REVIEW ARTICLE

CURRENT CONCEPTS

Diverse Causes of Hypoglycemia-Associated Autonomic Failure in Diabetes

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I ATROGENIC HYPOGLYCEMIA IS THE LIMITING FACTOR IN THE GLYCEMIC management of diabetes.[1,2] It causes recurrent symptomatic and sometimes, at least temporarily, disabling episodes in most people with type 1 diabetes as well as in many with advanced type 2 diabetes, and is sometimes fatal. Furthermore, iatrogenic hypoglycemia precludes maintenance of euglycemia during the lifetime of a person with diabetes and, thus, full realization of the well-established benefits of glycemic control.[3-5]

In this article, I discuss the clinical problem of hypoglycemia in diabetes from the perspective of pathophysiology. First, the syndromes of defective glucose counterregulation and hypoglycemia without warning symptoms (known as "hypoglycemia unawareness") are described, followed by the unifying concept of hypoglycemia-associated autonomic failure — the idea that recent episodes of hypoglycemia cause both syndromes. Next, the notion that there are additional forms of the phenomenon of hypoglycemia-associated autonomic failure is introduced. These forms are exercise-related and sleep-related hypoglycemia-associated autonomic failure. Finally, the implications for clinical management of these conditions are discussed.

Although current pharmacologic approaches to the glycemic management of diabetes are improving steadily, they are still far from ideal. Nonetheless, it is now possible both to improve glycemic control and to reduce the frequency of episodes of iatrogenic hypoglycemia in many people with diabetes. These are worthwhile goals.[3-5] However, lifelong maintenance of euglycemia is the ultimate goal. Such maintenance would probably eliminate the risk of microvascular complications that are specific to diabetes — retinopathy, nephropathy, and neuropathy — and might also reduce the risk of macrovascular complications to the level among nondiabetic persons.

DEFECTIVE GLUCOSE COUNTERREGULATION AND HYPOGLYCEMIA UNAWARENESS

Decrements in insulin, increments in glucagon, and in the absence of the latter, increments in epinephrine stand high in the hierarchy of redundant glucose-counterregulatory factors that normally prevent or rapidly correct hypoglycemia.[6] Glucose is an obligate metabolic fuel for the brain under physiologic conditions. Blood-to-brain glucose transport, facilitated by GLUT-1, across the capillary wall is thought to occur largely in astrocyte podocytes that surround the capillaries.[7] Within astrocytes, glucose can be stored as glycogen, or it can be glycolyzed to lactate, which is then exported to neurons, where it serves as an oxidative fuel. Because the brain cannot synthesize glucose or store more than a few minutes' supply as glycogen, it is critically dependent on a continuous

supply of glucose from the circulating blood. If arterial plasma glucose concentrations fall below the physiologic postabsorptive range, blood-to-brain glucose transport becomes inadequate for brain glucose metabolism and, ultimately, survival.

Falling arterial glucose concentrations are sensed in widespread regions of the brain as well as in the hepatic portal vein and the carotid body. The most extensively characterized mechanism of glucose sensing is glucokinase-mediated sensing in pancreatic beta cells; similar mechanisms may be operative in brain neurons.[8] As arterial plasma glucose concentrations decline within the physiologic range, insulin secretion decreases. This favors the increased production of hepatic (and renal) glucose. As concentrations of glucose in arterial plasma fall just below the physiologic range, the secretion of glucagon and epinephrine increases. Glucagon stimulates hepatic glycogenolysis; it also favors gluconeogenesis when precursors are abundant. Epinephrine stimulates hepatic (and renal) glucose production; it also reduces the clearance of glucose by tissues such as muscle and mobilizes gluconeogenic precursors such as lactate, amino acids, and glycerol.

All three of these physiologic defenses against the development of hypoglycemia — decrements in insulin and increments in glucagon and epinephrine — are compromised in most people with type 1 diabetes and in many with advanced type 2 diabetes[1,2] (Table 1). To the extent that endogenous secretion of insulin is deficient, therapeutic insulin levels do not fall, and glucagon levels do not rise as glucose levels fall. In addition, the response of epinephrine to a given level of hypoglycemia is often attenuated, with the glycemic threshold for that response shifted to lower plasma glucose concentrations. The combination of an absent glucagon response and an attenuated epinephrine response causes the clinical syndrome of defective glucose counterregulation.[1,2] An attenuated sympathoadrenal (sympathetic neural as well as adrenomedullary) response causes the clinical syndrome of hypoglycemia unawareness.[1,2] Hypoglycemia unawareness occurs as a result of the loss of the neurogenic (autonomic) warning symptoms (e.g., palpitations, tremor, anxiety, diaphoresis, and hunger) that previously allowed the patient to recognize and correct developing hypoglycemia. Both syndromes are associated with a substantially increased risk of severe iatrogenic hypoglycemia.[1,2]

HYPOGLYCEMIA-ASSOCIATED AUTONOMIC FAILURE

The concept of hypoglycemia-associated autonomic failure in type 1 diabetes and advanced type 2 diabetes[1,2,9-11] suggests that recent iatrogenic hypoglycemia causes both syndromes. It causes defective glucose counterregulation by reducing the response of adrenomedullary epinephrine to a given level of subsequent hypoglycemia in the setting of an absent glucagon response. It causes hypoglycemia unawareness by reducing the sympathoadrenal response and the resulting responses, consisting of neurogenic symptoms, to a given level of subsequent hypoglycemia. Thus, there is a vicious cycle of recurrent hypoglycemia.

The clinical effect of hypoglycemia-associated autonomic failure is well established in type 1 diabetes. Recent hypoglycemia, even asymptomatic nocturnal hypoglycemia, reduces the response of epinephrine and symptomatic responses to subsequent hypoglycemia.[12] Recent hypoglycemia also reduces cognitive dysfunction during subsequent hypoglycemia[12,13] and makes it difficult to detect hypoglycemia in the clinical setting.[13] It impairs the glycemic defense against hyperinsulinemia.[10] Finally, the finding that in most affected patients as little as two to three weeks of scrupulous avoidance of iatrogenic hypoglycemia reverses hypoglycemia unawareness and improves the epinephrine component of glucose counterregulation[14-17] provides compelling support for the clinical relevance of established hypoglycemia-associated autonomic failure in type 1 diabetes.

The clinical effect of hypoglycemia-associated autonomic failure in type 2 diabetes is less well established. However, the glucagon response to hypoglycemia is virtually absent in patients who are near the insulin-deficient end of the spectrum.[11] Furthermore, the thresholds for the responses of epinephrine and neurogenic symptoms to hypoglycemia are shifted to lower plasma glucose concentrations after recent hypoglycemia.[11] These patterns — endogenous insulin deficiency resulting in unregulated (exogenous) insulin levels, an absence of glucagon, and reduced responses of epinephrine and neurogenic symptoms to a given level of hypoglycemia — are the key features of hypoglycemia-associated autonomic failure in type 1 diabetes. Therefore, patients with advanced (i.e., insulin-deficient) type 2 diabetes are at risk for hypoglycemia-associated autonomic failure.

Overall, the frequency of episodes of hypoglycemia is lower in type 2 diabetes than in type 1.[1,2] However, hypoglycemia becomes progressively more limiting with respect to glycemic control over time in type 2 diabetes,[18] and the incidence of severe hypoglycemia has been reported to be similar in patients with type 2 diabetes and those with type 1 diabetes if such patients are matched for the duration of insulin therapy.[19] Population-based data indicate that the incidence of severe hypoglycemia in type 2 diabetes that is treated with insulin is approximately 40 percent[20] or even 100 percent[21] of the incidence in type 1 diabetes. Taken together, these data indicate that the incidence of iatrogenic hypoglycemia approximates that in type 1 diabetes in patients near the insulin-deficient end of the spectrum of type 2 diabetes. This is perhaps a result of the pathophysiological features discussed above (Table 1).

Hypoglycemia-associated autonomic failure is a functional disorder distinct from classic diabetic autonomic neuropathy. It is a dynamic phenomenon that can be induced (by prior hypoglycemia) and reversed (by avoidance of hypoglycemia) and is manifested clinically by recurrent iatrogenic hypoglycemia. In contrast, diabetic autonomic neuropathy is a structural disorder that is manifested clinically by gastrointestinal or genitourinary symptoms or by orthostatic hypotension. Nonetheless, there is evidence that the key features of hypoglycemia-associated autonomic failure are more prominent in patients with diabetic autonomic neuropathy than in those without diabetic autonomic neuropathy.[22,23]

Despite the clinical impact of hypoglycemia-associated autonomic failure, its mediators and mechanisms are largely unknown.[1,2] Davis and colleagues[24,25] suggested that the cortisol response to antecedent hypoglycemia mediates hypoglycemia-associated autonomic failure through actions of cortisol on the brain. That suggestion was based on two findings: cortisol infusions given on one day reduced the responses of adrenomedullary epinephrine and sympathetic nerve activity in the muscles to hypoglycemia on the next day (any effects on symptomatic responses were not reported),[24] and the effect of antecedent hypoglycemia in reducing responses to subsequent hypoglycemia was not apparent in cortisol-deficient patients.[25] Indeed, marked $\alpha_{1\text{-}24}$ corticotropin-induced cortisol elevations were found to reduce adrenomedullary and neurogenic symptoms in response to hypoglycemia the following day.[26] However, less marked elevations of antecedent cortisol, to levels more comparable to those that occur during hypoglycemia, were not found to reduce adrenomedullary epinephrine or neurogenic symptoms in response to subsequent hypoglycemia.[27] For this reason, among others,[27] cortisol does not appear to be the major mediator of hypoglycemia-associated autonomic failure.

On the basis of a body of evidence in rodents showing that hypoglycemia for a period of days to weeks results in increased uptake of glucose in the brain and in blood–brain-barrier GLUT-1 messenger RNA and protein,[28] the hypothesis of brain glucose transport suggests that increased blood-to-brain glucose transport at a given level of hypoglycemia is the mechanism of hypoglycemia-associated autonomic failure. Boyle and colleagues reported that uptake of glucose in the brain (calculated from arteriovenous differences across the brain and cerebral blood flow) was preserved during hypoglycemia after approximately 56 hours of between-meal hypoglycemia in healthy persons[29] and in patients with well-controlled (i.e., frequently hypoglycemic) type 1 diabetes.[30] However, using [1-^{11}C]glucose and positron emission tomography, Segel and colleagues[31] found that global blood-to-brain glucose transport during hypoglycemia did not increase after approximately 24 hours of between-meal hypoglycemia. Furthermore, de Vries et al.[32] found that, in rats, at the same concentrations of blood glucose, concentrations of interstitial glucose in the ventromedial hypothalamus were slightly lower, not higher, during euglycemia and hypoglycemia after three days of hypoglycemia.

Table 1. Neuroendocrine and Symptomatic Responses to Hypoglycemia in Nondiabetic Persons, Patients with Type 1 Diabetes, and Those with Type 2 Diabetes.*

Response	Nondiabetic	Type 1 Diabetes	Type 2 Diabetes
Pancreatic islets			
Insulin	↓↓	No ↓†	↓↓-No ↓
Glucagon	↑↑	No ↑†	↑↑-No ↑
Sympathoadrenal system			
Epinephrine	↑↑	↑ †	↑↑-↑
Neurogenic symptoms	↑↑	↑ ‡	↑↑-↑

* A single arrow denotes a smaller decrease or increase, and double arrows a larger decrease or increase.
† Absent glucagon and attenuated epinephrine responses result in defective glucose counterregulation.
‡ Loss of neurogenic warning symptoms result in hypoglycemia unawareness.

The findings above[31,32] are not consistent with increased blood-to-brain glucose transport induced by antecedent hypoglycemia. Thus, it may be that the alteration lies beyond the blood–brain barrier.[33] A difference in ^{18}F-fluorodeoxyglucose accumulation in the subthalamic region of the brain has been reported in patients with type 1 diabetes with hypoglycemia unawareness and those without it.[34]

The mechanism for the loss of the glucagon response to hypoglycemia in type 1 and advanced type 2 diabetes is not known, but it is closely linked to insulin deficiency.[1,2] There is evidence that a decrease in intra-islet insulin in rodents and in humans is normally a signal to increase glucagon secretion during hypoglycemia.[35] If so, loss of that intra-islet signal in insulin-deficient diabetes might explain loss of the glucagon response. However, the intra-islet–insulin hypothesis remains to be documented fully in humans.[35]

A reduced sympathoadrenal response to a given level of hypoglycemia is a fundamental feature of hypoglycemia-associated autonomic failure. Because the neurogenic symptoms of hypoglycemia are largely the result of sympathetic neural, rather than adrenomedullary, activation,[36] clinical hypoglycemia unawareness must be largely the result of reduced sympathetic nervous system responses to hypoglycemia.

Initially, my colleagues and I[9-11] attributed hypoglycemia-associated autonomic failure in diabetes exclusively to recent hypoglycemia; that is, to hypoglycemia-induced autonomic failure. However, it may well be that in addition to recent hypoglycemia, exercise and sleep can cause the phenomenon of hypoglycemia-associated autonomic failure (Fig. 1).

EXERCISE-RELATED, HYPOGLYCEMIA-ASSOCIATED AUTONOMIC FAILURE

Galassetti and colleagues[37] found that exercise reduced the responses of adrenomedullary epinephrine and sympathetic nerve activity in the muscles to hypoglycemia the following day. The neurogenic symptoms of hypoglycemia are the result of the perception of physiological changes caused by the autonomic discharge mediated by the central nervous system and triggered by hypoglycemia.[38] These symptoms are largely the result of sympathetic neural, rather than adrenomedullary, activation.[36] Therefore, to the extent that the reduced response to hypoglycemia of sympathetic nerve activity in the muscles after exercise, as observed by Galassetti et al.,[37] reflected a reduction of the more generalized sympathetic neural response, one would anticipate reduced responses of neurogenic symptoms. However, that was not the case.[37] McGregor and colleagues[39] also found that exercise reduced the epinephrine response to subsequent hypoglycemia. Again, however, responses of neurogenic symptoms to hypoglycemia were not reduced. Thus, since antecedent exercise does not reduce symptoms and does not cause hypoglycemia unawareness, hypoglycemia-associated autonomic failure that is related to exercise appears to be a partial syndrome.

SLEEP-RELATED, HYPOGLYCEMIA-ASSOCIATED AUTONOMIC FAILURE

Sleep is a more compelling cause of the phenomenon of hypoglycemia-associated autonomic failure. Persons with type 1 diabetes have substantially
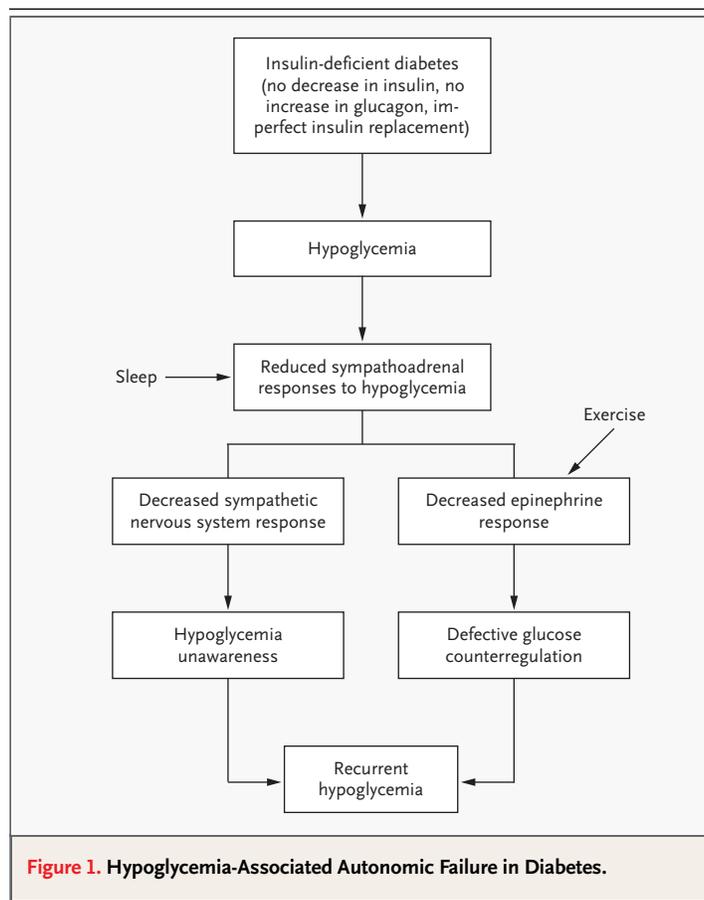

Figure 1. Hypoglycemia-Associated Autonomic Failure in Diabetes.

reduced sympathoadrenal responses to a given level of hypoglycemia,[1,2] and these responses are further reduced during sleep.[40,41] Moreover, probably because of their markedly reduced sympathoadrenal responses, persons with type 1 diabetes are much less likely to be awakened by hypoglycemia than are nondiabetic persons (Fig. 2).[41] Thus, while sleeping, patients with type 1 diabetes have both defective glucose counterregulation (an epinephrine response that is further reduced in the absence of a glucagon response) and a form of hypoglycemia unawareness (reduced arousal from sleep), which are the two components of hypoglycemia-associated autonomic failure in diabetes.[1,2,9-11]

CLINICAL IMPLICATIONS

Comprehensive treatment makes a difference for people with diabetes. For example, one study showed that an intensive approach that targeted hyperglycemia, hypertension, dyslipidemia, and microalbuminuria reduced the risk of microvascular and macrovascular events by more than 50 percent in patients with type 2 diabetes.[42] Aggressive glucose-lowering therapy reduces, but does not eliminate, microvascular complications — retinopathy, nephropathy, and neuropathy — in patients with

type 1 diabetes[3] and in those with type 2 diabetes.[4,5] Extrapolation of the data from the Diabetes Control and Complications Trial suggests that maintaining euglycemia during a lifetime of diabetes would eliminate these complications.[43]

On the other hand, despite abundant epidemiologic evidence of a direct association between glycemia and macrovascular disease in diabetes,[44,45] controlled trials have shown that partial control of glycemia has limited effects on the development of macrovascular disease.[3-5,46,47] The relationship between the mean glycosylated hemoglobin concentration and the risk of myocardial infarction appears to be shifted to a lower glycosylated hemoglobin value than is the relationship between mean glycosylated hemoglobin concentration and the risk of microvascular complications.[44] Thus, although it is practical to reduce, but not eliminate, the risk of microvascular complications with available therapies to lower glucose, because of the barrier of iatrogenic hypoglycemia it might not be practical to hold glucose levels low enough, for a long enough period, to reduce the risk of macrovascular complications in a substantial portion of patients with diabetes.[1,2]

Strategies to minimize the risk of hypoglycemia while improving glycemic control[2] include addressing the problem of hypoglycemia at each patient contact, applying the principles of aggressive therapy through education of patients, encouraging frequent self-monitoring of blood glucose, setting up flexible regimens of treatment with insulin or other drugs and providing individualized glycemic goals and ongoing professional support, and considering both the conventional risk factors for hypoglycemia and the risk factors for hypoglycemia-associated autonomic failure. The conventional risk factors — doses of insulin or insulin secretagogue that are excessive, ill-timed, or of the wrong type; missed meals or the overnight fast; exercise; and alcohol ingestion — are based on the premise that an absolute or relative excess of therapeutic insulin is the sole determinant of risk. However, iatrogenic hypoglycemia is more appropriately viewed as the result of the interplay of an excess of therapeutic insulin and compromised physiological and behavioral defenses against the development of hypoglycemia (i.e., defective glucose counterregulation and hypoglycemia unawareness).[1,2] Established risk factors for the latter include a marked deficiency of endogenous insulin; a history of severe hypoglycemia, hypoglycemia un-
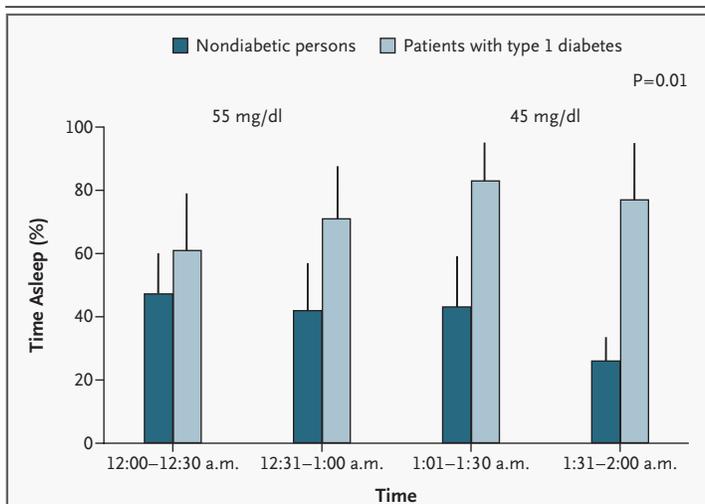

Figure 2. Mean (±SE) Sleep Efficiency during Hypoglycemia in Eight Nondiabetic Persons and Four Patients with Type 1 Diabetes.
Sleep efficiency was measured as the percentage of time that the subject was asleep. Hypoglycemia was induced with a glucose clamp at 55 mg per deciliter (3.1 mmol per liter) and at 45 mg per deciliter (2.5 mmol per liter), as shown. Adapted from Banarer and Cryer.[41]

awareness, or both; and lower glycemic goals, lower levels of glycosylated hemoglobin, or both. These are clinical surrogates of hypoglycemia-associated autonomic failure.

A deficiency of endogenous insulin indicates that (exogenous) insulin levels will not decrease and glucagon levels will not increase as plasma glucose levels fall. Prior hypoglycemia causes a reduced sympathoadrenal response to subsequent hypoglycemia, and hypoglycemia unawareness typically implies prior hypoglycemia, even if it has not been recognized. Lower glycemic goals and lower levels of glycosylated hemoglobin are associated with an increased probability of prior hypoglycemia.

A detailed discussion of glucose-lowering drugs is beyond the scope of this article. Briefly, the use of a long-acting insulin analogue (e.g., glargine) as the basal insulin and of a rapid-acting insulin analogue (e.g., lispro or aspart) before meals in a regimen of basal-bolus insulin minimizes the risk of hypoglycemia. A regimen of continuous subcutaneous insulin infusion (with a rapid-acting insulin analogue) that provides basal and premeal bolus replacement of insulin also reduces this risk.[2,48] Of the sulfonylureas, glimepiride and glipizide are the least likely to cause hypoglycemia. Metformin monotherapy should not cause hypoglycemia, although it has been reported to do so.[49] Monotherapy with a thiazolidinedione or an α-glucosidase inhibitor should not cause hypoglycemia.

Hypoglycemia-associated autonomic failure due to prior episodes of hypoglycemia is diagnosed clinically on the basis of a history of severe hypoglycemia, hypoglycemia unawareness, or both, particularly in an insulin-deficient patient with a relatively low glycosylated hemoglobin level. Two to three weeks of scrupulous avoidance of hypoglycemia is a rational approach to correcting this problem.[14-17] The efficacy of this approach is reflected by the return of symptoms. Provision of less insulin action, more carbohydrate intake, or both late after exercise are the logical approaches to hypoglycemia-associated autonomic failure that is related to exercise.[2] With respect to hypoglycemia-associated autonomic failure related to sleep, nocturnal hypoglycemia is often a problem, despite the use of bedtime snacks.[2,50] The use of a long-acting basal insulin and a rapid-acting premeal insulin in a basal-bolus regimen, or the use of a continuous subcutaneous insulin infusion with adjustments of the basal infusion rates, minimizes the risk of nocturnal hypoglycemia. A reliable blood, or even tissue, glucose sensor with an alarm could compensate for reduced arousal from sleep. In theory, such a sensor could be linked to a device that would deliver plasma glucose–regulated insulin, a glucose-raising hormone (e.g., glucagon or epinephrine), an epinephrine-simulating drug such as the β_2-adrenergic agonist terbutaline,[50] or a combination of these agents.

SUMMARY

The original concept of hypoglycemia-associated autonomic failure in type 1 diabetes and advanced type 2 diabetes posited that recent iatrogenic hypoglycemia causes both defective glucose counterregulation (by reducing the epinephrine response in the absence of a glucagon response) and hypoglycemia unawareness (by reducing the sympathoadrenal response and the resulting response of neurogenic symptoms), and thus, a vicious cycle of recurrent hypoglycemia. The clinical relevance of this phenomenon is now well established, but the mediators and mechanisms remain largely unknown. Recent data indicate that there are diverse causes of hypoglycemia-associated autonomic failure. In addition to hypoglycemia-induced autonomic failure, the disorder can be related to exercise or sleep.

The ultimate goal of lifelong maintenance of euglycemia in patients with diabetes remains elusive because of the pharmacokinetic imperfections of all current glucose-lowering therapies and the resulting barrier of hypoglycemia. Achievement of that goal will require plasma glucose–regulated insulin replacement or secretion. Nonetheless, it is now possible both to improve the control of glycemia and to reduce the frequency of hypoglycemia in many people with diabetes. These results can be accomplished by recognizing the problem of hypoglycemia, applying the principles of aggressive glycemic therapy, and reducing the risk factors for hypoglycemia in people with diabetes.

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