Frequency of Severe Hypoglycemia in Patients With Type I Diabetes With Impaired Awareness of Hypoglycemia

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OBJECTIVE — To determine the frequency of hypoglycemia in patients with type I diabetes and impaired awareness of hypoglycemia by prospective assessment.

RESEARCH DESIGN AND METHODS — A prospective study was undertaken for 12 months in 60 patients with type I diabetes: 29 had impaired awareness of hypoglycemia and 31 retained normal awareness of hypoglycemia. The two groups of patients were matched for age, age at onset of diabetes, duration of diabetes, and glycemic control. Episodes of severe hypoglycemia were recorded within 24 h of the event and verified where possible by witnesses.

RESULTS — During the 12 months, 19 (66%) of the patients with impaired awareness had one or more episodes of severe hypoglycemia with an overall incidence of 2.8 episodes · patient^{-1} · year^{-1}. By comparison, 8 (26%) of the patients with normal awareness experienced severe hypoglycemia ($P < 0.01$) with an annual incidence of 0.5 episode · patient^{-1} · year^{-1} ($P < 0.001$). Severe hypoglycemia occurred at different times of the day in the two groups: patients with impaired awareness experienced a greater proportion of episodes during the evening ($P = 0.03$), and patients with normal awareness experienced a greater proportion in the early morning ($P = 0.05$). An assessment of fear of hypoglycemia revealed that patients with impaired awareness of hypoglycemia worried more about hypoglycemia than did patients with normal awareness ($P = 0.008$), but did not modify their behavior accordingly.

CONCLUSIONS — This prospective evaluation demonstrated that impaired awareness of hypoglycemia predisposes to a sixfold increase in the frequency of severe hypoglycemia, much of which occurred at home during waking hours.

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DCCT, Diabetes Control and Complications Trial.

Hypoglycemia is a common and potentially dangerous side effect of treatment with insulin in diabetic patients and has a significant morbidity (1–3). When severe hypoglycemia is defined as an episode that the patient is unable to self-treat, retrospective studies of the frequency of severe hypoglycemia have produced consistent estimates of around 1.1–1.6 episodes · patient^{-1} · year^{-1} (1,4,5). Impaired awareness of hypoglycemia is recognized to occur in patients with insulin-treated diabetes (6–10) and may be defined as the impaired ability of the patient to perceive the onset of hypoglycemia; it may develop irrespective of the species of insulin used. The etiology of impaired awareness of hypoglycemia is probably multifactorial (11–14) and has been classified into two separate clinical entities, one of which is transient, reversible, and related to strict glycemic control whereas the other is chronic, irreversible, and related to duration of diabetes (14). In addition, recurrent episodes of hypoglycemia per se (15) result in defective counterregulation and reduced symptomatic responses, which will predispose to further episodes of severe hypoglycemia. The term "impaired awareness" is preferred to the term "hypoglycemia unawareness," as few patients have complete loss of the premonitory warning symptoms of hypoglycemia.

About 50% of patients with type I diabetes have been shown to experience a change in the symptoms of hypoglycemia after 15–20 years of insulin therapy (4), and this acquired defect has been associated with more frequent episodes of severe hypoglycemia (2,4,16,17). Severe hypoglycemia produces profound neuroglycopenia, which may impair the patient's subsequent recollection of the episode. Retrospective assessment may therefore underestimate the true frequency of severe hypoglycemia experienced by affected patients. In this study, the frequency of severe hypoglycemia in patients with type I diabetes with normal awareness of hypoglycemia was docu-

Table 1—*Demographic data for patients with type I diabetes*

	Group 1 (normal awareness)	Group 2 (impaired awareness)	*P* value
n	31	29	
Gender distribution (M/F)	18/13	17/12	NS
Age (years)	43.9 ± 10.6	48.4 ± 11.7	NS
Age at onset (years)	25.3 ± 10.3	27.8 ± 10.8	NS
Duration of type I diabetes (years)	18.6 ± 7.6	21.0 ± 8.1	NS
Daily insulin dose (U/kg)	0.63 ± 0.09	0.69 ± 0.10	NS
Hb_{A1} (%)			
Start of study	10.0 ± 1.2	10.2 ± 1.5	NS
End of study	10.2 ± 1.4	10.0 ± 1.2	NS
Complications			
Microalbuminuria	4 (12.9)	4 (13.7)	NS
Macroproteinuria (>0.3 g/l)	0	1 (3.4)	NS
Hypertension	4 (12.9)	5 (17.2)	NS
Retinopathy			
Background	23 (74.2)	26 (89.6)	NS
Proliferative	8 (23.8)	3 (10.4)	NS
Awareness on linear analogue scale (median)	5	1.5	<0.0005

Data are means ± SD. For complications, data are numbers of patients (percentage).

mented prospectively during 12 months and compared with that of a matched group of patients who had a history of impaired awareness of hypoglycemia.

RESEARCH DESIGN AND METHODS

— Permission for the study was granted by the local medical ethics committee, and written consent was obtained from all patients before participation.

Definition of alteration in awareness of hypoglycemia

The symptoms that patients usually experienced during hypoglycemia during waking hours were documented, and each symptom was assessed on a visual analogue scale of 1 to 7 (1 = not present; 7 = present a great deal); the symptoms were subdivided into autonomic, neuroglycopenic, and nonspecific groups (18). Awareness of hypoglycemia was defined as normal if the patient reported no subjective alteration in warning symptoms since commencing insulin therapy and experienced predominantly autonomic warning symptoms associated with the onset of acute hypoglycemia. The patients with normal awareness of hypoglycemia scored between 1 and 2 on a visual analogue scale of 1 to 7, which was used to record awareness of hypoglycemia (1 = always aware of the onset of hypoglycemia; 7 = never aware of the onset of hypoglycemia). Patients were considered to have impaired awareness if they had noticed a definite change in their warning symptoms of hypoglycemia for at least 2 years, during which at least two episodes of hypoglycemia had occurred. These patients now experienced predominantly neuroglycopenic symptoms and scored more than 4 on the visual analogue scale assessing awareness. Hypoglycemia awareness was defined by clinical history criteria rather than by the response to experimental hypoglycemia induced in a laboratory setting, as this was considered to be more relevant to the hypoglycemia experienced during daily life and takes into account the patient's subjective reality.

Patient groups

Sixty patients with type I diabetes were recruited from the diabetic outpatient clinic of the Royal Infirmary of Edinburgh. Type I diabetes was determined by the rapid onset of symptomatic hyperglycemia associated with ketonuria, which required early treatment with insulin. The patients were subdivided into two groups on the basis of their self-reported awareness of hypoglycemia: group 1 was 31 patients with normal awareness of hypoglycemia, and group 2 was 29 patients with impaired awareness of hypoglycemia.

The patients in the two groups were recruited simultaneously to try to ensure close matching. The two groups had not differed in their self-reported symptom profiles at the time of diagnosis of diabetes (assessed retrospectively), but at the time of recruitment into the study, the patients with impaired awareness were experiencing significantly fewer autonomic symptoms than those patients with normal awareness (autonomic symptom score 14 in patients with normal awareness versus 10 in patients with impaired awareness, $P < 0.001$). Where possible, confirmation of impaired awareness was obtained by questioning their spouses, partners, or other close relatives about the patients' preceding history of hypoglycemia.

Patient characteristics

The characteristics of each patient group are shown in Table 1. The groups were matched for age, duration of diabetes, age at onset, and glycemic control at the start of the survey. Details of complications of diabetes were ascertained by physical examination, including direct ophthalmoscopy, and from clinical records. Patients were excluded if they were taking any medication that may have impaired awareness of hypoglycemia, e.g., β-blocking agents. Both groups had few diabetic complications and did not differ in the incidence or severity of retinopathy, peripheral neuropathy (assessed by clinical examination), or frank proteinuria or microalbuminuria signifying nephropathy

Table 2—*Frequency of hypoglycemia in patients with type I diabetes*

	Group 1 (normal awareness)	Group 2 (impaired awareness)	*P* value
Severe hypoglycemia			
Total episodes	15	82	<0.001
>1 Episode (%)	8 (25.8)	19 (65.5)	<0.01
Episodes · patient^{-1} · year^{-1}	0.48	2.83	<0.0001
Mild hypoglycemia			
Total episodes	73	137	NS
> 1 Mild episode (%)	80.1	62	NS
Episodes · patient^{-1} · year^{-1}	2.8	4.7	NS

(Table 2). Autonomic function tests (19) were performed in all patients and indicated that three in each group had abnormal autonomic function. Total glycated hemoglobin was measured using high-speed liquid chromatography based on an ion-exchange reverse-phase partition method (Hi Auto A1c HA 8121) (The nondiabetic range for our laboratory was 4.5–8%.) Mean concentrations did not differ between the groups either at the beginning or at the end of the study.

The number of daily injections of insulin did not differ between the groups; >70% of both groups were taking a twice-daily regimen. Four patients in each group were using pork insulin, and all other patients had been using human insulin for at least 5 years before the study. The pattern of home blood glucose monitoring did not differ significantly between the groups; on average, 52% of patients with normal awareness and 62% with impaired awareness monitored capillary blood glucose regularly, at least on alternate days, and 45% of those with impaired awareness monitored blood glucose daily compared with 33% of the patients with normal awareness.

Protocol for survey

"Severe" hypoglycemia was defined as any episode requiring external assistance; all other episodes that the patient was able to self-treat were considered to be "mild." Episodes of asymptomatic biochemical hypoglycemia, identified by the random blood glucose monitoring diaries described below, were not included in the total number of episodes of mild hypoglycemia. Patients were asked to document each episode of hypoglycemia within 24 h of its occurrence, and details about the hypoglycemic episode were documented: time of day of episode, activity at the time of hypoglycemia (including whether asleep), any obvious predisposing factors (e.g., delayed or missed meals, strenuous exertion), the need for external help, the treatment required, and any resultant morbidity such as physical injury, loss of consciousness, convulsions, or accidents. The patients were asked to monitor capillary blood glucose on a regular basis, either visually or using a meter, and complete three 10-point diaries during each 3-month period. This diary comprised 10 different time points at 2-h intervals throughout a 24-h period, at which the patient was asked to measure and record random blood glucose levels. Wherever possible, witnessed accounts (by relatives, friends, or colleagues) of each episode of hypoglycemia were recorded. After enrollment, patients were reviewed at 3-month intervals, glycemic control was reappraised at each visit, and adjustments in insulin doses were made if necessary. If considered appropriate on clinical grounds, changes in insulin regimen were made in patients who were experiencing severe hypoglycemia: two of the patients with impaired awareness of hypoglycemia were changed to multiple injection regimens to try to diminish the frequency of hypoglycemia; no changes in glycemic control were observed in individual patients as a result of these modifications. Although this may have affected the estimated frequency of hypoglycemia, inaction was considered to be ethically unacceptable.

A questionnaire documenting fear of hypoglycemia (20) was undertaken at the beginning of the study to identify any differences in attitude and behavioral responses toward hypoglycemia. The patients' driving history and number and nature of any previous road traffic accidents were documented.

Statistical analysis

Demographic data were analyzed using Student's *t* tests for unpaired samples. All other data that were not normally distributed were analyzed using Wilcoxon rank-sum tests and, where applicable, χ^2 tests (with Yates correction) were used to analyze group differences.

RESULTS

Frequency of hypoglycemia

The frequency of all episodes of hypoglycemia is shown in Table 2. The patients with impaired awareness of hypoglycemia experienced significantly more episodes of severe hypoglycemia than did

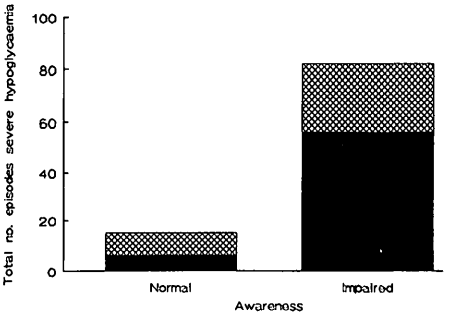

Figure 1—*Total number of episodes of severe hypoglycemia experienced by patients with type I diabetes.* ▨, *Episodes of hypoglycemia occurring during sleep;* ■, *episodes occurring while awake.*

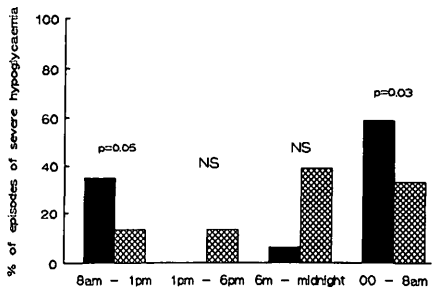

Figure 2—*Percentages of total number of episodes of severe hypoglycemia occurring at different times of the day in patients with type I diabetes with normal (■) and impaired (▩) awareness of hypoglycemia.*

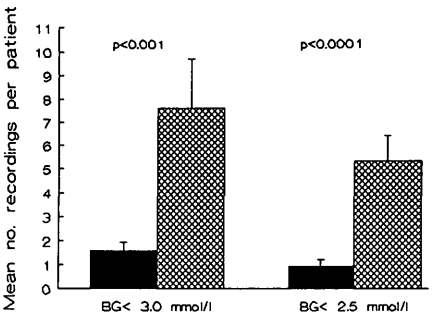

Figure 3—*Mean number of home blood glucose (BG) recordings <3 and <2.5 mM and not accompanied by symptoms of hypoglycemia in patients with type I diabetes with normal (■) and impaired (▩) awareness of hypoglycemia.*

the patients with normal awareness. Approximately 85% of all episodes of severe hypoglycemia were verified by witnesses. The frequency of mild episodes did not differ significantly between the two groups.

The number of episodes of severe hypoglycemia occurring either while the patients were awake or asleep are shown in Fig. 1, and the times of occurrence throughout the day of the episodes of severe hypoglycemia are shown in Fig. 2. The periodicity of severe hypoglycemia differed between the two groups. In the patients with normal awareness, 60% of all episodes occurred between 2400 and 0800, and 53% of all episodes occurred during sleep, compared with the patients with impaired awareness in whom 31% of all episodes occurred between 2400 and 0800, and 31% of episodes occurred during sleep. The patients with normal awareness of hypoglycemia therefore experienced a significantly greater proportion of episodes of severe hypoglycemia during the night (usually during sleep) compared with those with impaired awareness ($P = 0.05$). The patients with impaired awareness of hypoglycemia experienced a significantly greater proportion of episodes during the evening before retiring to bed compared with the patients with normal awareness of hypoglycemia. No differences in the causes of hypoglycemia identified either by patients or by witnesses could be ascertained between the two groups. In the patients with normal awareness, 60% of the episodes of severe hypoglycemia could not be explained, as were 54% of the episodes in the patients with impaired awareness. The methods by which severe hypoglycemia was treated did not differ proportionately between the groups; 14% of episodes ($n = 2$) in patients with normal awareness required glucagon compared with 21% ($n = 17$) of episodes in patients with impaired awareness; all other episodes were treated with oral carbohydrate.

Morbidity

Only five episodes of severe hypoglycemia required hospital treatment. On two different occasions the same patient (who had impaired awareness) required admission for treatment of a fractured hip and a head injury. Two of the other three episodes occurred in another patient who had impaired awareness. Five (33%) of the 15 episodes of severe hypoglycemia in the patients with normal awareness of hypoglycemia resulted in loss of consciousness compared with 29 (35%) of the 82 episodes in the patients who had impaired awareness. Only two patients, both of whom had impaired awareness of hypoglycemia, experienced convulsions during hypoglycemia; one experienced nocturnal convulsions associated with hypoglycemia on five occasions and the other experienced hypoglycemic convulsions on two occasions, also during the night. Neither patient had idiopathic epilepsy.

Fear of hypoglycemia

Responses to the fear questionnaire indicated that patients with normal awareness of hypoglycemia worried less about hypoglycemia (median score 31.5) than patients with impaired awareness (median score 41) ($P = 0.008$). However, despite their greater concern and anxiety about hypoglycemia, the patients with impaired awareness had not modified their behavior (median score 30) to avoid hypoglycemia when compared with the patients with normal awareness (median score 29).

Home blood glucose monitoring

Similar numbers of blood glucose measurements in the 10-point diaries were made by both groups; an average of ~90 random measurements were made by each patient in addition to their usual monitoring practices. The mean number (in 12 months) of home blood glucose measurements with values <3.0 and <2.5 mM, which were not accompanied by symptoms of hypoglycemia, were significantly fewer in the patients with normal awareness of hypoglycemia compared with the patients with impaired awareness (Fig. 2) (blood glucose values <3.0 mM, $P < 0.001$; blood glucose <2.5 mM, $P < 0.0001$) (Fig. 3).

Driving experience

The questionnaire assessed overall driving experiences since commencing treatment with insulin and was not restricted to the study period. Of patients with normal awareness of hypoglycemia, 24 held a valid driving license (restricted to 3 years); 8 had previously experienced hypoglycemia while driving, but none of the episodes had resulted in road traffic accidents. Of these patients, 11 had been involved in minor motor vehicle accidents at other times, which were not related to

hypoglycemia. Only 11 patients with impaired awareness of hypoglycemia currently held valid driving licenses, which was significantly fewer than the patients with normal awareness ($P < 0.01$); five patients with impaired awareness had ceased driving voluntarily because of concern about the risk of causing accidents during hypoglycemia and no longer held driving licenses, and one patient's license had been revoked by the licensing authority. However, of those patients who had impaired awareness and had continued to drive, five had experienced hypoglycemia while driving. Only one such patient had ever been involved in a road traffic accident, which was not related to hypoglycemia and was the fault of a third party. Comparison of the accident rates of both groups using χ^2 showed that the patients with impaired awareness tended to have fewer driving-related accidents ($0.1 > P > 0.05$).

CONCLUSIONS — Assessment of the frequency of severe hypoglycemia in insulin-treated diabetic patients potentially may be complicated by incomplete self-reporting of episodes, possibly because of transient amnesia caused by neuroglycopenia. In addition, other medical events such as transient ischemic attacks or syncopal episodes may be misattributed to hypoglycemia (9), and diabetic patients with poor glycemic control often experience symptoms of hypoglycemia within a hyperglycemic range (21) and so overestimate the true frequency of hypoglycemia (22). A prospective assessment of hypoglycemia with patients recording all episodes, supported by objective witnessed accounts where possible, is the most accurate method of establishing the frequency with accuracy. Despite this approach, the frequency obtained possibly may be an underestimate, particularly in the patients with impaired awareness of hypoglycemia. In this prospective survey, treatment regimens were reviewed frequently to try to prevent severe hypoglycemia. In two of the patients with impaired awareness who had experienced episodes of severe hypoglycemia, as well as recording multiple episodes of asymptomatic biochemical hypoglycemia in the first 6 months of the study, multiple injection insulin regimens were begun, which diminished the frequency of biochemical and severe hypoglycemia during the subsequent 6 months. Although this therapeutic change was considered to be necessary, it probably reduced the true frequency of severe hypoglycemia in these patients, introducing a modest underestimate in the group with impaired awareness of hypoglycemia.

A further variable in all such studies is the necessity to study patients with diabetes who are attending an outpatient clinic for regular review. This probably influences management of their disease and modifies the patients' approach to self-treatment and avoidance of hypoglycemia by comparison with clinic nonattenders. The difficulty of extrapolating results from a clinic group to the entire population of insulin-treated diabetic patients remains an insoluble problem with all studies of frequency of hypoglycemia. However, despite these potential inaccuracies in reporting, the frequency of severe hypoglycemia was observed to be almost sixfold higher in the group of type I diabetic patients who had impaired awareness of hypoglycemia. Although the frequency of mild hypoglycemia did not differ between the groups, such estimates are recognized to be inaccurate with a pronounced discrepancy between biochemical hypoglycemia and symptomatic episodes (23). In the present study, patients with impaired awareness frequently recorded low random blood glucose concentrations, which were unaccompanied by symptoms, and this was significantly more common than in the group with normal awareness.

The proportion of all patients who had experienced severe hypoglycemia in this study was greater than in a previous study in France (24) and may reflect a tendency to underestimate the frequency of hypoglycemia by retrospective reporting. In this study the overall incidence of severe hypoglycemia in all of the patients was estimated at 1.6 episodes · patient^{-1} · year^{-1}, which is very similar to frequencies estimated previously in different cohorts of patients with type I diabetes, both retrospectively (2) and prospectively (4). The use of a similar definition of severe hypoglycemia is essential for studies to be compared; in several previous studies (16,25,26), the incidence of hypoglycemia was estimated to be lower than in this study because only those episodes were documented that had required resuscitation with parenteral glucagon or dextrose or necessitated treatment in hospital. Application of this restricted definition in the present study would provide an incidence of severe hypoglycemia of 0.06 episode · patient^{-1} · year^{-1} in the patients with normal awareness, which is consistent with rates reported retrospectively in other studies (26,27), and a frequency of 0.23 episode · patient^{-1} · year^{-1} in the patients with impaired awareness. Application of this more limited definition of severe hypoglycemia still preserves the relative difference in frequency between the two groups. In the Diabetes Control and Complications Trial (DCCT), in which data were collected prospectively, the incidence of severe hypoglycemia in patients receiving intensive insulin therapy was reported to be 0.62 episode · patient^{-1} · year^{-1} (17). This trial used an identical definition of severe hypoglycemia, but there were important differences in the study population, which was much younger with a shorter duration of diabetes, was strongly motivated, and had intensive monitoring of control of the disease (17). Most importantly, the DCCT excluded patients with a history of recurrent severe hypoglycemia or hypoglycemic coma, with no warning symptoms, who comprise the subgroups most susceptible to a high frequency of severe hypoglycemia.

In assessing the frequency of severe hypoglycemia, most previous studies have not differentiated between the patient groups on the basis of awareness of hypoglycemia. In this study, the percent-

age of patients with normal awareness who had experienced severe hypoglycemia (25.8%) was similar to previous reports (4,17), but the proportion of patients with impaired awareness who had experienced severe hypoglycemia was significantly higher, with two-thirds (65.5%) reporting severe hypoglycemia. This proportion is comparable to that observed previously in our clinic by Hepburn et al. (16) in a retrospective assessment. Both of the diabetic groups in this study exhibited a similar quality of glycemic control, which did not change throughout the study, and the groups were also matched for age, duration of diabetes, and age at onset of diabetes. Differences in the frequency of severe hypoglycemia cannot be attributed to a disparity in the quality of glycemic control.

In this study, severe hypoglycemia occurred at all times of day in the patients with impaired awareness but more often after their evening meal when the patients were at home. The reason for this was not evident and did not appear to be related to the nature of their insulin regimens. The estimate of the proportion of severe episodes of hypoglycemia occurring between 2400 and 0800 was lower in the patients with impaired awareness (31%) than in those patients with normal awareness (60%); 53% of all episodes of severe hypoglycemia occurred during sleep in the patients with normal awareness compared with 31% of all episodes in the patients with impaired awareness of hypoglycemia. In the DCCT, 43% of all episodes of severe hypoglycemia occurred between 2400 and 0800, and 55% of all episodes occurred during sleep (28), although the comparative frequencies in patients with normal awareness and impaired awareness of hypoglycemia were not reported. This study confirms the increased risk of severe hypoglycemia occurring during sleep. It also indicates that patients who have normal awareness of hypoglycemia during waking hours may have impaired perception of hypoglycemia during sleep, thereby predisposing them to more frequent hypoglycemia during the night. Previous retrospective studies have suggested that the majority of episodes of severe hypoglycemia can be attributed to excessive insulin dosage or to patient error, with about a quarter being unexplained (4,24,25,29). However, in this study only about half of the episodes were explicable, and this may be a consequence of different methods of data collection.

This study is consistent with previous studies in which patients with impaired awareness of hypoglycemia have been shown to be more worried about hypoglycemia than are patients with normal awareness and did not appear to modify their behavior accordingly (30); severe hypoglycemia occurred more frequently in patients who had experienced difficulty in controlling their diabetes (24). Similarly, patients exposed to recurrent severe hypoglycemia have been shown to have an increased level of anxiety and feel more unhappy (31). In the present survey, the morbidity of severe hypoglycemia was limited, and injuries requiring admission to hospital occurred in a single patient who had impaired awareness of hypoglycemia. None of the patients had a history of hypoglycemia-related driving accidents, and those with impaired awareness actually reported fewer driving accidents. This was probably a consequence of impaired driving behavior with increased care being taken when driving. Many patients who had experienced recurrent severe hypoglycemia had ceased driving voluntarily, reducing their risk of motor vehicle accidents, an observation that has been reported previously (32,33).

This study confirms that diabetic patients who have the chronic form of impaired awareness of hypoglycemia have a sixfold increase in frequency of severe hypoglycemia. The completion of the DCCT has emphasized the benefit of intensive insulin treatment in the prevention of diabetic retinopathy; however, this benefit occurs at the cost of a threefold incidence of severe hypoglycemia (17). Therefore, patients who have already been identified to be at a sixfold risk of severe hypoglycemia by association with their impaired awareness should be assessed individually before targets for glycemic control are established. They will require regular reinforcement of education of the causes and risks of hypoglycemia and continuous reappraisal of glycemic control to reduce the frequency of this potentially dangerous complication of insulin therapy.

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