RESEARCH ARTICLE

Diabetes Management

Recurrent severe hypoglycemia in Type 1 diabetes: potential for prevention?

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Summary points

Results

- A total of 39 episodes of severe hypoglycemia were reported by 86 out of 230 patients (37%) with Type 1 diabetes, corresponding to 1.0 episode per patient per year; 82% of the episodes were recurrent.
- More recurrent than solitary severe hypoglycemia occurred during daytime.
- Recurrent severe hypoglycemia tended more often to have no explainable causes compared with solitary severe hypoglycemia.
- The majority of recurrent severe hypoglycemia occurred in patients with impaired hypoglycemia awareness, which is consistent with the fact that recurrent severe hypoglycemia episodes were rarely preceded by hypoglycemia warning symptoms.

Discussion

- Episodes without warning symptoms, for example, the majority of recurrent severe hypoglycemia, may potentially be preventable by improvement of self-care; for example, frequent scheduled snacks between meals, intensified glucose monitoring (self-monitored blood glucose or real-time continuous glucose monitoring).
- Patients with recurrent severe hypoglycemia were often assisted by relatives, which underscores the need for education of close relatives to high-risk patients in early detection and treatment of severe hypoglycemia.

Conclusion

- To prevent especially recurrent severe hypoglycemia focus should be directed towards patients with reduced hypoglycemia awareness and include efforts to restore awareness.

SUMMARY **Aim:** To compare characteristics of solitary and recurrent episodes of severe hypoglycemia in order to explore the potential for prevention of recurrent severe hypoglycemia (SH) in a cohort of patients with Type 1 diabetes. **Methods:** 230 patients with Type 1 diabetes were followed prospectively for 1 year and reported characteristics of SH within 24 h. **Results:** 239 episodes of SH were reported by 86 patients, corresponding to 1.0 episode per patient year; 82% of the episodes were recurrent (≥2 episodes per patient year). Compared with solitary SH, recurrent SH occurred more often during daytime, primarily in subjects with reduced hypoglycemia awareness, and were characterized by absence of warning symptoms. **Conclusion:** A large proportion of SH in Type 1 diabetes is recurrent and thereby potentially preventable. Focus should be directed towards patients with reduced hypoglycemia awareness.

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KEYWORDS
• recurrent hypoglycemia • risk factors • severe hypoglycemia • Type 1 diabetes

Recurrent episodes (≥2 per patient per year) of severe hypoglycemia (SH) is a major clinical problem in Type 1 diabetes, affecting up to 20% of patients [1]. The single most important risk factor for recurrent SH in Type 1 diabetes is hormonal counter-regulatory failure and associated impaired hypoglycemia awareness [2–5]. Furthermore, the level of self-care is important [6]. This ranges from general self-care to specific issues such as compliance with insulin treatment, blood glucose self-monitoring recommendations [7], timing of meals, and use or abuse of alcohol and drugs [8].

Despite current knowledge of risk factors for recurrent SH and the general improvement of diabetes care including the introduction of insulin analogues, insulin pump therapy and continuous glucose monitoring, it has not been possible to reduce the problem significantly.

The aim of our study was to compare characteristics of solitary and recurrent episodes of severe hypoglycemia in order to explore the potential for prevention of development of recurrent episodes of SH in a well-defined cohort of patients with Type 1 diabetes.

Materials & methods

• Subjects

The study was a 1-year, observational, single-center study, which recruited 230 consecutive adult (>18 years of age) patients with Type 1 diabetes for more than 2 years. The study was conducted from October 1999 until March 2001 in the outpatient diabetes clinic at Nordsjællands Hospital Hillerød. The influence of risk markers on rate of severe hypoglycemia has been published separately [9]. The authors defined Type 1 diabetes by insulin treatment from the time of diagnosis and unstimulated C-peptide less than 300 pmol/l or stimulated (venous blood glucose concentration >12 mmol/l) C-peptide less than 600 pmol/l. Excluded from participation were pregnant women, subjects on hemodialysis and subjects suffering from concomitant malignant disease. The baseline clinical characteristics of the patients are shown in **Table 1**. State of awareness was assessed by the Pedersen–Bjergaard method and the question "Do you have symptoms when you have a hypo?". Patients answering "always" were categorized as being "aware", those answering "usually" as having "impaired awareness" and those answering "occasionally" or "never" as being "unaware" [10]. This method was chosen because it is simple and is proven to be equal to other methods to assess the state of awareness [11]. The Regional Committee on Biomedical Research Ethics approved the study and written informed consent was obtained from all participants.

• Reporting & classification of hypoglycemia

At entry into the study, the participants filled in well-tested questionnaires regarding different aspects of hypoglycemia awareness, lifestyle and demography [12]. During the study the patients reported episodes of severe hypoglycemia, defined as episodes of hypoglycemia with need for assistance from another person, by telephone to the research nurse within 24 h after the event. Structured telephone interviews were then carried out to establish the level of documentation according to Whipple's triad, classify severity and explore circumstances of the incidents. Severity was subclassified according to level of consciousness, kind of assistance, treatment and length of recovery period. Specific questions explored the possible cause(s) of the low glucose level, the reason for not treating the episode in due time, and use of alcohol and drugs with potential influence on self-care and cognitive function. Episodes of severe hypoglycemia were divided into two groups: 1) solitary episodes of severe hypoglycemia defined as one episode per patient, and 2) recurrent episodes of severe hypoglycemia defined as two or more episodes per patient during 1-year follow-up. Night was defined as the period 0:00–7:00 am, morning from 7:00 to 12:00 pm, afternoon from 12:00 to 18:00 pm and evening from 18.00 to 0.00 am (daytime: 7.00–0.00 pm).

• Statistical analyses

Standard descriptive statistics were used to characterize groups, and comparisons were made by parametric or nonparametric methods as appropriate. Results are expressed as mean ± 1 standard deviation (SD), median (interquartile range) or percentages when indicated. When multiple episodes were reported by one patient, each episode was interpreted as an independent event because the characteristics and circumstances of episodes reported by the same subject most often were not similar and therefore would not bias the results. Data were processed using the statistical software SPSS (Version 19). The level of significance was chosen as $p < 0.05$ (two-sided).

Table 1. Baseline patient characteristics.†

	Total	No SH	Solitary SH	Recurrent SH
Subjects, n (%)	230 (100%)	144 (63%)	41 (18%)	45 (19%)
Age (years)***	44 (18)	43 (19)	51 (16)	48 (15)
Gender (female/male) (%)	40/60	38/62	46/54	38/62
Age at onset of diabetes (years)*	25 ± 14	24 ± 14	26 ± 17	26 ± 12
Duration of diabetes (years)*	21 ± 12	20 ± 12	24 ± 13	22 ± 10
C-peptide negative (undetectable/low)‡ (%)	43/57	40/60	44/56	49/51
BMI (kg/m^2)*	25.0 ± 3.6	25.5 ± 3.8	24.0 ± 3.0	24.4 ± 3.4
≥4 insulin injections per day (%)	84	86	71	91
Insulin dose (units/kg)*	0.7 ± 0.2	0.7 ± 0.2	0.6 ± 0.1	0.7 ± 0.2
Insulin (human/analogue) (%)	5/95	6/94	7/93	2/98
β-blockers (%)	2	1	2	7
HbA_{1C} (%)	8.5 ± 1.0	8.7 ± 1.1	8.5 ± 1.4	8.3 ± 1.0
HbA_{1C} (mmol/mol)	69 ± 5	72 ± 6	69 ± 7	67 ± 5
Diabetic complications (%):				
– Retinopathy	55	56	46	60
– Nephropathy (excluding/including microalbuminuria)	9/25	10/27	8/26	4/18
– Peripheral neuropathy	35	33	41	36
– Autonomic neuropathy	15	16	8	17
– Macrovascular complications (stroke, myocardial infarction)	7	7	7	9
– Hypertension	20	20	22	16
Awareness (aware/impaired/unaware)§ (%)	40/47/13	51/39/10	32/54/14	11/64/25
Episodes of SH (per patient-last year)**	1.2 ± 0.3	0.3 ± 0.7	1.4 ± 0.4	3.9 ± 1.2
Self-reported threshold for hypoglycemic symptoms (mmol/l)*	2.9 ± 0.8	3.0 ± 0.7	2.8 ± 1.0	2.5 ± 0.7
Dominating hypoglycemia symptom category (%)# (autonomic/both/neuroglycopenic)	50/15/35	59/13/28	22/24/54	47/13/40

†Data are presented as *mean (SD), **mean (SE), ***median (interquartile range) or percentage.
‡Undetectable: <10 pmol/l; low: <300 pmol/l (unstimulated) or <600 pmol/l (stimulated).
§Subjects always recognizing their symptoms of hypoglycemia were categorized as being "aware", those usually recognizing as having "impaired awareness" and those occasionally or never recognizing their symptoms as having "unawareness".
#According to the Edinburgh Scale.
SH: Severe hypoglycemia.

Results

During the study, 239 episodes of SH were reported by 86 (37%) of the 230 patients, corresponding to 1.0 episode per patient per year. A total of 18% of the episodes were solitary whereas the remaining 82% episodes were recurrent **(Figure 1)**.

• Characteristics of patients reporting recurrent severe hypoglycemia

A higher proportion of patients with reduced hypoglycemia awareness, including those with impaired awareness and unawareness, was observed in patients with recurrent SH (89%) than with solitary SH (68%) (p = 0.02) **(Table 1)**. Age, duration of diabetes, insulin dose and HbA1C did not differ between patients reporting solitary or recurrent episodes. Among solitary SH 71% of the patients received ≥4 insulin injections per day (basal-bolus therapy or insulin pump therapy), while 91% of the patients experiencing recurrent SH received ≥4 insulin injections per day (p = 0.015) **(Table 1)**.

• Time and places of events

More recurrent (42%) than solitary (26%) SH occurred during daytime (07:00–18:00; p = 0.042) whereas 20% of both solitary and recurrent SH occurred in the evening (18:00–24:00). Forty-nine percent of solitary SH and 35% of recurrent SH occurred during night (00:00–07:00; p = 0.082) **(Table 2)**. The incidence of both solitary and recurrent SH peaked around 0:002–05, where approximately 33% of the events took place. Few SH occurred in the early morning and late in the evening. The majority of episodes of SH took place at home (solitary: 65%; recurrent: 71%) and only few at work (solitary: 2%; recurrent: 8%) or elsewhere (solitary: 30%; recurrent: 20%) with no differences between solitary and recurrent episodes **(Table 2)**.

• Activity at onset of events

Recurrent SH tended to occur more frequently while the patients were awake (solitary: 42%; recurrent: 56%; p = 0.1) and this is in accordance with the clock distribution, i.e., recurrent SH occurred more often during daytime than solitary SH.

• Causes of events

Recurrent SH tended more often to have no explainable causes as compared with solitary SH (46 vs 33%; p = 0.11). Self-reported probable causes of SH did not differ between solitary and recurrent SH **(Table 3)**.

• Reasons for not self-treating the events

A total of 42% of solitary SH and 66% of recurrent SH were reported not to have been preceded by hypoglycemic warning symptoms (p < 0.005). The majority of solitary SH (54%) were preceded by warning symptoms that were either recognized too late, ignored or misinterpreted **(Table 3)**.

• Discovery of the events and need for assistance

Solitary SH, as opposed to recurrent SH, were more often discovered by the patients themselves, although they were in need of assistance (solitary: 30%; recurrent: 16%; p = 0.035) **(Table 3)**. Patients with recurrent SH were more often assisted by relatives (solitary: 60%; recurrent: 74%; p = 0.02), primarily the spouse, while patients with solitary SH more often needed assistance from persons outside the family – for example, healthcare professionals (paramedics, doctors, emergency room; solitary: 28%, recurrent: 12%, p = 0.015) **(Figure 2)**.

• Treatment of the events

The most frequent manner to treat both solitary and recurrent SH was orally (food, juice, sugar; solitary: 79%, recurrent: 84%, p = 0.45). Solitary SH were more often treated with intravenous glucose than recurrent SH (solitary: 9%, recurrent: 1%, p < 0.005) **(Figure 3)**.

Discussion

The present study was conducted to collect thorough information of causes and circumstances of both solitary and recurrent episodes of prospectively recorded SH in a well-defined cohort of patients with Type 1 diabetes in order to explore the potential for prevention of recurrent SH. Knowing the causes of SH is a prerequisite for reducing their incidence. Unfortunately, uncovering these causes has proven very difficult, especially when it comes to the recurrent events. In our study almost half of the recurrent SH had no obvious cause even though the patients were carefully interviewed within 24 h of the incident. Probable causes of SH were reported in the other half of the recurrent events and in almost 70% of the solitary events in the present study. In five surveys of probable causes of severe hypoglycemic episodes in patients with insulin-treated diabetes (mixtures of patients with Type 1 and Type 2 diabetes) treated in emergency rooms probable causes of SH were reported for 64–95% of the events [13–18].

We did not observe any differences in probable causes between solitary and recurrent SH. All causes – except for unforeseen physical activity – are preventable, thereby creating an impetus for intensified education in self-care. In order to detect possible risk activity prior to the episodes of both solitary and recurrent SH, patients recorded the type of activity both 6 h before and at onset of the episode. Neither the activity prior to nor at onset of the episode differed between solitary and recurrent SH. Activities, that could explain SH such as physical activity or partying, were relatively rare causes and not associated more often with recurrent SH than solitary SH. On the contrary, both solitary and recurrent SH were often associated with sleeping, relaxation or performance of daily activities. Alcohol consumption was reported in approximately one third of the SH episodes in both groups. This number appears disturbingly high, as it is well known that alcohol interferes with cognitive function and compromises awareness of hypoglycemic symptoms [19]. However, only few patients had consumed more than five units of alcohol (i.e., an excessive amount of alcohol likely to affect patients' cognitive function and self-care) before the episode of SH.

Hypoglycemic warning symptoms preceded one fourth of the solitary SH, but were often recognized too late, ignored or misinterpreted. In accordance, a high proportion (30%) of the solitary SH was discovered by the patients themselves. In contrast, the majority of recurrent SH (66%) were reported not to have been preceded by hypoglycemic warning symptoms and a significantly smaller proportion (16%) was discovered by the patients themselves. SH preceded by early warning symptoms would potentially have

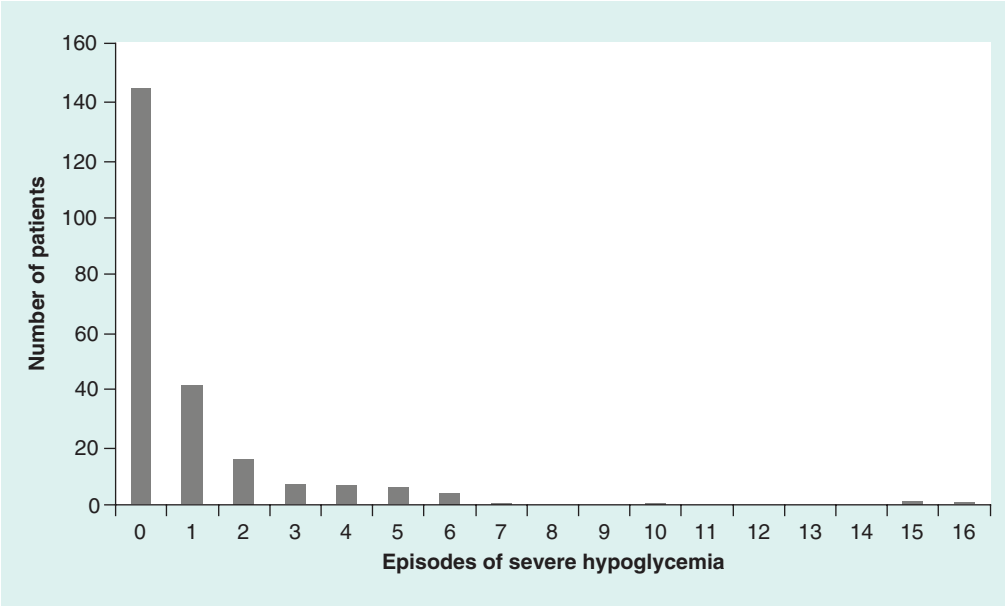

Figure 1. Episodes of severe hypoglycemia per year in 230 patients with Type 1 diabetes.

been preventable if the perception of and the reaction to the symptoms had been adequate. Episodes without warning symptoms – that is, the majority of recurrent SH – may potentially be preventable by education [20] and means of frequent 'life lines', for example, scheduled snacks between meals [21] or by use of real-time continuous glucose monitoring (CGM) units with hypoglycemia alarm function [22,23].

In 89% of recurrent SH patients were classified as having impaired awareness or as being unaware, which was the case in 69% of solitary SH. This is consistent with the fact that recurrent SH episodes were rarely preceded by warning symptoms in the present study and that patients with recurrent SH reported a higher rate of SH in the previous year before entering the study. Restoring hypoglycemia awareness in unaware patients and patients with impaired awareness would be vital in order to prevent especially recurrent SH. This may to some degree be possible by means of temporary avoidance of exposure to hypoglycemia by relaxation of glycemic control, which may at least partially restore the warning symptoms [24–27]. Real-time CGM has been reported to be useful to reduce hypoglycemic exposure and restore counterregulatory responses [28]. Alternatively, blood

Table 2. Place of severe hypoglycemic events and time of day.

	Solitary SH n = 43 (18%), n (%)	Recurrent SH n = 196 (82%), n (%)	p-value
Place of event			
At home	28 (65)	140 (71)	0.41
Outside home:	14 (32)	54 (28)	
– At work	1 (2)	16 (8)	0.18
– On the street	3 (7)	9 (5)	0.52
– At a party	1 (2)	4 (2)	0.91
– Other	9 (21)	25 (13)	0.16
Time of day			
00:00–07:00	21 (49)	68 (35)	0.08
07:00–12:00	3 (7)	25 (13)	
12:00–18:00	8 (19)	58 (30)	0.042
18:00–24:00	8 (19)	37 (19)	0.96

SH: Severe hypoglycemia.

Table 3. Causes of severe hypoglycemic events and reasons for not treating the events.

	Solitary SH n = 43 (18%), n (%)	Recurrent SH n = 196 (82%), n (%)	p-value
Probable cause of SH			
Unknown	14 (33)	90 (46)	0.11
Insufficient food intake	10 (23)	29 (15)	0.17
Unplanned physical activity	8 (19)	21 (11)	0.15
Planned physical activity	5 (12)	35 (18)	0.32
Excess insulin	2 (5)	16 (8)	0.43
The episode discovered by			
Patient	13 (30)	32 (16)	0.035
Others:	30 (70)	164 (84)	
– Relatives	29 (67)	149 (76)	0.24
– Others	1 (2)	15 (8)	
Reason for not treating the episode in time			
No symptoms recognized	18 (42)	130 (66)	<0.005
Symptoms recognized:	23 (54)	61 (31)	0.005
– But too late	12 (28)	42 (21)	
– But preoccupied	1 (2)	7 (4)	
– But misinterpreted	5 (12)	10 (5)	
– But ignored	5 (12)	2 (1)	
– Other reason	1 (2)	2 (1)	
Alcohol consumption			
1–5 units	11 (26)	52 (27)	0.9
>5 units	3 (7)	6 (3)	0.22
Sedatives	2 (5)	15 (8)	0.49
Coma	9 (21)	46 (23)	0,7
Seizure	5 (12)	27 (14)	0.7

SH: Severe hypoglycemia.

glucose awareness training (BGAT) may improve recognition of hypoglycemic symptoms [29–31].

Patients with recurrent SH were more often assisted by relatives (primarily the spouse), while patients with solitary SH more often needed assistance from others, for example, healthcare professionals (paramedics, doctors, emergency room). This underscores the need for education of close relatives to high-risk patients in early detection and treatment of SH.

A possible limitation of our study is the 1-year duration. However, this is the same duration as previous studies concerning SH, thereby enhancing the comparability [3,4]. Furthermore, driver license regulations could have influenced the patients' omission to report SH but the data collection was conducted at a time where there were no operational rates for SH and driver license withdrawal in Denmark.

Conclusion

In patients with Type 1 diabetes, recurrent SH is often unexplained and occurs in subjects with impaired hypoglycemia awareness in the absence of hypoglycemia warning symptoms. In order to prevent SH focus should be directed towards patients with reduced hypoglycemia awareness and measures should include efforts to restore awareness or replace the missing awareness by intensified glucose monitoring (self-monitored blood glucose or real-time CGM). Finally, frequent scheduled carbohydrate intake and education of relatives are important measures in preventing recurrent SH.

Future perspective

Despite general improved management, severe hypoglycemia is still a risk for people with Type 1 diabetes. Recurrent severe hypoglycemia affects up to 20% of patients with Type 1 diabetes. As we have shown in the present study, these patients often have impaired hypoglycemia awareness. In the future, different interventions may improve awareness and thereby reduce the rate of recurrent severe hypoglycemia, helping the patients prone to recurrent hypoglycemia.

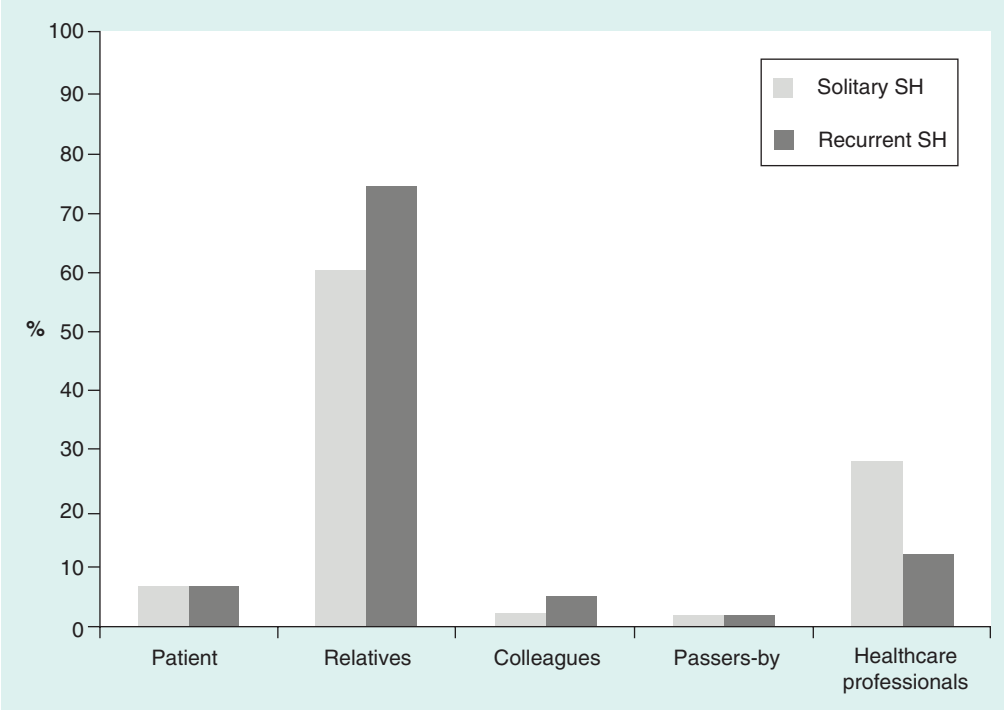

Figure 2. Need for assistance.
SH: Severe hypoglycemia.

These interventions include new types of insulin and technologic advances.

Studies show that treatment with insulin analogues may reduce the risk of hypoglycemia [32];

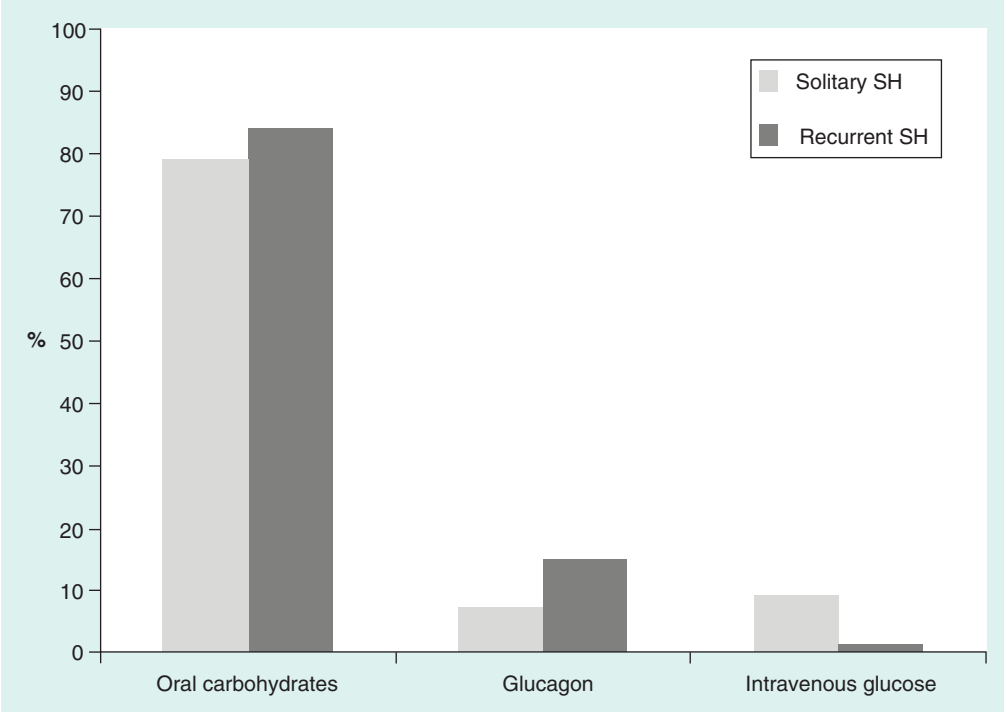

Figure 3. Treatment of severe hypoglycemia.
SH: Severe hypoglycemia.

however, these studies primarily include patients without recurrent severe hypoglycemia. A recent study that includes patients with recurrent hypoglycemia has shown that these patients, who are prone to severe hypoglycemia, experience fewer episodes of hypoglycemia during treatment with insulin analogues as well [33].

Ultra long-acting basal insulin analogues have recently been introduced and the future will show if these will reduce the clinical problem of recurrent severe hypoglycemia further.

A recent technological advance in the management of Type 1 diabetes is the introduction of real-time continuous glucose monitoring (CGM) units with hypoglycemia alarm function and sensor-augmented insulin pumps. The sensor-augmented insulin pump is an insulin pump combined with the CGM unit with the hypoglycemia alarm function. Furthermore, some sensor-augmented insulin pumps have a low glucose suspend (LGS) feature, which suspends basal insulin delivery at a preset sensor glucose value. Studies have shown that these sensor-augmented insulin pumps with the LGS feature can reduce the frequency of hypoglycemia [23,34,35]. Therefore these systems may be of value in the quest to avoid recurrent severe hypoglycemia, especially in unaware patients prone to recurrent hypoglycemia.

After the introduction of CGM and insulin pump therapy in the treatment of Type 1 diabetes, efforts have been made to develop a closed-loop insulin delivery system. The closed-loop system is likely to combine a glucose monitor, an insulin pump and a control algorithm (determines amounts and rates of the insulin delivery) [36]. Thus, this closed-loop system may in the future be able to help the patients with Type 1 diabetes prone to recurrent severe hypoglycemia. Further testing is ongoing and required before the closed-loop insulin delivery system is ready to take part in diabetes management in a real-world setting.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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