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 non-glucose 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 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 insulin.
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 β2-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 α2-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 medulla [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.

<table>
<thead>
<tr>
<th>Plasma glucose</th>
<th>Individuals</th>
<th>Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-diabetic</td>
<td>Insulin</td>
</tr>
<tr>
<td>↓</td>
<td>T1DM*</td>
<td>No ↓</td>
</tr>
<tr>
<td>↓</td>
<td>Early T2DM</td>
<td>↓</td>
</tr>
<tr>
<td>↓</td>
<td>Late T2DM*</td>
<td>No ↓</td>
</tr>
</tbody>
</table>

* 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 β1-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
Part 6  Treatment of Diabetes

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 33.2 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.
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.
Hypoglycemia-associated autonomic failure

Early T2DM (Relative β-cell failure)
Marked absolute therapeutic hyperinsulinemia
Falling glucose levels
Isolated episodes of hypoglycemia

Advanced T2DM and T1DM (Absolute β-cell failure)
Relative or mild–moderate absolute therapeutic hyperinsulinemia
Falling glucose levels
β-cell failure
No insulin↓ and no ↑glucagon
Epidoses of hypoglycemia
Exercise
Sleep
Attenuated sympathoadrenal responses to hypoglycemia (HAAF)
↓Adrenomedullary epinephrine responses
↓Sympathetic neural responses
Defective glucose counter-regulation
Hypoglycemia unawareness
Recurrent hypoglycemia

Figure 33.5 Hypoglycemia-associated autonomic failure (HAAF) in the pathogenesis of iatrogenic hypoglycemia in diabetes.

Nominal glucose (mmol/L)

<table>
<thead>
<tr>
<th>5.6</th>
<th>5.0</th>
<th>4.4</th>
<th>3.9</th>
<th>3.3</th>
<th>2.8</th>
<th>2.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>60</td>
<td>120</td>
<td>180</td>
<td>240</td>
<td>300</td>
<td>360</td>
</tr>
</tbody>
</table>

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.
	herefore 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 perfused 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
flow with \[^{15}O\] 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 \[^{18}F\] 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 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 HbA1c, 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 HbA1c level consistently report higher rates of hypoglycemia in the group treated to lower HbA1c 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>
<thead>
<tr>
<th>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].</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Citation</strong></td>
</tr>
<tr>
<td><strong>Type 1 diabetes</strong></td>
</tr>
<tr>
<td>UK Hypoglycemia Study Group [63]</td>
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<tr>
<td>MacLeod et al. [64]</td>
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<td>Donnelly et al. [65]</td>
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<tr>
<td>Reichard &amp; Pihl [66]</td>
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<tr>
<td>DCCT Research Group [67]</td>
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<tr>
<td><strong>Type 2 diabetes</strong></td>
</tr>
<tr>
<td>MacLeod et al. [64]</td>
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<tr>
<td>UK Hypoglycemia Study Group [63]</td>
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<td>Akram et al. [69]</td>
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<td>Donnelly et al. [65]</td>
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<td>Henderson et al. [70]</td>
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<td>Murata et al. [71]</td>
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<td>Saudek et al. [72]</td>
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<td>Gürelk et al. [73]</td>
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<td>Abraira et al. [74]</td>
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<td>Yki-Järvinen et al. [75]</td>
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<tr>
<td>Ohkubo et al. [76]</td>
</tr>
</tbody>
</table>

* Insulin treatment for >15 years.
1 Insulin treatment for <5 years.
2 Insulin treatment for >5 years.
3 Insulin treatment for <2 years.
† Definite (8 per 100 patient-years) plus suspected (10 per 100 patient-years).


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\textsubscript{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.
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 ≤70mg/dL (3.9mmol/L)

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

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
   • 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)
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, gliclazide 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 hypoglycemia 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 (CSI) 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 HbA1c 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 HbA1c 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 [157].

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 HbA1c 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 [50–52,110–113]. 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 an 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.

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This chapter was written shortly after completion of the author’s Perspective in Diabetes [1] and his book Hypoglycemia in Diabetes: Pathophysiology, Prevalence and Prevention [2]. Therefore, much of the factual and interpretive content here is the same, as is no small part of the phraseology.

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

Evidence for a vicious cycle of exercise and hypoglycemia

Avoidance of Sandoval DA, Aftab Guy DL, Richardson MA, Ertl AC, Davis SN. Avoidance of hypoglycemia in type 1 diabetes mellitus.


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, sulphonylurea, metformin, or insulin for 6 years from diagnosis: UKPDS73. J Diabetes Complications 2006; 20:395–401.


57 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, sulphonylurea, metformin, or insulin for 6 years from diagnosis: UKPDS73. J Diabetes Complications 2006; 20:395–401.


61 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, sulphonylurea, metformin, or insulin for 6 years from diagnosis: UKPDS73. J Diabetes Complications 2006; 20:395–401.


63 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, sulphonylurea, metformin, or insulin for 6 years from diagnosis: UKPDS73. J Diabetes Complications 2006; 20:395–401.


66 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, sulphonylurea, metformin, or insulin for 6 years from diagnosis: UKPDS73. J Diabetes Complications 2006; 20:395–401.


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, sulphonylurea, metformin, or insulin for 6 years from diagnosis: UKPDS73. J Diabetes Complications 2006; 20:395–401.

69 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, sulphonylurea, metformin, or insulin for 6 years from diagnosis: UKPDS73. J Diabetes Complications 2006; 20:395–401.

70 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, sulphonylurea, metformin, or insulin for 6 years from diagnosis: UKPDS73. J Diabetes Complications 2006; 20:395–401.


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