a more intense sympathoadrenal – sympathetic neural as well as adrenomedullary – response and symptoms. Even lower plasma glucose concentrations cause functional brain failure [4].

Clinical manifestations of hypoglycemia

The symptoms and signs of hypoglycemia are not specific [8,9]. Thus, clinical hypoglycemia is most convincingly documented by Whipple's triad: symptoms, signs, or both, consistent with hypoglycemia; a low measured plasma glucose concentration; and resolution of those symptoms and signs after the plasma glucose concentration is raised.

Neuroglycopenic symptoms, which are the result of brain glucose deprivation per se, include cognitive impairments, behavioral changes and psychomotor abnormalities and, at lower plasma glucose concentrations, seizure and coma [1,2,4,8,9]. Neurogenic (or autonomic) symptoms, which are largely the result of the perception of physiologic changes caused by the sympathoadrenal – particularly the sympathetic neural [9] – discharge triggered by hypoglycemia, include both adrenergic (e.g. palpitations, tremulousness and anxiety/arousal) and cholinergic (e.g. sweating, hunger and paresthesias) symptoms [8]. Central mechanisms may also be involved in some of the latter symptoms such as hunger [10]. Awareness of hypoglycemia is largely the result of the perception of neurogenic symptoms [8].

Signs of hypoglycemia include pallor and diaphoresis, the result of adrenergic cutaneous vasoconstriction and cholinergic

Table 33.1 Physiologic responses to decreasing plasma glucose concentrations.

Response	Glycemic threshold* (mg/dL [mmol/L])	Physiologic effects	Role in prevention or correction of hypoglycemia (glucose counter-regulation)
↓ Insulin	80–85 [4.4–4.7]	↑R_a (↓R_d)	Primary glucose regulatory factor, first defense against hypoglycemia
↑ Glucagon	65–70 [3.6–3.9]	↑R_a	Primary glucose counter-regulatory factor, second defense against hypoglycemia
↑ Epinephrine	65–70 [3.6–3.9]	↑R_a, ↓R_d	Involved, critical when glucagon is deficient, third defense against hypoglycemia
↑ Cortisol and growth hormone	65–70 [3.6–3.9]	↑R_a, ↓R_d	Involved but not critical
Symptoms	50–55 [2.8–3.1]	↑ Exogenous glucose	Prompt behavioral defense (food ingestion)
↓ Cognition	<50 [<2.8]	–	Compromises behavioral defense

R_a, rate of glucose appearance, glucose production by the liver and kidneys; R_d, rate of glucose disappearance, glucose utilization by insulin-sensitive tissues such as skeletal muscle (no direct effect on central nervous system glucose utilization).
* Arterialized venous, not venous, plasma glucose concentrations.
Reproduced from Cryer PE. Glucose homeostasis and hypoglycemia. In: Kronenberg HM, Melmed S, Polonsky KS, Larsen PR, eds. *Williams Textbook of Endocrinology*, 11th edn. Philadelphia: Saunders, 2008: 1503–1533, with permission.

activation of sweat glands, respectively [1,2]. Neuroglycopenic manifestations are often observable.

Maintenance of systemic glucose balance

Because obligatory glucose utilization, largely by the brain, is fixed and exogenous glucose delivery from ingested carbohydrates is intermittent, systemic glucose balance is maintained, and hypoglycemia (as well as hyperglycemia) is prevented, by dynamic regulation of endogenous glucose production from the liver (and the kidneys) and of glucose utilization by non-neural tissues such as muscle [1,11]. Although an array of hormones, neurotransmitters and metabolic substrates are involved, endogenous glucose production and glucose utilization by non-neural tissues are regulated primarily by insulin (Figure 33.1; Table 33.1) [11].

The first physiologic defense against hypoglycemia is a decrease in pancreatic islet β-cell insulin secretion. That occurs as plasma glucose concentrations decline within the physiologic range (Table 33.1) and favors increased hepatic (and renal) glucose production with virtual cessation of glucose utilization by insu-
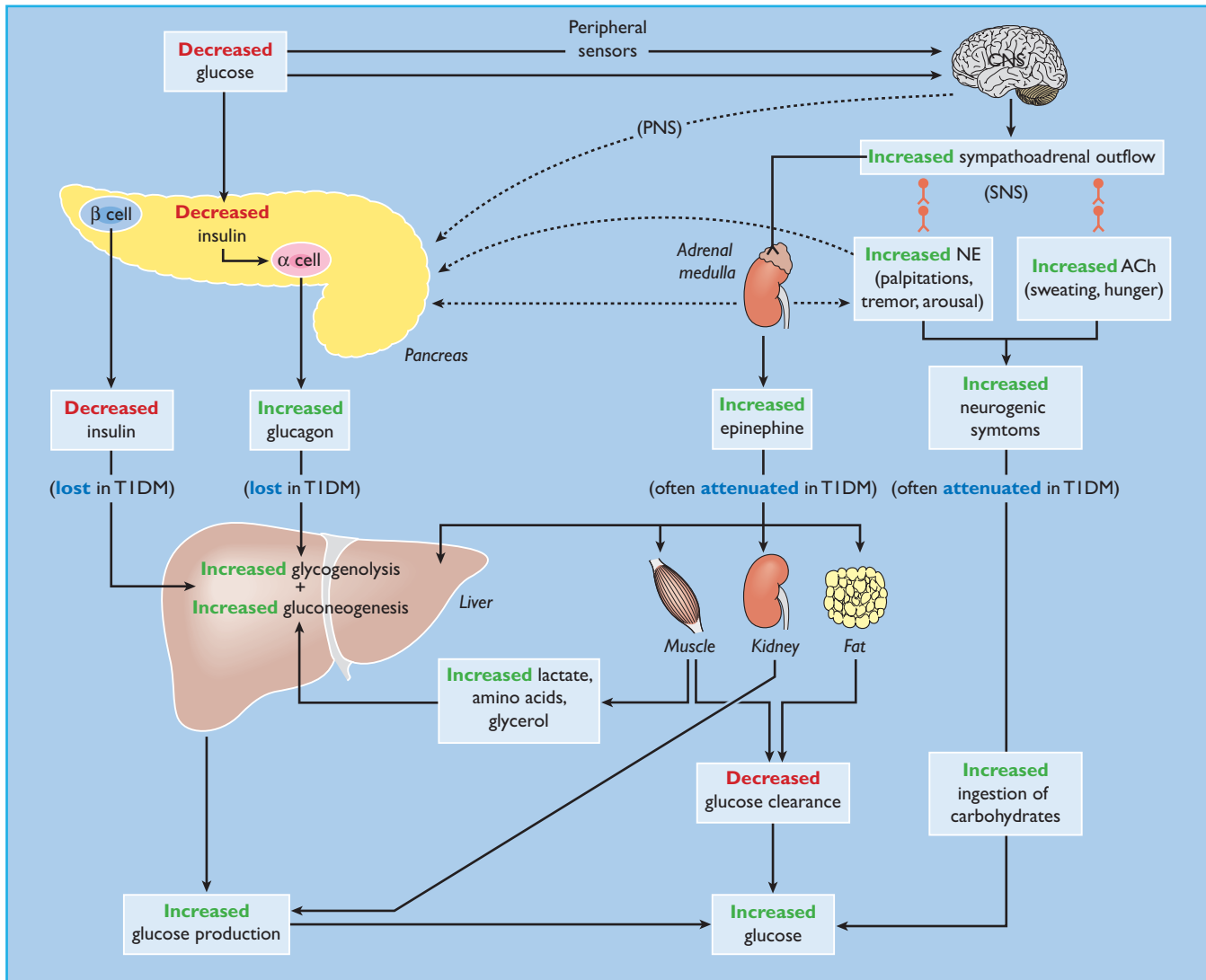
Figure 33.1 Physiologic and behavioral defenses against hypoglycemia in humans. ACh, acetylcholine; α-cell, pancreatic islet α-cell; β-cell, pancreatic islet β-cell; NE, norepinephrine; PNS, parasympathetic nervous system; SNS, sympathetic nervous system; T1DM, type 1 diabetes mellitus. Reproduced from Cryer PE. Mechanisms of sympathoadrenal failure and hypoglycemia in diabetes. *J Clin Invest* 2006; **116**:1470–1473, with permission from the American Society for Clinical Investigation.

lin-sensitive tissues such as muscle (Figure 33.1). The second physiologic defense is an increase in pancreatic islet α-cell glucagon secretion. That occurs as plasma glucose concentrations fall just below the physiologic range (Table 33.1) and stimulates hepatic glucose production (largely by stimulating glycogenolysis) (Figure 33.1). Increased glucagon secretion is signaled primarily by a decrease in intra-islet insulin, perhaps among other β-cell secretory products, in the setting of low glucose concentrations [1,2,12] and secondarily by increased autonomic nervous system – sympathetic, parasympathetic and adrenomedullary – inputs [1,2,13]. The third physiologic defense, which becomes critical when glucagon is deficient, is an increase in adrenomedullary epinephrine secretion [1,2,11]. That, too, occurs as plasma glucose concentrations fall just below the physiologic range

(Table 33.1). It raises plasma glucose concentrations largely by β_2-adrenergic stimulation of hepatic (and renal) glucose production (Figure 33.1), but the glucose-raising actions of epinephrine also involve limitation of glucose clearance by insulin sensitive tissues, mobilization of gluconeogenic substrates such as lactate and amino acids from muscle and glycerol from fat and α_2-adrenergic limitation of insulin secretion [1,2,14]. Sympathoadrenal activity, including epinephrine secretion, is regulated in the brain [1,2,11]. Circulating epinephrine is almost exclusively derived from the adrenal medulle [9]; while circulating norepinephrine is largely derived from sympathetic nerves under resting and many stimulated (e.g. exercise) conditions, the plasma norepinephrine response to hypoglycemia is also largely adrenomedullary in origin [9].

Table 33.2 Responses to falling plasma glucose concentrations in humans.

Plasma glucose	Individuals	Plasma		
		Insulin	Glucagon	Epinephrine
↓	Non-diabetic	↓	↑	↑
↓	T1DM*	No ↓	No ↑	Attenuated ↑
↓	Early T2DM	↓	↑	↑
↓	Late T2DM*	No ↓	No ↑	Attenuated ↑

*These alterations account for the appearance of defective glucose counter-regulation and hypoglycemia unawareness in T1DM and late T2DM.

If these physiologic defenses fail to abort an episode of developing hypoglycemia, lower plasma glucose concentrations cause a more intense sympathoadrenal response that causes neurogenic symptoms (Figure 33.1) [1,2,11]. Those symptoms cause awareness of hypoglycemia that prompts the behavioral defense of ingestion of carbohydrates [1,2,11].

All of these defenses against hypoglycemia, not just insulin secretion, are typically compromised in people with T1DM and those with advanced (i.e. absolutely endogenous insulin deficient) T2DM (Figure 33.1) [1,2].

Pathophysiology of glucose counter-regulation in diabetes

Insulin excess

While substantial insulin excess alone can cause hypoglycemia, the integrity of the defenses against falling plasma glucose concentrations determines whether a typical episode of therapeutic hyperinsulinemia results in clinical hypoglycemia [1,2]. Thus, iatrogenic hypoglycemia is typically the result of the interplay of relative or absolute therapeutic hyperinsulinemia and compromised physiologic and behavioral defenses against falling plasma glucose concentrations (Figure 33.1; Table 33.2) [1,2,15,16].

Defective glucose counter-regulation and hypoglycemia unawareness

In fully developed (i.e. C peptide negative) T1DM circulating insulin concentrations cannot decrease as plasma glucose concentrations fall in response to therapeutic (exogenous) hyperinsulinemia (Table 33.2) [1,2,15]. That is the result of β-cell failure which also causes loss of the increase in circulating glucagon concentrations (Figure 33.2; Table 33.2) [1,2,12,15]. The latter conclusion is based on the finding that indirect reciprocal β-cell-mediated signaling normally predominates over direct α-cell signaling in the regulation of glucagon secretion in humans [1,2,12]. Thus, the absence of a decrease in intra-islet insulin, perhaps among other β-cell secretory products, in concert with low glucose levels, plausibly explains loss of the glucagon response [1,2,12]. Therefore, both the first and second physiologic defenses

against hypoglycemia are lost. Furthermore, the increase in circulating epinephrine, the third physiologic defense, is typically attenuated (Figure 33.2; Table 33.2) [1,15]. In the setting of absent insulin and glucagon responses, the attenuated epinephrine response causes the clinical syndrome of defective glucose counter-regulation (Table 33.2) [1,2,15,17,18] which is associated with a 25-fold [17] or greater [18] increased risk of severe iatrogenic hypoglycemia in T1DM. In addition, the attenuated epinephrine response is a marker for an attenuated sympathoadrenal, including sympathetic neural, response (Table 33.2) which is largely responsible for reduced neurogenic symptom responses and therefore the clinical syndrome of hypoglycemia unawareness [1,2,9] which is associated with a sixfold increased risk of severe iatrogenic hypoglycemia in T1DM [19]. Attenuated sympathoadrenal responses to falling plasma glucose concentrations can be caused by recent antecedent hypoglycemia (Figures 33.3 and 33.4) [1,2,15,16,20], prior exercise [1,2,21–23] or sleep [1,2,24–26].

While hypoglycemia unawareness is largely the result of reduced release of the neurotransmitters norepinephrine and acetylcholine [1,9], there is evidence of decreased β-adrenergic sensitivity, specifically reduced cardiac chronotropic sensitivity to isoproterenol, in affected patients [27,28]. However, vascular sensitivity to β_2-adrenergic agonism was not found to be reduced in patients with unawareness [29], reduced sensitivity to β-adrenergic signaling of neurogenic symptoms remains to be demonstrated in patients with unawareness and it would be necessary to postulate decreased cholinergic sensitivity as well to explain reduced cholinergic symptoms such as sweating.

The pathophysiology of glucose counterregulation is the same in T1DM and advanced (i.e. absolutely endogenous insulin deficient) T2DM, albeit with different time courses (Table 33.2) [1,2,15,16]. The pathogenesis of an episode of iatrogenic hypoglycemia involves therapeutic hyperinsulinemia resulting in falling plasma glucose concentrations and loss of the appropriate decrements in insulin and increments in glucagon. The hypoglycemia, in turn, reduces the sympathoadrenal responses to subsequent hypoglycemia. Because β-cell failure, which causes loss of both the insulin and the glucagon responses [1,2,15,16], occurs rapidly in T1DM but slowly in T2DM, the syndromes of defective glucose counterregulation and hypoglycemia unawareness develop early in T1DM but later in T2DM. This temporal pattern of compromised glycemic defenses explains why iatrogenic hypoglycemia becomes progressively more frequent as patients approach the insulin deficient end of the spectrum of T2DM as discussed later in this chapter.

Hypoglycemia-associated autonomic failure

The concept of hypoglycemia-associated autonomic failure (HAAF) in diabetes posits that recent antecedent hypoglycemia (Figures 33.3 and 33.4) [1,2,15,16,20] – as well as prior exercise [1,2,21–23] or sleep [1,2,24–26] – causes both defective glucose counter-regulation (by attenuating the epinephrine responses to subsequent hypoglycemia in the setting of absent decrements in
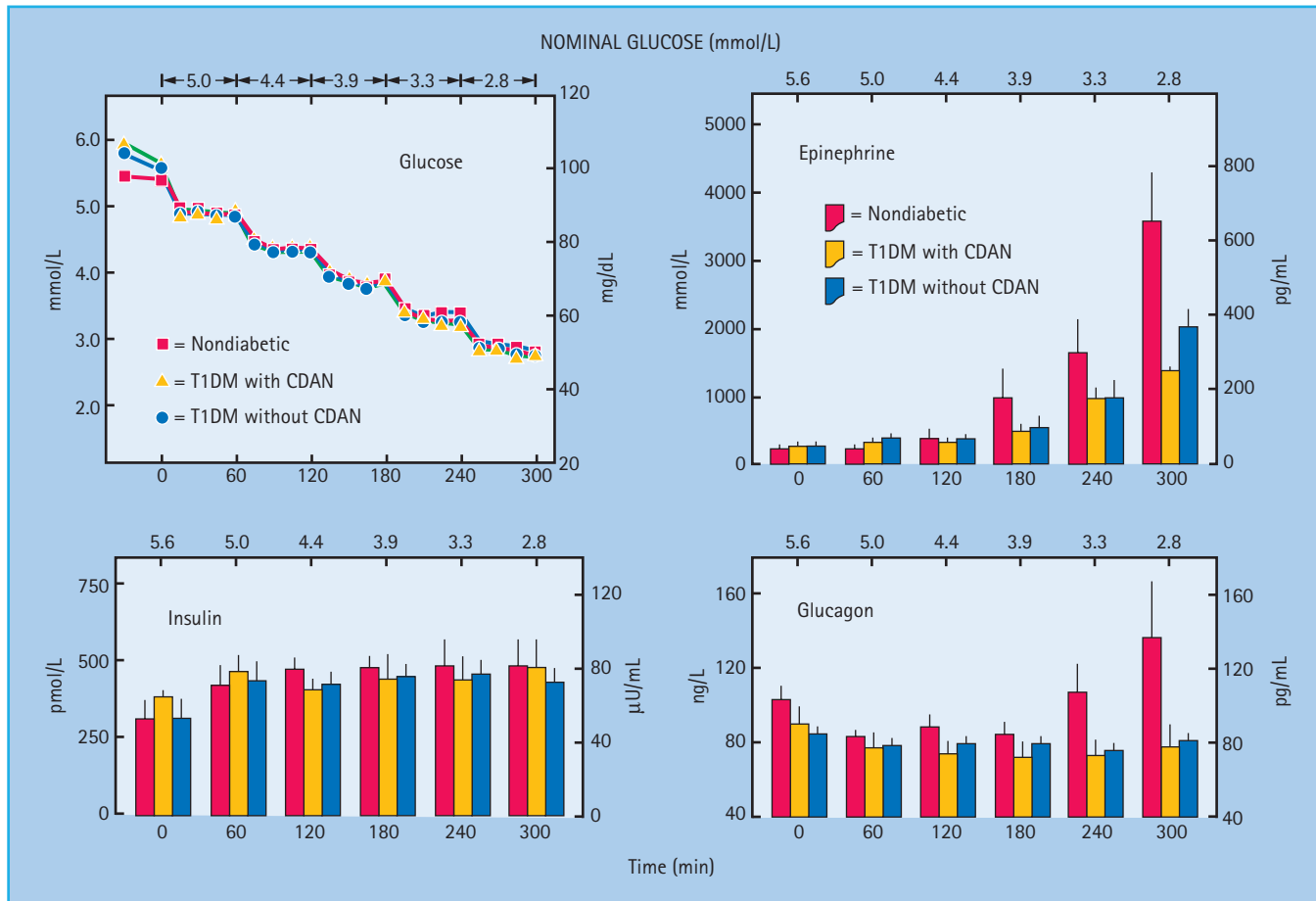
Figure 33.2 Mean (± SE) plasma glucose, insulin, epinephrine and glucagon concentrations during hyperinsulinemic stepped hypoglycemic glucose clamps in individuals without diabetes (red squares and columns), people with type 1 diabetes (T1DM, insulin-dependent diabetes mellitus) with classic diabetic autonomic neuropathy (CDAN) (yellow triangles and columns) and people with type 1 diabetes without CDAN (blue circles and columns). Reproduced from Dagogo-Jack *et al.* [15] with permission from the American Society for Clinical Investigation.

insulin and absent increments in glucagon) and hypoglycemia unawareness (by attenuating the sympathoadrenal, including the sympathetic neural, and resulting neurogenic symptom responses to subsequent hypoglycemia). It therefore leads to a vicious cycle of recurrent iatrogenic hypoglycemia (Figure 33.5). Thus, HAAF is, at least in large part, a dynamic functional disorder that is distinct from classic diabetic autonomic neuropathy [1,2]. Nonetheless, the key feature of HAAF, an attenuated sympathoadrenal response to a given level of hypoglycemia, is more prominent in patients with diabetic autonomic neuropathy (Figure 33.2) [30,31].

The clinical impact of HAAF is well established in T1DM [1,2,15,32–37]. Recent antecedent hypoglycemia, even asymptomatic nocturnal hypoglycemia, reduces epinephrine, symptomatic and cognitive dysfunction responses to a given level of subsequent hypoglycemia [32], reduces detection of hypoglycemia in the clinical setting [33] and reduces defense against hyperinsulinemia [15] in T1DM. Perhaps the most compelling support for the concept of HAAF is the finding, initially by three independent research teams [34–37], that as little as 2–3 weeks of

scrupulous avoidance of hypoglycemia reverses hypoglycemia unawareness (Figure 33.6) and improves the attenuated epinephrine component of defective glucose counter-regulation in most affected patients.

People with advanced T2DM are also at risk for HAAF [1,2,16]. Glucagon responses to hypoglycemia are lost [16], as they are in T1DM. Furthermore, the glycemic thresholds for sympathoadrenal and symptomatic (among other) responses to hypoglycemia are shifted to lower plasma glucose concentrations by recent antecedent hypoglycemia [16], as they are in T1DM.

The three recognized causes of HAAF each cause attenuated sympathoadrenal and symptomatic (among other) responses to a given level of hypoglycemia [1,2]. Antecedent hypoglycemia-related HAAF [1,2,15,16,20] led to the concept. Exercise-related HAAF [1,2,21–23] is exemplified by late post-exercise hypoglycemia which typically occurs 6–15 hours after strenuous exercise and is often nocturnal [38,39]. Sleep-related HAAF [1,2,24–26] is the result of further attenuation of the sympathoadrenal response to hypoglycemia during sleep. Sleeping patients are
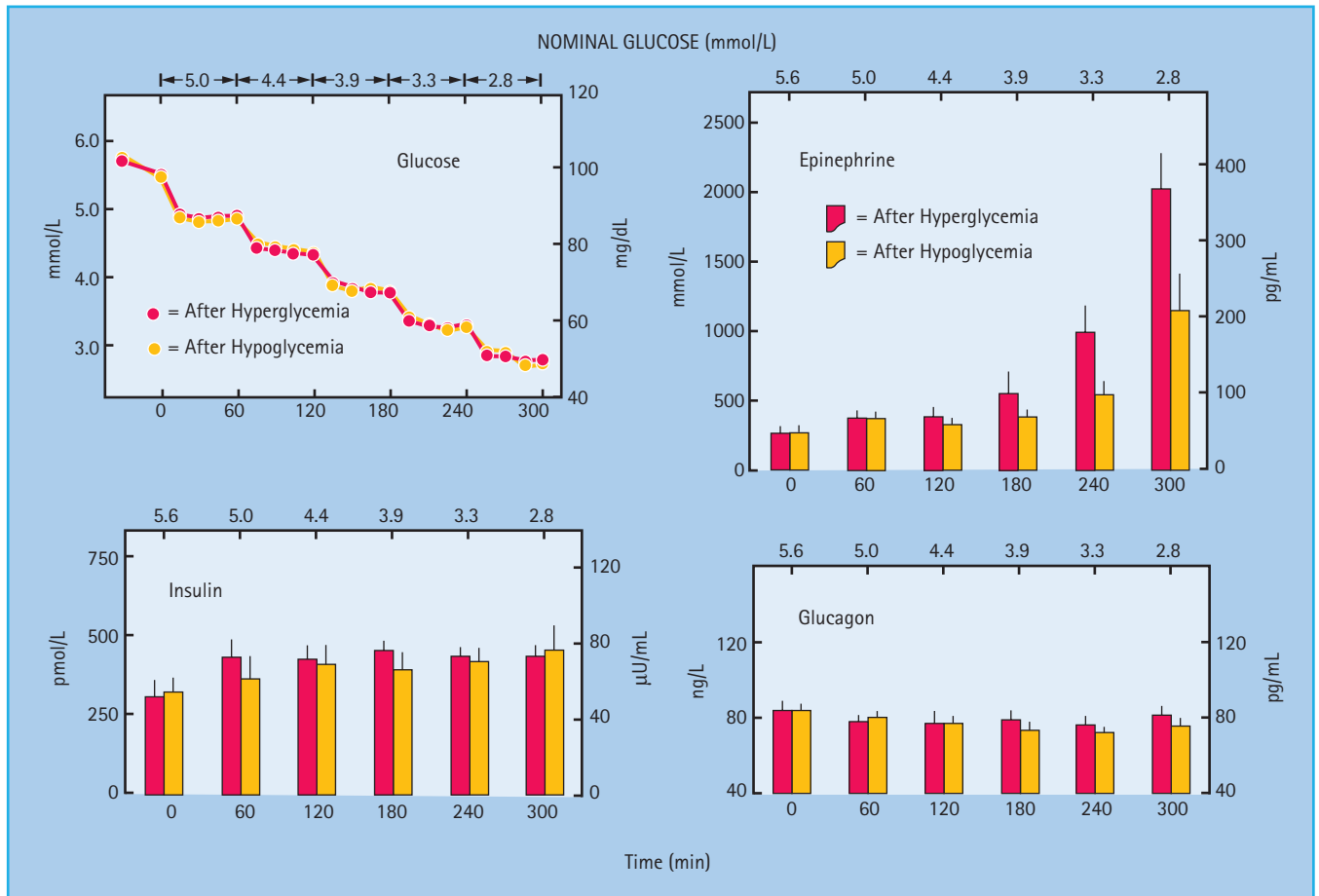
Figure 33.3 Mean (± SE) plasma glucose, insulin, epinephrine and glucagon concentrations during hyperinsulinemic stepped hypoglycemic glucose clamps in patients with type 1 diabetes without classic diabetic autonomic neuropathy on mornings following afternoon hyperglycemia (red circles and columns) and on mornings following afternoon hypoglycemia (yellow circles and columns). From Dagogo-Jack *et al.* [15] with permission from the American Society for Clinical Investigation.

Figure 33.4 Mean (± SE) total, neurogenic and neuroglycopenic symptom scores during hyperinsulinemic stepped hypoglycemic clamps in patients with type 1 diabetes without classic diabetic autonomic neuropathy on mornings following afternoon hyperglycemia (red columns) and on mornings following afternoon hypoglycemia (yellow columns). Reproduced from Dagogo-Jack *et al.* [15] with permission from the American Society for Clinical Investigation.
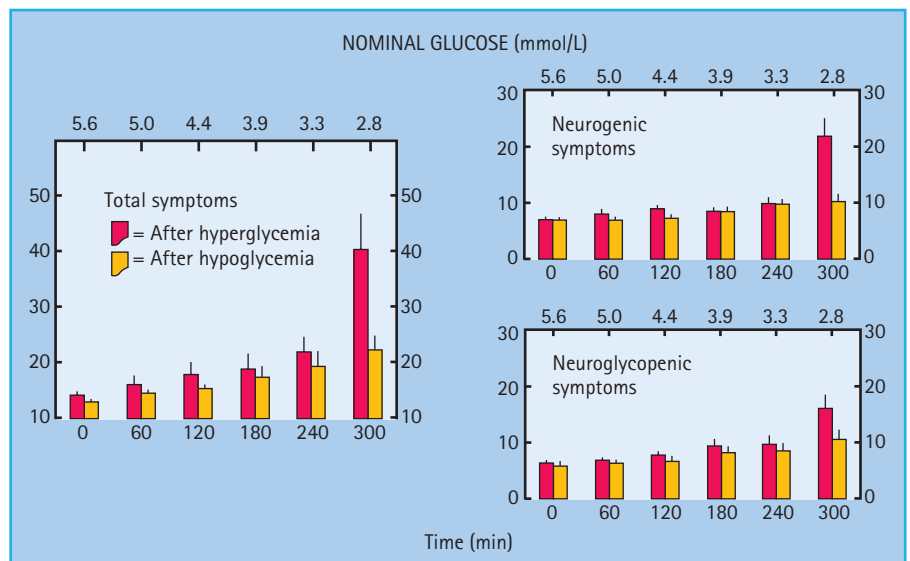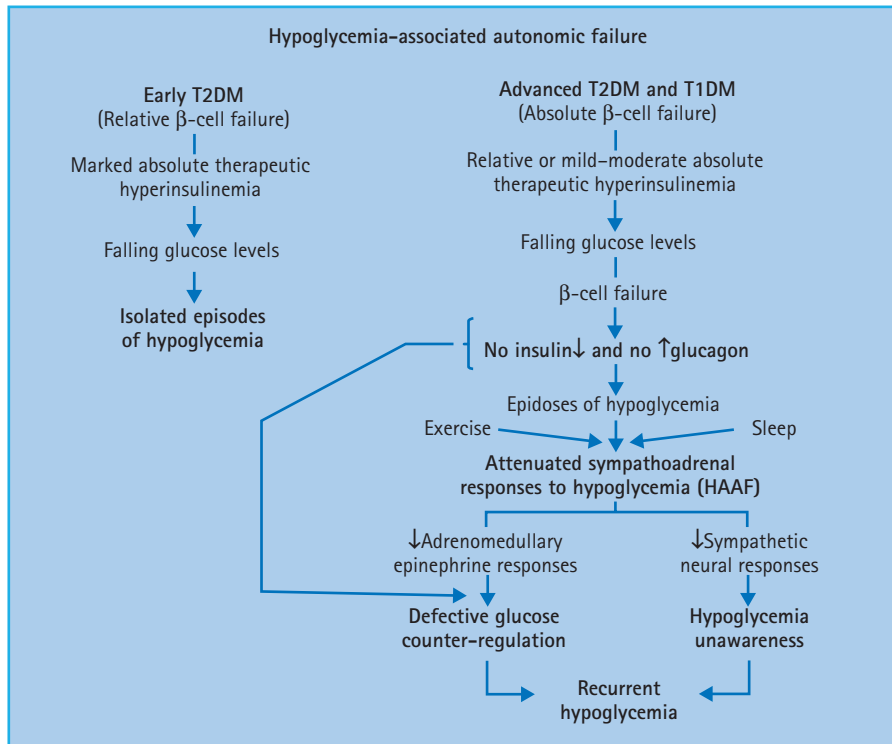
Figure 33.5 Hypoglycemia-associated autonomic failure (HAAF) in the pathogenesis of iatrogenic hypoglycemia in diabetes.
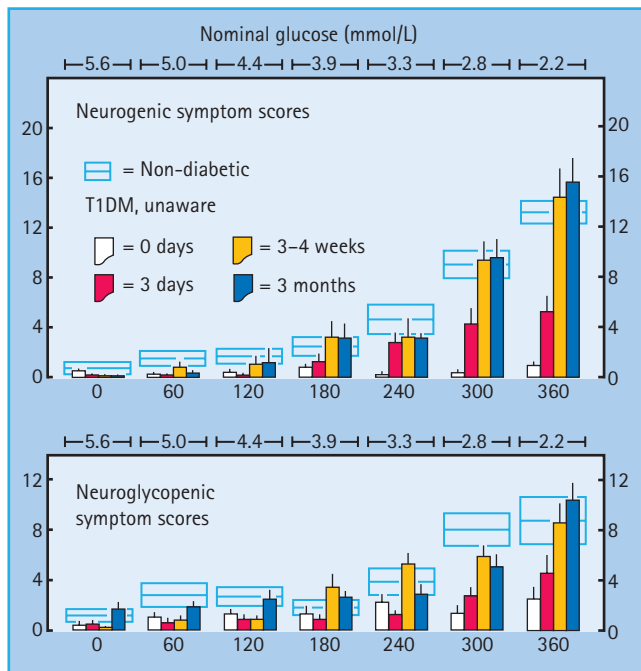

Figure 33.6 Mean (± SE) neurogenic and neuroglycopenic symptom scores during hyperinsulinemic stepped hypoglycemic clamps in individuals without diabetes (open rectangles) and in patients with T1DM (columns) at baseline (0 days), after 3 days of inpatient strict avoidance of hypoglycemia and after 3–4 weeks and 3 months of outpatient scrupulous avoidance of hypoglycemia. From Dagogo-Jack *et al.* [37] with permission from the American Diabetes Association.

therefore much less likely to be awakened by hypoglycemia than individuals without diabetes [25,26]. There may well be additional, as yet unrecognized, functional, and therefore potentially reversible, causes of HAAF [1,2]. In addition, there may be a structural component [1,2].

The mechanisms of HAAF are summarized in Figure 33.7 [1,2]. Loss of the insulin and glucagon responses to falling plasma glucose concentrations caused by therapeutic hyperinsulinemia is the result of β-cell failure in T1DM and advanced T2DM. Because normal insulin and glucagon responses to low glucose concentrations occur in patients with a transplanted (i.e. denervated) pancreas [40] and in dogs with a denervated pancreas [41] – as well as from the perfused pancreas and perifused pancreatic islets – innervation is not required.

In the setting of absent insulin and glucagon responses to falling plasma glucose concentrations, attenuated sympathoadrenal responses cause both defective glucose counter-regulation and hypoglycemia unawareness, the two components of HAAF [1,2]. The mechanism of the attenuated sympathoadrenal response is not known, but it must be at the level of the brain (or the afferent or efferent components of the sympathoadrenal system) (Figure 33.7). The proposed mechanisms include the systemic mediator, brain fuel transport and brain metabolism hypotheses, all of which have been reviewed [1,2,42,43].

Much of the research into the pathogenesis of HAAF has focused on the hypothalamus, the central integrator of the sympathoadrenal responses to hypoglycemia [43]. While the primary alteration could reside in the hypothalamus, the changes in hypothalamic function could be secondary to those in other brain regions. For example, measurements of regional cerebral blood
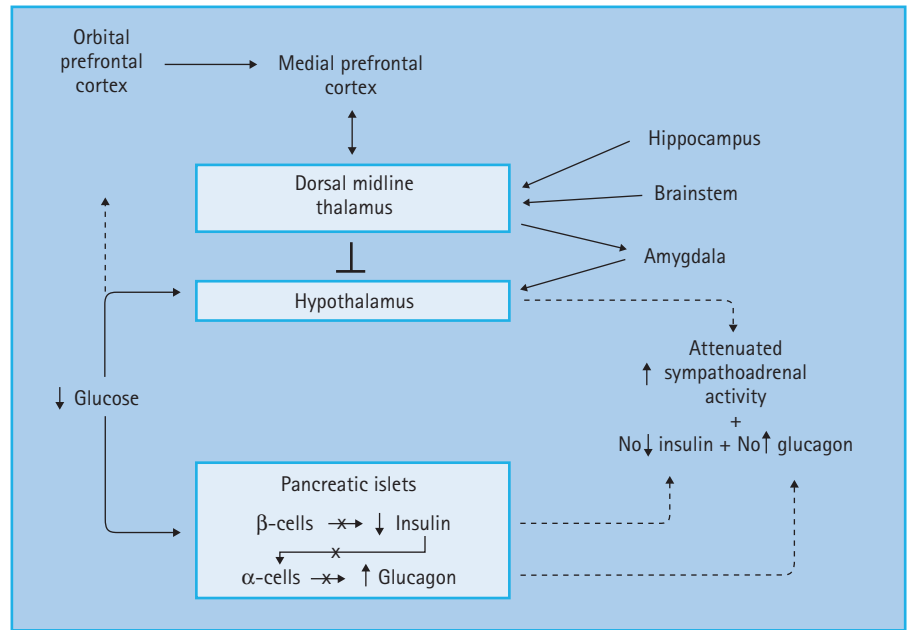
Figure 33.7 Pancreatic islet, hypothalamic and cerebral network mechanisms of hypoglycemia-associated autonomic failure (HAAF) in diabetes. Reproduced from Cryer [1] with permission from the American Diabetes Association.

flow with [¹⁵O] water and positron emission tomography (PET) [44] indicate that hypoglycemia activates widespread but interconnected brain regions, including the medial prefrontal cortex, the lateral orbitofrontal cortex, the thalamus, the globus pallidus and the periaqueductal gray. These studies also show that recent antecedent hypoglycemia both reduces the sympathoadrenal and symptomatic responses (a model of HAAF) and causes a greater increase in synaptic activity in the dorsal midline thalamus during subsequent hypoglycemia [45]. Thus, it has been suggested that there may be a cerebral network that results in thalamic inhibition of hypothalamic activity in HAAF (Figure 33.7) [45]. That suggestion is generically consistent with the findings of various patterns of [¹⁸F] deoxyglucose uptake in T1DM patients with and without hypoglycemia unawareness [46].

Risk factors for hypoglycemia in diabetes

The risk factors for hypoglycemia in diabetes follow directly from the pathophysiology of glucose counter-regulation and are based on the principle that iatrogenic hypoglycemia is typically the result of the interplay of relative or absolute therapeutic insulin excess and compromised physiologic and behavioral defenses against falling plasma glucose concentrations (i.e. HAAF) in T1DM and advanced T2DM [1,2,47].

Absolute or relative insulin excess

The conventional risk factors for hypoglycemia in diabetes are based on the premise that absolute or relative therapeutic insulin excess is the sole determinant of risk (Table 33.3) [1,2,47]. Absolute therapeutic insulin excess occurs when insulin secretagogue or insulin doses are excessive, ill-timed or of the wrong

Table 33.3 Risk factors for hypoglycemia in diabetes.

Relative or absolute insulin excess
1 Insulin or insulin secretagogue doses are excessive, ill-timed or of the wrong type
2 Exogenous glucose delivery is decreased (e.g. following missed meals and during the overnight fast)
3 Glucose utilization is increased (e.g. during and shortly after exercise)
4 Endogenous glucose production is decreased (e.g. following alcohol ingestion)
5 Sensitivity to insulin is increased (e.g. in the middle of the night and following weight loss or improved glycemic control)
6 Insulin clearance is decreased (e.g. with renal failure)

Hypoglycemia-associated autonomic failure
1 Absolute endogenous insulin deficiency
2 A history of severe hypoglycemia, hypoglycemia unawareness, or both as well as recent antecedent hypoglycemia, prior exercise and sleep
3 Aggressive glycemic therapy per se (lower HbA_{1c} levels, lower glycemic goals)

type, or when insulin clearance is reduced as in renal failure. Relative therapeutic insulin excess occurs under a variety of conditions. It occurs when exogenous glucose delivery is decreased (as following missed or low carbohydrate meals and during the overnight fast), when glucose utilization is increased (as during and shortly after exercise), when endogenous glucose production is decreased (as following alcohol ingestion) and when sensitivity to insulin is increased (as following weight loss or improved glycemic control and in the middle of the night). People with diabetes and their caregivers must consider each of these risk factors when the problem of iatrogenic hypoglycemia is recog-

nized. Overall, however, they explain only a minority of episodes of hypoglycemia [48].

Compromised defenses against hypoglycemia

The risk factors indicative of HAAF (Table 33.3) [1,2,47,49–55] include absolute endogenous insulin deficiency [1,2,47,49–53], a history of severe iatrogenic hypoglycemia, hypoglycemia unawareness, or both as well as recent antecedent hypoglycemia, prior exercise or sleep [1,2,47,50–52,54] and aggressive glycemic therapy per se (i.e. lower HbA_{1c} levels, lower glycemic goals, or both) [1,2,47,50–55]. The degree of endogenous insulin deficiency (i.e. β-cell failure) determines the extent to which insulin levels will not decrease and glucagon levels will not increase as plasma glucose concentrations fall in response to therapeutic hyperinsulinemia. A history of severe hypoglycemia indicates, and that of hypoglycemia unawareness implies, recent antecedent hypoglycemia. The latter causes attenuated sympathoadrenal and symptomatic responses to subsequent hypoglycemia, the key feature of HAAF. In addition, prior exercise and sleep cause that feature of HAAF. Studies of intensive glycemic therapy with a control group treated to a higher HbA_{1c} level consistently report higher rates of hypoglycemia in the group treated to lower HbA_{1c} levels in T1DM [56–58] and T2DM [54,59,60]. That does not mean that one cannot both improve glycemic control and minimize the risk of hypoglycemia [1,2,47] as discussed below.

Magnitude of the clinical problem of hypoglycemia in diabetes

Diabetes is an increasingly common disease. It has been estimated that its prevalence will rise from 285 million people in the year 2009 to 435 million people by the year 2030 [61]. Iatrogenic hypoglycemia affects most of the minority with T1DM and many of the majority with T2DM [1,2]. Indeed, because it precludes maintenance of euglycemia over a lifetime of diabetes, the barrier of hypoglycemia ultimately affects all people with diabetes [1,2].

Frequency of hypoglycemia

Hypoglycemia is a fact of life for people with T1DM (Table 33.4) [1,2,55,62,63]. The average patient has untold numbers of episodes of asymptomatic hypoglycemia and experiences two episodes of symptomatic hypoglycemia per week – thousands of such episodes over a lifetime of diabetes – and one or more episodes of severe, temporarily disabling hypoglycemia, often with seizure or coma, per year. There is no evidence that this problem has abated since it was highlighted by the report of the Diabetes Control and Complications Trial (DCCT) in 1993 [56]. For example, in 2007 the UK Hypoglycemia Study Group [63] reported an incidence of severe hypoglycemia that was twice that in the DCCT in patients with T1DM for <5 years and an incidence fivefold higher than that in the DCCT in those with T1DM for >15 years (Table 33.4). An incidence comparable to the latter was also found in a large observational study [55].

Table 33.4 Event rates for severe hypoglycemia (that requiring the assistance of another person), expressed as episodes per 100 patient-years, in insulin-treated diabetes [2].

Citation	n	Event rate	Comment
Type 1 diabetes			
UK Hypoglycemia Study Group [63]	57*	320	Prospective multicenter study
	50†	110	
MacLeod et al. [64]	544	170	Retrospective clinic survey, randomly selected sample
Donnelly et al. [65]	94	115	Prospective study, population-based random sample
Reichard & Pihl [66]	48	110	Clinical trial, intensive insulin group
DCCT Research Group [67]	711	62	Clinical trial, intensive insulin group
Type 2 diabetes			
MacLeod et al. [64]	56	73	Retrospective clinic survey, randomly selected sample
UK Hypoglycemia Study Group [63]	77‡	70	Prospective multicenter study
	89§	10	
Akram et al. [69]	401	44	Retrospective clinic survey
Donnelly et al. [65]	173	35	Prospective study, population-based random sample
Henderson et al. [70]	215	28	Retrospective clinic survey, randomly selected sample
Murata et al. [71]	344	21	Prospective study, random Veterans Affairs sample
Saudek et al. [72]	62	18¶	Clinical trial, multiple insulin injection group
Gürlek et al. [73]	114	15	Retrospective clinic survey
Abraira et al. [74]	75	3	Clinical trial, intensive insulin group
Yki-Järvinen et al. [75]	88	0	Clinical trial, initial insulin therapy
Ohkubo et al. [76]	52	0	Clinical trial, initial insulin therapy

* Insulin treatment for >15 years.
† Insulin treatment for <5 years.
‡ Insulin treatment for >5 years.
§ Insulin treatment for <2 years.
¶ Definite (8 per 100 patient-years) plus suspected (10 per 100 patient-years).
Reproduced from Cryer PE, Axelrod L, Grossman AB, Heller SR, Montori VM, Seaquist ER, Service FJ. Evaluation and management of adult hypoglycemic disorders: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2009, with permission from the Endocrine Society.

Overall, hypoglycemia is less frequent in T2DM (Table 33.4) [1,2,55,63–80], but for the pathophysiologic reasons discussed, hypoglycemia becomes progressively more frequent as patients approach the insulin deficient end of the spectrum of T2DM [1,2,63,78]. Indeed, its frequency has been reported to be similar in those with T2DM and T1DM matched for duration of insulin therapy [78]. When the UK Hypoglycemia Study Group [63] contrasted patients with T2DM treated with insulin for <2 years

with those treated with insulin for >5 years they found severe hypoglycemia prevalences of 7% and 25% and incidences of 10 and 70 episodes per 100 patient-years, respectively. The pattern for self-treated hypoglycemia was similar [63]. Thus, while the incidence of iatrogenic hypoglycemia is relatively low (with current less than euglycemic goals) in the first few years of insulin treatment of T2DM, the risk increases substantially, approaching that in T1DM, in advanced of T2DM.

Because asymptomatic episodes will almost invariably be missed, symptomatic episodes may not be recognized as the result of hypoglycemia [81] and, even if they are, they are not long remembered [82,83], estimates of the frequency of iatrogenic hypoglycemia are underestimates. Although they represent only a small fraction of the total hypoglycemic experience, because they are dramatic events that are more likely to be reported (by the patient or an associate) [82,83], estimates of the frequency of severe hypoglycemia, requiring the assistance of another person, are more reliable, particularly if they are determined in population-based prospective studies that include a focus on hypoglycemia [1,2].

The prospective population-based data of Donnelly *et al.* [65] indicate that the overall incidence of hypoglycemia in insulin treated T2DM is approximately one-third of that in T1DM (Table 33.4). The incidence of any and of severe hypoglycemia was approximately 4300 and 115 episodes per 100 patient-years, respectively, in T1DM and approximately 1600 and 35 episodes per 100 patient-years, respectively, in insulin-treated T2DM. In addition, in population-based studies the incidence of severe hypoglycemia requiring emergency treatment in insulin-treated T2DM was approximately 40% [79] and approximately 100% [80] of that in T1DM. Because the prevalence of T2DM is approximately 20-fold greater than that of T1DM, and most people with T2DM ultimately require treatment with insulin, these data suggest that most episodes of iatrogenic hypoglycemia, including severe hypoglycemia, occur in people with T2DM.

Impact of hypoglycemia

Iatrogenic hypoglycemia causes recurrent physical and psychologic morbidity, and some mortality, impairs defenses against subsequent hypoglycemia and precludes maintenance of euglycemia over a lifetime of diabetes [1,2]. In the short-term it causes brain fuel deprivation that, if unchecked, results in functional brain failure that is typically corrected after the plasma glucose concentration is raised [4]. Rarely, it causes sudden, presumably cardiac arrhythmic [84,85], death or, if it is profound and prolonged, brain death [4].

The physical morbidity of an episode of hypoglycemia ranges from unpleasant symptoms to seizure and coma [1,2,4]. It can impair judgment, behavior and performance of physical tasks. Permanent neurologic damage is rare. While there is concern that recurrent hypoglycemia might cause chronic cognitive impairment, long-term follow-up of the DCCT patients is reassuring in that regard [86]. Nonetheless, the possibility that it does so in young children remains [87,88], and there are no corresponding

data in the elderly [86]. The psychologic morbidity includes fear of hypoglycemia [89], which can be a barrier to glycemic control.

Three early reports indicated that 2–4% of people with diabetes die from hypoglycemia [90–92]. More recent reports indicated that 6% [86], 7% [93] and 10% [94] of deaths of people with T1DM were the result of hypoglycemia. Similar data are not available for T2DM but mortality rates of up to 10% during episodes of severe sulfonylurea induced hypoglycemia have been reported [95,96].

The cause of excess mortality during intensive glycemic therapy of patients with T2DM in the large Action to Control Cardiovascular Risk in Diabetes (ACCORD) study [60] is not known, and likely will not be known with certainty [1,2]. It could have been chance; excessive mortality during intensive glycemic therapy was not observed in the ADVANCE trial [59] although there was less glycemic separation between the groups. It could have been the result of a non-glycemic effect of the intensive therapy regimen (e.g. an adverse effect of a drug, weight gain or something else). Nonetheless, the most plausible cause of excess mortality during intensive glycemic therapy in ACCORD is hypoglycemia [1,2]:

1 Median glycemia (HbA$_{1c}$) was lower in the intensive glycemic therapy group.
2 Lower median glycemia is associated with a higher frequency of hypoglycemia in T2DM [59,60,68].
3 Hypoglycemia can be fatal in T2DM [4,84,85,95,96].
4 More patients died in the intensive glycemic therapy group.

Clinical definition and classification of hypoglycemia

The American Diabetes Association (ADA) Workgroup on Hypoglycemia [97] defined hypoglycemia in diabetes as "all episodes of abnormally low plasma glucose concentration that expose the individual to potential harm." It is not possible to state a specific plasma glucose concentration that defines clinical hypoglycemia. Although symptoms typically develop at a plasma glucose concentration of approximately 50–55 mg/dL (2.8–3.1 mmol/L) (Table 33.1) [11] in individuals without diabetes, the glycemic threshold for symptoms (as well as those for glucose counter-regulatory and cognitive dysfunction responses) shift to lower plasma glucose concentrations in people with tightly controlled diabetes and recurrent hypoglycemia [98,99] and to higher plasma glucose concentrations in those with poorly controlled diabetes [98,100].

The ADA Workgroup recommended that people with drug-treated diabetes (implicitly those treated with an insulin secretagogue or insulin) become concerned about the possibility of developing hypoglycemia at a plasma glucose concentration of ≤70 mg/dL (3.9 mmol/L) [97]. Within the error of self-monitoring of blood glucose (or continuous glucose sensing), that conservative alert value approximates the lower limit of the non-diabetic post-absorptive plasma glucose concentration range [11] and the normal glycemic thresholds for activation of physiologic glucose counter-regulatory systems [11], and is low enough to reduce glycemic defenses against subsequent hypoglycemia

Table 33.5 American Diabetes Association Workgroup on Hypoglycemia classification of hypoglycemia in people with diabetes [97].

Severe hypoglycemia

An event requiring assistance of another person to administer actively carbohydrate, glucagon or other resuscitative actions. Plasma glucose measurements may not be available during such an event, but neurologic recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration

Documented symptomatic hypoglycemia

An event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentrations ≤70 mg/dL (3.9 mmol/L)

Asymptomatic hypoglycemia

An event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration ≤70 mg/dL (3.9 mmol/L)

Probable symptomatic hypoglycemia

An event during which symptoms typical of hypoglycemia are not accompanied by a plasma glucose determination but that was presumably caused by a plasma glucose concentration ≤70 mg/dL (3.9 mmol/L)

Relative hypoglycemia

An event during which the person with diabetes reports any of the typical symptoms of hypoglycemia, and interprets those as indicative of hypoglycemia, with a measured plasma glucose concentration >70 mg/dL (3.9 mmol/L) but approaching that level

Table 33.6 Hypoglycemic risk factor reduction.

1 Acknowledge the problem
2 Apply the principles of aggressive glycemic therapy
  • Diabetes self-management (patient education and empowerment)
  • Frequent self-monitoring of blood glucose (and in some instances continuous glucose sensing)
  • Flexible and appropriate insulin (and other drug) regimens
  • Individualized glycemic goals
  • Ongoing professional guidance and support
3 Consider the conventional risk factors for hypoglycemia (Table 33.3)
4 Consider the risk factors indicative of hypoglycemia-associated autonomic failure (Table 33.3)

[101], in individuals without diabetes. It also generally provides some margin for the relative inaccuracy of glucose monitors at low plasma glucose concentrations [102]. The use of this plasma glucose cutoff value, compared with lower values, will result in higher frequencies of hypoglycemia, and a greater proportion of episodes that are asymptomatic.

The recommended generic alert value does not mean that people with diabetes should always treat for hypoglycemia at an estimated plasma glucose concentration of ≤70 mg/dL (3.9 mmol/L). Rather, it indicates that they should consider actions ranging from repeating the measurement in the near-term through behavioral changes such as avoiding exercise or driving without treatment to carbohydrate ingestion and subsequent regimen adjustments.

The ADA Workgroup also recommended a clinical classification of hypoglycemia (Table 33.5) [97].

Prevention and treatment of hypoglycemia in diabetes

Prevention of hypoglycemia: hypoglycemia risk factor reduction

Iatrogenic hypoglycemia is a barrier to glycemic control in people with diabetes [1,2], but that barrier can be lowered in individual patients with diabetes by the practice of hypoglycemia risk factor reduction (Table 33.6) [1,2,47]. That involves four steps:

1 Acknowledge the problem;
2 Apply the principles of aggressive glycemic therapy [1,2,47,103–107];
3 Consider the conventional risk factors for hypoglycemia (Table 33.3); and
4 Consider the risk factors for hypoglycemia-associated autonomic failure (HAAF) in diabetes (Table 33.3).

The issue of hypoglycemia should be addressed in every contact with people with diabetes, at least those treated with an insulin secretagogue or with insulin [1,2,47]. Acknowledging the problem allows the caregiver either to move on if hypoglycemia is not an issue or to address it, and keep it in perspective, if hypoglycemia is an issue. Patient concerns about the reality, or even the possibility, of hypoglycemia can be a barrier to glycemic control [108,109]. It is often also helpful to question close associates of the patient because they may have observed clues to episodes of hypoglycemia not recognized by the patient. Even if no concerns are expressed, examination of the self-monitoring of blood glucose records (or continuous glucose sensing data) will often disclose that hypoglycemia is a problem.

If hypoglycemia is an issue, the principles of aggressive glycemic therapy in diabetes [1,2,47,103–107] should be reviewed and applied. Those include diabetes self-management based on patient education and empowerment, frequent self-monitoring of blood glucose (and in some instances continuous glucose sensing), flexible and appropriate insulin (and other drug) regimens, individualized glycemic goals, and ongoing professional guidance and support (Table 33.6).

Patient education and empowerment are fundamentally important. As the therapeutic regimen becomes progressively more complex – early in T1DM and later in T2DM – the success of glycemic management becomes progressively more dependent on the many management decisions and skills of the well-informed person with diabetes. In addition to basic training about diabetes, people with insulin secretagogue or insulin-treated diabetes need to be taught about hypoglycemia [110]. They need to know the common symptoms of hypoglycemia, and their individual most meaningful symptoms, and how to treat (and not overtreat) an episode. Close associates also need to be

taught the symptoms and signs of hypoglycemia, and when and how to administer glucagon. Patients need to understand the relevant conventional risk factors for hypoglycemia (Table 33.3) including the effects of the dose and timing of their individual secretagogue or insulin preparation(s) as well as the effects of missed meals and the overnight fast, exercise and alcohol ingestion. They also need to know that episodes of hypoglycemia signal an increased likelihood of future, often more severe, hypoglycemia [50–52,54,110–113]. Finally, patients using an online glucose sensor need to apply those data critically to their attempts to minimize hypoglycemia as well as hyperglycemia.

In patients treated with an insulin secretagogue, and particularly those treated with insulin, frequent self-monitoring of blood glucose becomes progressively more key to diabetes self-management as the therapeutic regimen becomes more complex, early in T1DM and later in T2DM. Ideally, patients should estimate their glucose levels whenever they suspect hypoglycemia. That would not only confirm or deny an episode of hypoglycemia, it would also help the individual learn the key symptoms of their hypoglycemic episodes and might lead to regimen adjustments. It is particularly important for people with hypoglycemia unawareness to monitor their glucose level before performing a critical task such as driving. Self-monitoring of blood glucose provides a glucose estimate only at one point in time; it does not indicate whether glucose levels are falling, stable or rising. That limitation is addressed by evolving technologies for continuous glucose sensing [114–118]. While the utility of such data seems self-evident, critical clinical data on that point are needed.

Flexible and appropriate drug regimens are key components of hypoglycemia risk factor reduction [1,2,47]. Hypoglycemia is typically the result of relative or absolute therapeutic (endogenous or exogenous) insulin excess and compromised defenses against falling plasma glucose concentrations. The relevant treatments include insulin or an insulin secretagogue such as a sulfonylurea (e.g. glibenclamide [glyburide], glipizide, glimepiride and gliclazide) or a glinide (e.g. repaglinide or nateglinide). Early in the course of T2DM, patients may respond to drugs that do not raise insulin levels at low or normal plasma glucose concentrations and therefore should not, and probably do not, cause hypoglycemia [119]. Those include the biguanide metformin, which nonetheless has been reported to cause self-reported hypoglycemia [68,120], thiazolidinediones (e.g. pioglitazone, rosiglitazone), α-glucosidase inhibitors (e.g. acarbose, miglitol), glucagon-like peptide 1 (GLP-1) receptor agonists (e.g. exenatide, liraglutide) and dipeptidyl peptidase 4 (DPP-4) inhibitors (e.g. sitagliptin, vildagliptin). All of these drugs require endogenous insulin secretion to lower plasma glucose concentrations, and insulin secretion declines appropriately as glucose levels fall into the normal range. That is true even for the GLP-1 receptor agonists and the DPP-4 inhibitors which enhance glucose stimulated insulin secretion (among other actions). They do not stimulate insulin secretion at normal or low plasma glucose concentrations (i.e. they increase insulin secretion in a glucose-dependent fashion); however, the latter feature may be lost, and hypogly-

cemia can occur, when they are used with an insulin secretagogue [121]. Indeed, all five categories of drugs increase the risk of hypoglycemia if used with an insulin secretagogue or insulin.

Among the commonly used sulfonylureas, the longer acting glibenclamide (glyburide) is more often associated with hypoglycemia than the shorter acting glimepiride [122,123]. The use of long-acting insulin analogs (e.g. glargine or detemir), rather than neutral protamine Hagedorn (NPH) insulin, as the basal insulin in a multiple daily injection (MDI) insulin regimen reduces at least the incidence of nocturnal hypoglycemia, and perhaps that of total, symptomatic and nocturnal hypoglycemia as well, in T1DM and T2DM [124–126]. The use of a rapid-acting analog (e.g. lispro, aspart or glulisine) as the prandial insulin in a MDI regimen reduces the incidence of nocturnal hypoglycemia, at least in T1DM [124,126]. Albeit conceptually attractive, the superiority of continuous subcutaneous insulin infusion (CSII) over MDI with insulin analogs with respect to the frequency and severity of hypoglycemia at comparable levels of glycemic control remains to be established convincingly [127,128]. In addition to the use of insulin analogs [124–126], approaches to the prevention of nocturnal hypoglycemia include attempts to produce sustained delivery of exogenous carbohydrate or sustained endogenous glucose production throughout the night [129].

Partial glycemic control reduces, but does not eliminate, the development of microvascular complications of diabetes, namely retinopathy, nephropathy and neuropathy, in T1DM [56,57] and in T2DM [67,130]. Extrapolation of the DCCT retinopathy data suggests that long-term maintenance of euglycemia might eliminate those complications [131]. Follow-up of the DCCT patients seemingly indicates that a period of earlier partial glycemic control also reduces macrovascular complications in T1DM [132]. Aside from the metformin subset of the UK Prospective Diabetes Study (UKPDS) [130], randomized controlled trials have not documented a cardiovascular mortality benefit of partial glycemic control in T2DM [59,60,67]; however, those trials do not exclude a macrovascular benefit of glycemic control, or even partial glycemic control, if that could be maintained over a longer period of time. Indeed, follow-up of the UKPDS patients also seemingly indicates a macrovascular benefit of a period of earlier partial glycemic control [133]. In any event, given its documented microvascular benefit, maintenance of euglycemia over a lifetime of diabetes would be in the best interests of people with diabetes if that could be accomplished safely [1,2]. Unfortunately, it cannot be accomplished safely in the vast majority of patients with currently available treatment methods because of the barrier of hypoglycemia [1,2]. Thus, the generic glycemic goal is a HbA_{1c} level as close to the non-diabetic range as can be accomplished safely in a given patient [134,135] at a given point in the evolution of his or her diabetes. Nonetheless, there is substantial long-term benefit from reducing HbA_{1c} levels from higher to lower, although still above recommended levels [56,57,67,130,136]. Clearly, glycemic goals should be individualized and may need to be reconsidered over time because of progression of endogenous insulin deficiency, the development of co-morbid illness and

functional impairment that negates the benefit of glycemic control, or both [137].

Because the glycemic management of diabetes is empirical, caregivers should work with each individual patient over time to find the most effective and safest method of glycemic control at a given point in the course of that patient's diabetes. Care is best accomplished by a team that includes, in addition to a physician, professionals trained in, and dedicated to, translating the standards of care into the care of individual patients and making full use of modern communication and computing technologies.

Having recognized the problem and reviewed and applied the principles of aggressive glycemic therapy, the next step is to consider the conventional risk factors for hypoglycemia, those that result in relative as well as absolute therapeutic insulin excess. In addition to insulin secretagogue or insulin doses, timing and type, those include conditions in which exogenous glucose delivery or endogenous glucose production is decreased, glucose utilization or sensitivity to insulin is increased, or insulin clearance is reduced (Table 33.3).

Finally, the risk factors for HAAF need to be considered. Those include the degree of endogenous insulin deficiency, a history of severe hypoglycemia, hypoglycemia unawareness, or both, as well as any relationship between hypoglycemic episodes and recent antecedent hypoglycemia, prior exercise or sleep, and lower HbA_{1c} levels (Table 33.3). Unless the cause is easily remediable, a history of severe hypoglycemia should prompt consideration of a fundamental regimen adjustment. Without that, the risk of a subsequent episode of severe hypoglycemia is high [50–52,54,110–113]. Given a history of hypoglycemia unawareness, a 2–3 week period of scrupulous avoidance of hypoglycemia, which may require acceptance of somewhat higher glycemic goals in the short term, is advisable because that can be expected to restore awareness [34–37]. A history of late post-exercise hypoglycemia, nocturnal hypoglycemia, or both, should prompt appropriately timed regimen adjustments (generically, less insulin action, more carbohydrate ingestion, or both).

When prevention fails, treatment of hypoglycemia becomes necessary. Most episodes of asymptomatic hypoglycemia (detected by self-monitoring of blood glucose or continuous glucose sensing) and of mild–moderate symptomatic hypoglycemia are effectively self-treated by ingestion of glucose tablets or carbohydrate containing juice, soft drinks, candy, other snacks or a meal [138,139]. A reasonable dose is 20 g glucose [139]. Clinical improvement should occur in 15–20 minutes, however, in the setting of ongoing hyperinsulinemia, the glycemic response to oral glucose is transient, typically less than 2 hours [139]. Thus, ingestion of a more substantial snack or meal shortly after the plasma glucose concentration is raised is generally advisable.

Parenteral treatment is required when a hypoglycemic patient is unwilling (because of neuroglycopenia) or unable to take carbohydrate orally. Glucagon, injected subcutaneously or intramuscularly (in a usual dose of 1.0 mg in adults) by an associate of the patient, is often used. That can be life-saving, but it often causes substantial, albeit transient, hyperglycemia and it can cause nausea or even vomiting. Smaller doses of glucagon (e.g. 150 μg), repeated if necessary, have been found to be effective without side effects [140]. Because it acts by stimulating hepatic glycogenolysis, glucagon is ineffective in glycogen depleted individuals (e.g. following a binge of alcohol ingestion).

Although glucagon can be administered intravenously by medical personnel, intravenous glucose is the standard parenteral therapy. A common initial dose is 25 g [138]. The glycemic response to intravenous glucose is, of course, transient in the setting of ongoing hyperinsulinemia.

The duration of an episode of iatrogenic hypoglycemia is a function of its cause. An episode caused by a rapid-acting insulin secretagogue or insulin analog will be relatively brief, that caused by a long-acting sulfonylurea or insulin analog substantially longer. The latter can result in prolonged hypoglycemia requiring hospitalization.

Perspective on hypoglycemia in diabetes

Glycemic control, a focus of this chapter, is but one aspect of the management of diabetes. It is now possible to drive plasma low density lipoprotein (LDL) cholesterol concentrations to subphysiologic levels and to normalize blood pressure pharmacologically, usually without major side effects, in most people with diabetes. Weight loss and smoking cessation are more challenging. While it is not possible to maintain euglycemia over a lifetime of diabetes, because of the barrier of hypoglycemia, maintenance of the lowest mean glycemia that can be accomplished safely is in the best interest of people with diabetes.

Despite the difficulty, people with diabetes and their caregivers should keep the problem of iatrogenic hypoglycemia in perspective. Early in the course of T2DM, by far the most common type of diabetes, hyperglycemia may respond to lifestyle changes, specifically weight loss, or to glucose lowering drugs that do not raise insulin levels and therefore do not cause hypoglycemia. In theory, when such drugs are effective in the absence of side effects there is no reason not to accelerate their dosing until euglycemia is achieved. Over time, however, as people with T2DM become progressively more insulin deficient, those drugs, even in combination, fail to maintain glycemic control. Insulin secretagogues are also effective early in the course of T2DM, but they cause hyperinsulinemia and therefore introduce the risk of hypoglycemia. Euglycemia is not an appropriate goal during therapy with an insulin secretagogue or with insulin. Nonetheless, as discussed earlier, the frequency of hypoglycemia is relatively low (with current less than euglycemic goals) during treatment with an insulin secretagogue or even with insulin early in the course of T2DM when glycemic defenses against falling plasma glucose concentrations are still intact. Thus, over much of the course of the most common type of diabetes it is possible to maintain a meaningful degree of glycemic control with no risk or relatively low risk of hypoglycemia.

The challenge is greater in people with advanced T2DM and T1DM caused by compromised defenses against falling plasma glucose concentrations and the resulting higher barrier of iatrogenic hypoglycemia. In such patients therapy with insulin is demonstrably effective, but it is not demonstrably safe. Nonetheless, concerns about hypoglycemia should not be used as a excuse for poor glycemic control. It should be recalled that the DCCT data [56,136] document that the relationship between microvascular complications and mean glycemia is curvilinear; some degree of glycemic control puts the patient at substantially lower risk than little or no glycemic control.

Diabetes will someday be cured and prevented. Pending that, elimination of hypoglycemia from the lives of people with diabetes will likely be accomplished by new treatment methods that provide plasma glucose regulated insulin replacement or secretion. In the meantime, innovative research is needed if we are to improve the lives of all people affected by diabetes by lowering the barrier of iatrogenic hypoglycemia.

Acknowledgments

Disclosures

The author has served as a consultant to several pharmaceutical and device firms, including Amgen Inc., Johnson & Johnson, MannKind Corp., Marcadia Biotech, Medtronic MiniMed Inc., Merck and Co., Novo Nordisk A/S, Takeda Pharmaceuticals North America and TolerRx Inc., in recent years. He does not receive research funding from, hold stock in or speak for any of these firms.

References

1 Cryer PE. The barrier of hypoglycemia in diabetes. *Diabetes* 2008; **57**:3169–3176.

2 Cryer PE. *Hypoglycemia in Diabetes: Pathophysiology, Prevalence and Prevention*. Alexandria, VA: American Diabetes Association, 2009.

3 Clarke DD, Sokoloff L. Circulation and energy metabolism of the brain. In: Siegel G, Agranoff B, Albers RW, Molinoff P, eds. *Basic Neurochemistry: Molecular, Cellular and Medical Aspects*, 5th edn. New York: Raven Press, 1994: 645–680.

4 Cryer PE. Hypoglycemia, functional brain failure, and brain death. *J Clin Invest* 2007; **117**:868–870.

5 Schwartz NS, Clutter WE, Shah SD, Cryer PE. Glycemic thresholds for activation of glucose counterregulatory systems are higher than the threshold for symptoms. *J Clin Invest* 1987; **79**:777–781.

6 Mitrakou A, Ryan C, Veneman T, Mokan M, Jenssen T, Kiss I, *et al*. Hierarchy of glycemic thresholds for counterregulatory hormone secretion, symptoms and cerebral dysfunction. *Am J Physiol Endocrinol Metab* 1991; **260**:E67–74.

7 Fanelli C, Pampanelli S, Epifano L, Rambotti AM, Ciofetta M, Modarelli F, *et al*. Relative roles of insulin and hypoglycemia on induction of neuroendocrine responses to, symptoms of, and deterioration of cognitive function in hypoglycemia in male and female humans. *Diabetologia* 1994; **37**:797–807.

8 Towler DA, Havlin CE, Craft S, Cryer PE. Mechanism of awareness of hypoglycemia: perception of neurogenic (predominantly cholinergic) rather than neuroglycopenic symptoms. *Diabetes* 1993; **42**:1791–1798.

9 DeRosa MA, Cryer PE. Hypoglycemia and the sympathoadrenal system: neurogenic symptoms are largely the result of sympathetic neural, rather than adrenomedullary, activation. *Am J Physiol Endocrinol Metab* 2004; **287**:E32–41.

10 Schultes B, Oltmanns KM, Kern W, Fehm HL, Born J, Peters A. Modulation of hunger by plasma glucose and metformin. *J Clin Endocrinol Metab* 2003; **88**:1133–1141.

11 Cryer PE. The prevention and correction of hypoglycemia. In: Jefferson LS, Cherrington AD, eds. *Handbook of Physiology. Section 7, The Endocrine System*. Vol. II, *The Endocrine Pancreas and Regulation of Metabolism*. New York: Oxford University Press, 2001: 1057–1092.

12 Raju B, Cryer PE. Loss of the decrement in intraislet insulin plausibly explains loss of the glucagon response to hypoglycemia in insulin-deficient diabetes. *Diabetes* 2005; **54**:757–764.

13 Taborsky GJ Jr, Ahrén B, Havel PJ. Autonomic mediation of glucagon secretion during hypoglycemia. *Diabetes* 1998; **47**:995–1005.

14 Berk MA, Clutter WE, Skor D, Shah SD, Gingerich RP, Parvin CA, *et al*. Enhanced glycemic responsiveness to epinephrine in insulin-dependent diabetes mellitus is the result of the inability to secrete insulin. *J Clin Invest* 1985; **75**:1842–1851.

15 Dagogo-Jack SE, Craft S, Cryer PE. Hypoglycemia-associated autonomic failure in insulin-dependent diabetes mellitus. *J Clin Invest* 1993; **91**:819–828.

16 Segel SA, Paramore DS, Cryer PE. Hypoglycemia-associated autonomic failure in advanced type 2 diabetes. *Diabetes* 2002; **51**:724–733.

17 White NH, Skor DA, Cryer PE, Levandoski LA, Bier DM, Santiago JV. Identification of type 1 diabetic patients at increased risk for hypoglycemia during intensive therapy. *N Engl J Med* 1983; **308**:485–491.

18 Bolli GB, De Feo P, De Cosmo S, Perriello G, Ventura MM, Benedetti MM, *et al*. A reliable and reproducible test for adequate glucose counter-regulation in type 1 diabetes mellitus. *Diabetes* 1984; **33**:732–737.

19 Geddes J, Schopman JE, Zammitt NN, Frier BM. Prevalence of impaired awareness of hypoglycemia in adults with type 1 diabetes. *Diabet Med* 2008; **25**:501–504.

20 Heller SR, Cryer PE. Reduced neuroendocrine and symptomatic responses to subsequent hypoglycemia after 1 episode of hypoglycemia in nondiabetic humans. *Diabetes* 1991; **40**:223–226.

21 Galassetti P, Mann S, Tate D, Neill RA, Costa F, Wasserman DH, *et al*. Effects of antecedent prolonged exercise on subsequent counterregulatory responses to hypoglycemia. *Am J Physiol Endocrinol Metab* 2001; **280**:E908–917.

22 Sandoval DA, Aftab Guy DL, Richardson MA, Ertl AC, Davis SN. Effects of low and moderate antecedent exercise on counterregulatory responses to subsequent hypoglycemia in type 1 diabetes. *Diabetes* 2004; **53**:1798–1806.

23 Ertl AC, Davis SN. Evidence for a vicious cycle of exercise and hypoglycemia in type 1 diabetes mellitus. *Diabetes Metab Res Rev* 2004; **20**:124–130.

24 Jones TW, Porter P, Sherwin RS, Davis EA, O'Leary P, Frazer F, *et al*. Decreased epinephrine responses to hypoglycemia during sleep. *N Engl J Med* 1998; **338**:1657–1662.

25 Banarer S, Cryer PE. Sleep-related hypoglycemia-associated autonomic failure in type 1 diabetes: reduced awakening from sleep during hypoglycemia. *Diabetes* 2003; **52**:1195–1203.

26 Schultes B, Jauch-Chara K, Gais S, Hallschmid M, Reiprich E, Kern W, *et al*. Defective awakening response to nocturnal hypoglycemia in patients with type 1 diabetes mellitus. *PLoS Medicine* 2007; **4**:e69.

27 Berlin I, Grimaldi A, Payan C, Sachon C, Bosquet F, Thervet F, *et al*. Hypoglycemic symptoms and decreased β-adrenergic sensitivity in insulin dependent diabetic patients. *Diabetes Care* 1987; **10**:742–747.

28 Fritsche A, Stefan N, Häring H, Gerich J, Stumvoll M. Avoidance of hypoglycemia restores hypoglycemia awareness by increasing β-adrenergic sensitivity in type 1 diabetes. *Ann Intern Med* 2001; **134**:729–736.

29 de Galan BE, De Mol P, Wennekes L, Schouwenberg BJJ, Smits P. Preserved sensitivity to β2-adrenergic receptor agonists in patients with type 1 diabetes mellitus and hypoglycemia unawareness. *J Clin Endocrinol Metab* 2006; **91**:2878–2881.

30 Bottini P, Boschetti E, Pampanelli S, Ciofetta M, Del Sindaco P, Scionti L, *et al*. Contribution of autonomic neuropathy to reduced plasma adrenaline responses to hypoglycemia in IDDM: evidence for a nonselective defect. *Diabetes* 1997; **46**:814–823.

31 Meyer C, Grossman R, Mitrakou A, Mahler R, Veneman T, Gerich J, *et al*. Effects of autonomic neuropathy on counterregulation and awareness of hypoglycemia in type 1 diabetic patients. *Diabetes Care* 1998; **21**:1960–1966.

32 Fanelli CG, Paramore DS, Hershey T, Terkamp C, Ovalle F, Craft S, *et al*. Impact of nocturnal hypoglycemia on hypoglycemic cognitive dysfunction in type 1 diabetes. *Diabetes* 1998; **47**:1920–1927.

33 Ovalle F, Fanelli CG, Paramore DS, Hershey T, Craft S, Cryer PE. Brief twice-weekly episodes of hypoglycemia reduce detection of clinical hypoglycemia in type 1 diabetes mellitus. *Diabetes* 1998; **47**:1472–1479.

34 Fanelli CG, Epifano L, Rambotti AM, Pampanelli S, Di Vincenzo A, Modarelli F, *et al*. Meticulous prevention of hypoglycemia normalizes the glycemic thresholds and magnitude of most of neuroendocrine responses to, symptoms of, and cognitive function during hypoglycemia in intensively treated patients with short-term IDDM. *Diabetes* 1993; **42**:1683–1689.

35 Cranston I, Lomas J, Maran A, Macdonald I, Amiel SA. Restoration of hypoglycemia awareness in patients with long-duration insulin-dependent diabetes. *Lancet* 1994; **344**:283–287.

36 Fanelli C, Pampanelli S, Epifano L, Rambotti AM, Di Vincenzo A, Modarelli F, *et al*. Long-term recovery from unawareness, deficient counterregulation and lack of cognitive dysfunction during hypoglycemia, following institution of rational, intensive therapy in IDDM. *Diabetologia* 1994; **37**:1265–1276.

37 Dagogo-Jack S, Rattarasarn C, Cryer PE. Reversal of hypoglycemia unawareness, but not defective glucose counterregulation, in IDDM. *Diabetes* 1994; **43**:1426–1434.

38 MacDonald MJ. Post exercise late onset hypoglycemia in insulin-dependent diabetic patients. *Diabetes Care* 1987; **10**:584–588.

39 Tansey MJ, Tsalikian E, Beck RW, Mauras N, Buckingham BA, Weinzimer SA, *et al*. for the Diabetes Research in Children Network (DirecNet) Study Group. The effects of erobic exercise on glucose and counterregulatory hormone concentrations in children with type 1 diabetes. *Diabetes Care* 2006; **29**:20–25.

40 Diem P, Redmon JB, Abid M, Moran A, Sutherland DE, Halter JB, *et al*. Glucagon, catecholamine and pancreatic polypeptide secretion in type 1 diabetic recipients of pancreatic allografts. *J Clin Invest* 1990; **86**:2008–2013.

41 Sherck SM, Shiota M, Saccomando J, Cardin S, Allen EJ, Hastings JR, *et al*. Pancreatic response to mild non-insulin induced hypoglycemia does not involve extrinsic neural input. *Diabetes* 2001; **50**:2487–2496.

42 Cryer PE. Mechanisms of hypoglycemia-associated autonomic failure and its component syndromes in diabetes. *Diabetes* 2005; **54**:3592–3601.

43 Sherwin RS. Bringing light to the dark side of insulin: a journey across the blood–brain barrier. *Diabetes* 2008; **57**:2259–2268.

44 Teves D, Videen TO, Cryer PE, Powers WJ. Activation of human medial prefrontal cortex during autonomic responses to hypoglycemia. *Proc Natl Acad Sci U S A* 2004; **101**:6217–6221.

45 Arbelez AM, Powers WJ, Videen TO, Price JL, Cryer PE. Attenuation of counterregulatory responses to recurrent hypoglycemia by active thalamic inhibition: a mechanism for hypoglycemia-associated autonomic failure. *Diabetes* 2008; **57**:470–475.

46 Dunn JT, Cranston I, Marsden PK, Amiel SA, Reed LJ. Attenuation of amygdala and frontal cortical responses to low blood glucose concentration in asymptomatic hypoglycemia in type 1 diabetes. *Diabetes* 2007; **56**:2766–2773.

47 Cryer PE, Davis SN, Shamoon H. Hypoglycemia in diabetes. *Diabetes Care* 2003; **26**:1902–1912.

48 Diabetes Control and Complications Trial Research Group. Epidemiology of severe hypoglycemia in the Diabetes Control and Complications Trial. *Am J Med* 1991; **90**:450–459.

49 Fukuda M, Tanaka A, Tahara Y, Ikegami H, Yamamoto Y, Kumahara Y, *et al*. Correlation between minimal secretory capacity of pancreatic β-cells and stability of diabetic control. *Diabetes* 1988; **37**:81–88.

50 Diabetes Control and Complications Trial Research Group. Hypoglycemia in the Diabetes Control and Complications Trial. *Diabetes* 1997; **46**:271–286.

51 Mühlhauser I, Overmann H, Bender R, Bott U, Berger M. Risk factors for severe hypoglycemia in adult patients with type 1 diabetes: a prospective population based study. *Diabetologia* 1997; **41**:1274–1282.

52 Allen C, LeCaire T, Palta M, Daniels K, Meredith M, D'Alessio DJ; Wisconsin Diabetes Registry Project. Risk factors for frequent and severe hypoglycemia in type 1 diabetes. *Diabetes Care* 2001; **24**:1878–1881.

53 Steffes MW, Sibley S, Jackson M, Thomas W. β-Cell function and the development of diabetes related complications in the Diabetes Control and Complications Trial. *Diabetes Care* 2003; **26**:832–836.

54 Wright AD, Cull CA, MacLeod KM, Holman RR; for the UKPDS Group. Hypoglycemia in type 2 diabetic patients randomized to and maintained on monotherapy with diet, sulfonylurea, metformin or insulin for 6 years from diagnosis: UKPDS 73. *J Diabetes Complications* 2006; **20**:395–401.

55 Lüddeke H-J, Sreenan S, Aczel S, Maxeiner S, Yenigun M, Kozlovski P, *et al.* on behalf of the PREDICTIVE Study Group. PREDICTIVE – a global, prospective observational study to evaluate insulin detemir treatment in types 1 and 2 diabetes: baseline characteristics and predictors of hypoglycemia from the European cohort. *Diabetes Obes Metab* 2007; **9**:428–434.

56 Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin dependent diabetes mellitus. *N Engl J Med* 1993; **329**:977–986.

57 Reichard P, Pihl M. Mortality and treatment side-effects during long-term intensified conventional insulin treatment in the Stockholm Diabetes Intervention Study. *Diabetes* 1994; **43**:313–317.

58 Egger M, Davey Smith G, Stettler C, Diem P. Risk of adverse effects of intensified treatment in insulin-dependent diabetes mellitus: a meta-analysis. *Diabet Med* 1997; **14**:919–928.

59 ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008; **358**:2560–2572.

60 Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008; **358**:2545–2559.

61 International Diabetes Federation. *Diabetes Facts and Figures.* Available from: http://www.diabetesatlas.org/content/diabetes-and-impaired-glucose-tolerance. Accessed on 8 January, 2010.

62 Diabetes Control and Complications Trial Research Group. Hypoglycemia in the Diabetes Control and Complications Trial. *Diabetes* 1997; **46**:271–286.

63 UK Hypoglycemia Study Group. Risk of hypoglycemia in type 1 and 2 diabetes: effects of treatment modalities and their duration. *Diabetologia* 2007; **50**:1140–1147.

64 MacLeod KM, Hepburn DA, Frier BM. Frequency and morbidity of severe hypoglycemia in insulin-treated diabetic patients. *Diabet Med* 1993; **10**:238–245.

65 Donnelly LA, Morris AD, Frier BM, Ellis JD, Donnan PT, Durrant R, *et al.* Frequency and predictors of hypoglycemia in type 1 and insulin-treated type 2 diabetes: a population-based study. *Diabet Med* 2005; **22**:749–755.

66 Reichard P, Pihl M. Mortality and treatment side-effects during long-term intensified conventional insulin treatment in the Stockholm Diabetes Intervention Study. *Diabetes* 1994; **43**:313–317.

67 UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998; **352**:837–853.

68 Wright AD, Cull CA, MacLeod KM, Holman RR; for the UKPDS Group. Hypoglycemia in type 2 diabetic patients randomized to and maintained on monotherapy with diet, sulfonylurea, metformin, or insulin for 6 years from diagnosis: UKPDS73. *J Diabetes Complications* 2006; **20**:395–401.

69 Akram K, Pedersen-Bjergaard U, Carstensen B, Borch-Johnsen K, Thorsteinsson B. Frequency and risk factors for severe hypoglycemia in insulin-treated type 2 diabetes: a cross-sectional survey. *Diabet Med* 2006; **23**:750–756.

70 Henderson JN, Allen KV, Deary IJ, Frier BM. Hypoglycemia in insulin-treated type 2 diabetes: frequency, symptoms and impaired awareness. *Diabet Med* 2003; **20**:1016–1021.

71 Murata GH, Duckworth WC, Shah JH, Wendel CS, Mohler MJ, Hoffman RM. Hypoglycemia in stable, insulin-treated veterans with type 2 diabetes: a prospective study of 1662 episodes. *J Diabetes Complications* 2005; **19**:10–17.

72 Saudek CD, Duckworth WC, Giobbie-Hurder A, Henderson WG, Henry RR, Kelley DE, *et al.* Implantable insulin pump vs. multiple dose insulin for non-insulin dependent diabetes mellitus: a randomized clinical trial. *JAMA* 1996; **276**:1322–1327.

73 Gürlek A, Erbas T, Gedik O. Frequency of severe hypoglycemia in type 1 and type 2 diabetes during conventional insulin therapy. *Exp Clin Endocrinol Diabetes* 1999; **107**:220–224.

74 Abraira C, Colwell JA, Nuttall FQ, Sawin CT, Nagel NJ, Comstock JP, *et al.* Veterans Affairs cooperative study on glycemic control and complications in type II diabetes (VA CSCM). *Diabetes Care* 1995; **18**:1113–1123.

75 Yki-Järvinen H, Ryysy L, Nikkilä K, Tulokas T, Vanamo R, Heikkilä M. Comparison of bedtime insulin regimens in patients with type 2 diabetes mellitus. *Ann Intern Med* 1999; **130**:389–396.

76 Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, *et al.* Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Res Clin Pract* 1995; **28**:103–117.

77 UK Prospective Diabetes Study Group. UK Prospective Diabetes Study 24: a six year, randomized, controlled trial comparing sulfonylurea, insulin and metformin therapy in patients with newly diagnosed type 2 diabetes that could not be controlled with diet therapy. *Ann Intern Med* 1998; **128**:165–175.

78 Hepburn DA, MacLeod KM, Pell AC, Scougal IJ, Frier BM. Frequency and symptoms of hypoglycemia experienced by patients with type 2 diabetes treated with insulin. *Diabet Med* 1993; **10**:231–237.

79 Holstein A, Plaschke A, Egberts E-H. Clinical characterization of severe hypoglycemia – a prospective population-based study. *Exp Clin Endocrinol Diabetes* 2003; **111**:364–369.

80 Leese GP, Wang J, Broomhall J, Kelly P, Marsden A, Morrison W, *et al.*; DARTS/MEMO Collaboration. Frequency of severe hypoglycemia requiring emergency treatment in type 1 and type 2 diabetes: a population based study of health service resource use. *Diabetes Care* 2003; **26**:1176–1180.

81 Clarke WL, Cox DJ, Gonder-Frederick LA, Julian D, Schlundt D, Polonsky W. Reduced awareness of hypoglycemia in IDDM adults: a prospective study of hypoglycemia frequency and associated symptoms. *Diabetes Care* 1995; **18**:517–522.

82 Pramming S, Thorsteinsson B, Bendtson I, Binder C. Symptomatic hypoglycemia in 411 type 1 diabetic patients. *Diabet Med* 1991; **8**:217–222.

83 Pedersen-Bjergaard U, Pramming S, Thorsteinsson B. Recall of severe hypoglycemia and self-estimated state of awareness in type 1 diabetes. *Diabetes Metab Res Rev* 2003; **19**:232–240.

84 Lee SP, Yeoh L, Harris ND, Davies CM, Robinson RT, Leathard A, *et al*. Influence of autonomic neuropathy on QTc interval lengthening during hypoglycemia in type 1 diabetes. *Diabetes* 2004; **53**:1535–1542.

85 Adler GK, Bonyhay I, Failing H, Waring E, Dotson S, Freeman R. Antecedent hypoglycemia impairs autonomic cardiovascular function: implications for rigorous glycemic control. *Diabetes* 2009; **58**:360–366.

86 Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study Research Group. Long-term effect of diabetes and its treatment on cognitive function. *N Engl J Med* 2007; **356**:1842–1852.

87 Hershey T, Perantie DC, Warren SL, Zimmerman EC, Sadler M, White NH. Frequency and timing of severe hypoglycemia affects spatial memory in children with type 1 diabetes. *Diabetes Care* 2005; **28**:2372–2377.

88 Perantie DC, Wu J, Koller JM, Lim A, Warren SL, Black KJ, *et al*. Regional brain volume differences associated with hyperglycemia and severe hypoglycemia in youth with type 1 diabetes. *Diabetes Care* 2007; **30**:2331–2337.

89 Jacobsen AM. The psychological care of patients with insulin-dependent diabetes mellitus. *N Engl J Med* 1996; **344**:1249–1253.

90 Deckert T, Poulsen JE, Larsen M. Prognosis of diabetics with diabetes before the age of 31. I. Survival, cause of deaths and complications. *Diabetologia* 1978; **14**:363–370.

91 Tunbridge WMG. Factors contributing to deaths of diabetics under 50 years of age. *Lancet* 1981; **2**:569–572.

92 Laing SP, Swerdlow AJ, Slater SD, Botha JL, Burden AC, Waugh NR, *et al*. The British Diabetic Association Cohort Study. I. All-cause mortality in patients with insulin-treated diabetes mellitus. *Diabetic Med* 1999; **16**:459–465.

93 Feltbower RG, Bodansky HJ, Patterson CC, Parslow RC, Stephenson CR, Reynolds C, *et al*. Acute complications and drug misuse are important causes of death for children and young adults with type 1 diabetes. *Diabetes Care* 2008; **31**:922–926.

94 Skrivarhaug T, Bangstad H-J, Stene LC, Sandvik L, Hanssen KF, Joner G. Long-term mortality in a nationwide cohort of childhood-onset type 1 diabetic patients in Norway. *Diabetologia* 2006; **49**:298–305.

95 Gerich JE. Oral hypoglycemic agents. *N Engl J Med* 1989; **34**:1231–1245.

96 Holstein A, Egberts EH. Risk of hypoglycemia with oral antidiabetic agents in patients with type 2 diabetes. *Exp Clin Endocrinol Metab* 2003; **111**:405–414.

97 American Diabetes Association Workgroup on Hypoglycemia. Defining and reporting hypoglycemia in diabetes. *Diabetes Care* 2005; **28**:1245–1249.

98 Amiel SA, Sherwin RS, Simonson DC, Tamborlane WV. Effect of intensive insulin therapy on glycemic thresholds for counterregulatory hormone release. *Diabetes* 1988; **37**:901–907.

99 Mitrakou A, Fanelli C, Veneman T, Perriello G, Calderone S, Platanisiotis D, *et al*. Reversibility of hypoglycemia unawareness in patients with an insulinoma. *N Engl J Med* 1993; **329**:834–839.

100 Boyle PJ, Schwartz NS, Shah SD, Clutter WE, Cryer PE. Plasma glucose concentrations at the onset of hypoglycemic symptoms in patients with poorly controlled diabetes and in nondiabetics. *N Engl J Med* 1988; **318**:1487–1492.

101 Davis SN, Shavers C, Mosqueda-Garcia R, Costa F. Effects of differing antecedent hypoglycemia on subsequent counterregulation in normal humans. *Diabetes* 1997; **46**:1328–1335.

102 Diabetes Research in Children Network (DirecNet) Study Group. A multicenter study of the accuracy of the One Touch Ultra home glucose meter in children with type 1 diabetes. *Diabetes Technol Ther* 2003; **5**:933–941.

103 Davis S, Alonso MD. Hypoglycemia as a barrier to glycemic control. *J Diabetes Complications* 2004; **18**: 60–68.

104 de Galan BE, Schouwenberg BJJW, Tack CJ, Smits P. Pathophysiology and management of recurrent hypoglycemia and hypoglycemia unawareness in diabetes. *Neth J Med* 2006; **64**:269–279.

105 Boyle PJ, Zrebiec J. Management of diabetes-related hypoglycemia. *Southern Med J* 2007; **100**:183–194.

106 Rossetti P, Porcellati F, Bolli GB, Fanelli CG. Prevention of hypoglycemia while achieving good glycemic control in type 1 diabetes. *Diabetes Care* 2008; **31**(Suppl 2):S113–120.

107 Heller SR. Minimizing hypoglycemia while maintaining glycemic control in diabetes. *Diabetes* 2008; **57**:3177–3183.

108 Gonder-Frederick LA, Fisher CD, Ritterband LM, Cox DJ, Hou L, DasGupta AA, *et al*. Predictors of fear of hypoglycemia in adolescents with type 1 diabetes and their parents. *Pediatr Diabetes* 2006; **7**:215–222.

109 Nordfeldt S, Ludvigsson J. Fear and other disturbances of severe hypoglycemia in children and adolescents with type 1 diabetes mellitus. *J Pediatr Endocrinol Metab* 2005; **18**:83–91.

110 Cox DJ, Kovatchev B, Koev D, Koeva L, Dachev S, Tcharakchiev D, *et al*. Hypoglycemia anticipation, awareness and treatment training (HAATT) reduces occurrence of severe hypoglycemia among adults with type with type 1 diabetes mellitus. *Int J Behav Med* 2004; **11**:212–218.

111 Kovatchev BP, Cox DJ, Gonder-Frederick LA, Young-Hyman D, Schlundt D, Clarke WL. Assessment of risk for severe hypoglycemia among adults with 1DDM: validation of the Low Blood Glucose Index. *Diabetes Care* 1998; **21**:1870–1875.

112 Kovatchev BP, Cox DJ, Kumar A, Gonder-Frederick LA, Clarke WL. Algorithmic evaluation of metabolic control and risk of severe hypoglycemia in type 1 and type 2 diabetes using self-monitoring blood glucose (SMBG) data. *Diabetes Technol Ther* 2003; **5**:817–828.

113 Cox DJ, Gonder-Frederick L, Ritterband L, Clarke W, Kovatchev BP. Prediction of severe hypoglycemia. *Diabetes Care* 2007; **30**:1370–1373.

114 Hovorka R. Continuous glucose monitoring and closed-loop systems. *Diabet Med* 2005; **23**:1–12.

115 Ellis SL, Bookout T, Garg SK, Izuora KE. Use of continuous glucose monitoring to improve diabetes mellitus management. *Endocrinol Metab Clinics NA* 2007; **36**(Suppl 2):46–68.

116 Deiss D, Hartmann R, Schmidt J, Kordonouri O. Results of a randomized controlled cross-over trial on the effect of continuous subcutaneous glucose monitoring (CSGM) on glycemic control in children and adolescents with type 1 diabetes. *Exp Clin Endocrinol Diabetes* 2006; **114**:63–67.

117 Wilson DM, Beck RW, Tamborlane WV, Dontchev MJ, Kollman C, Chase P, *et al*. and The DirecNet Study Group. The accuracy of the FreeStyle Navigator continuous glucose monitoring system in children with type 1 diabetes. *Diabetes Care* 2007; **30**:59–64.

118 Buckingham B, Caswell K, Wilson DM. Real-time continuous glucose monitoring. *Curr Opin Endocrinol Diabetes Obes* 2007; **14**:288–295.

119 Bolen S, Feldman L, Vassy J, Wilson L, Yeh HC, Marinopoulos S, *et al*. Systematic review: comparative effectiveness and safety of oral medications for type 2 diabetes mellitus. *Ann Intern Med* 2007; **147**:386–399.

120 UK Prospective Diabetes Study Group. Overview of 6 years of therapy of type II diabetes: a progressive disease. *Diabetes* 1995; **44**:1249–1258.

121 de Heer J, Holst JJ. Sulfonylurea compounds uncouple the glucose dependence of the insulinotropic effect of glucagon-like peptide 1. *Diabetes* 2007; **56**:438–443.

122 Holstein A, Egberts EH. Risk of hypoglycemia with oral antidiabetic agents in patients with type 2 diabetes. *Exp Clin Endocrinol Metab* 2003; **111**: 405–414.

123 Gangji AS, Cukierman T, Gerstein HC, Goldsmith GH, Clase CM. A systematic review and meta-analysis of hypoglycemia and cardio-vascular events. *Diabetes Care* 2007; **30**:389–394.

124 Hirsch IB. Insulin analogues. *N Engl J Med* 2005; **352**:174–183.

125 Horvath K, Jeitler K, Berghold A, Ebrahim SH, Gratzer TW, Plank J, *et al*. Long-acting insulin analogues versus NPH insulin (human isophane insulin) for type 2 diabetes. *Cochrane Database Syst Rev* 2007; **2**:CD005613.

126 Gough SCL. A review of human and analogue insulin trials. *Diabetes Res Clin Pract* 2007; **77**:1–15.

127 Fatourechi MM, Kudva YC, Murad MH, Elamin MB, Tabini CC, Montori VM. Hypoglycemia with intensive insulin therapy: a systematic review and meta-analysis of randomized trials of continuous subcutaneous insulin infusion versus multiple daily injections. *J Clin Endocrinol Metab* 2009; **94**:729–740.

128 Mukhopadhyay A, Farrell T, Fraser RB, Ola B. Continuous subcutaneous insulin infusion vs intensive conventional insulin therapy in pregnant diabetic women: a systematic review and metaanalysis of randomized, controlled trials. *Am J Obstet Gynecol* 2007; **197**:447–456.

129 Raju B, Arbelez AM, Breckenridge SM, Cryer PE. Nocturnal hypoglycemia in type 1 diabetes: an assessment of preventive bedtime treatments. *J Clin Endocrinol Metab* 2006; **91**:2087–2092.

130 UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in over-weight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998; **352**:854–865.

131 Diabetes Control and Complications Trial Research Group. The relationship of glycemic exposure (HbA$_{1c}$) to the risk of development and progression of retinopathy in the Diabetes Control and Complications Trial. *Diabetes* 1995; **44**:968–983.

132 Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 2005; **353**:2643–2653.

133 Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008; **359**:1577–1589.

134 American Diabetes Association. Standards of medical care in diabetes, 2008. *Diabetes Care* 2008; **31**(Suppl 1):S12–54.

135 Qaseem A, Vijan S, Snow V, Cross JT, Weiss KB, Owens DK; for the Clinical Efficacy Assessment Subcommittee of the American College of Physicians. Glycemic control and type 2 diabetes mellitus: the optimal hemoglobin A$_{1C}$ targets: a guidance statement from the American College of Physicians. *Ann Intern Med* 2007; **147**:417–422.

136 Lachin JM, Genuth S, Nathan DM, Zinman B, Rutledge BN for the DCCT/EDIC Research Group. Effect of glycemic exposure on the risk of microvascular complications in the Diabetes Control and Complications Trial – revisited. *Diabetes* 2008; **57**:995–1001.

137 Huang ES, Zhang Q, Gandra N, Chin MH, Meltzer DO. The effect of comorbid illness and functional status on the expected benefits of intensive glucose control in older patients with type 2 diabetes: a decision analysis. *Ann Intern Med* 2008; **149**:11–19.

138 MacCuish AC. Treatment of hypoglycemia. In: Frier BM, Fisher BM, eds. *Diabetes and Hypoglycemia*. London: Edward Arnold, 1993: 212–221.

139 Wiethop BV, Cryer PE. Alanine and terbutaline in the treatment of hypoglycemia in IDDM. *Diabetes Care* 1993; **16**:1131–1136.

140 Haymond MW, Schreiner B. Mini-dose glucagon rescue to children with type 1 diabetes. *Diabetes Care* 2001; **24**:643–645.