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Hypoglycemia in type 1A diabetes can develop before insulin therapy: A retrospective cohort study

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ABSTRACT

Aims: There are as yet no cohort studies of hypoglycemia in type 1 diabetes before starting insulin therapy. Our aim was to determine the frequency and clinical features of hypoglycemia in patients with type 1A diabetes prior to commencing insulin therapy.
Methods: Eighty-seven patients with type 1A diabetes were enrolled, and a retrospective chart review of the patients was conducted.
Results: Hypoglycemia before insulin therapy occurred in six of 87 patients (6.9%). The HbA1c levels at the diagnosis of type 1A diabetes in the hypoglycemia group were lower than in the non-hypoglycemia group (median: 7.3% (56 mmol/mol) vs. 11.9% (106 mmol/-mol), $p < 0.0001$). Similarly, the 24-hour urinary C-peptide (UCPR) levels of the former group were higher than those of the latter group (16.5 μg/day/m^2 vs. 7.0 μg/day/m^2, $p = 0.0075$). Hypoglycemic episodes occurred mostly in the postprandial period and gradually disappeared with a decrease in insulin secretion.
Conclusions: We demonstrated that some patients with type 1A diabetes experience hypoglycemic episodes before insulin therapy. Patients with early-stage type 1A diabetes with relatively low HbA1c or high UCPR have a risk of hypoglycemia. These findings may impact when and how insulin is introduced in the treatment of early-stage type 1A diabetes.

1. Introduction

Type 1 diabetes is characterized by an absolute deficiency of insulin secretion caused by autoimmune destruction of the pancreatic β-cells [1]. More than 80% of patients with type 1 diabetes are positive for pancreatic islet cell autoantibodies and are subcategorized as cases of type 1A diabetes.

Hypoglycemia in type 1 diabetes is almost exclusively associated with insulin therapy [2]. Only two type 1 diabetes cases with hypoglycemia before insulin therapy have been described [3,4]. Cohort studies of hypoglycemia in type 1A diabetes before starting insulin have not been reported.

For this study, self-monitoring of blood glucose (SMBG) data were obtained retrospectively from patients with type

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1A diabetes. Our study aimed to determine the frequency and clinical features of hypoglycemia prior to insulin therapy in these patients.

2. Materials and methods

2.1. Patients

One hundred-four patients with newly diagnosed type 1 diabetes were referred to the authors' institutions and affiliated hospitals between April 2002 and December 2016. Eighty-seven patients with type 1A diabetes were enrolled. The subjects were divided into the hypoglycemia and non-hypoglycemia groups as described below. The subjects in the hypoglycemia group had one or more episodes of hypoglycemia between the diagnosis of type 1 diabetes and the introduction of insulin therapy. The remaining patients were allocated to the non-hypoglycemia group. Blood glucose levels were measured either in the hospital or at home by SMBG. Glucose measurements by SMBG were mostly done four times a day at home (before each meal and before going to bed). The measurements were also done two hours after each meal and at midnight, for a maximum of eight times per day on admission.

2.2. Definition of hypoglycemia

Hypoglycemia in this study was defined as 70 mg/dL or below in accordance with the definition of the American Diabetes Association and National Institute of Diabetes and Digestive and Kidney Diseases.

2.3. Research design

A retrospective chart review of patients with type 1A diabetes was conducted. The information collected at the diagnosis of type 1 diabetes included the following: age, sex, BMI, islet cell autoantibody titer, HbA1c, and 24-hour urinary C-peptide (UCPR). Information obtained from the period between the diagnosis and start of insulin therapy consisted of the length of the period in days, the total number of SMBG measurements, the number of hypoglycemic episodes, and the minimum glucose level in each patient. The lower limit of two SMBG devices at each of the participating hospitals was 20 mg/dL, and the intrameasurement coefficiency of variation of our two devices was 2–3% when the glucose level was around 50 mg/dL.

The primary endpoint of this study was the frequency of hypoglycemia in patients with type 1A diabetes. The other endpoint was the determination of characteristic clinical features, if any, of the hypoglycemia group compared with the non-hypoglycemia group.

2.4. Statistical analysis

Statistical analyses were done using JMP Pro 12.2.0. The Wilcoxon rank sum test was used to compare the intergroup differences in each parameter, and Pearson's chi-square test was done to compare the intergroup positivity rates for islet cell autoantibodies. Significance was defined as $p < 0.05$. All values were expressed as the median (range). The ethical committee of Hokkaido University Hospital and Tokyo Metropolitan Children's Medical Center independently approved this study.

3. Results

3.1. Frequency of hypoglycemia in patients with type 1A diabetes

Hypoglycemia before insulin therapy occurred in six of 87 patients (6.9%). There was no statistical difference in age or BMI between the hypoglycemia and non-hypoglycemia groups (Table 1).

3.2. Severity of hypoglycemia

In the six patients in the hypoglycemia group, 44 out of 1555 SMBG measurements before insulin therapy satisfied the definition of hypoglycemia (2.8%). Seven of the 44 episodes (16%)

Table 1 – Baseline demographic and clinical characteristics of the study subjects.

	Hypoglycemia (n = 6)		Non-hypoglycemia (n = 81)		P value
Age (years)	10.1	(3.8–14.6)	8.9	(1.1–18.3)	0.4661
BMI (kg/m^2)	15.5	(14.4–20.3)	15.1	(10.2–22.0)	0.2116
GADA positive	6/6	(100%)	61/81	(75.3%)	0.3766
IAA positive	1/5	(20%)	32/72	(44.4%)	0.5480
IA-2A positive	3/6	(50%)	53/66	(79.1%)	0.2315
HbA1c (%)	7.3	(6.6–7.9)	11.9	(7.3–18.0)	<0.0001
UCPR (μg/day/m^2)	16.5	(11.6–42.2)	7.0	(0.4–86.5)	0.0075
Insulin initiation (days)	194	(13–359)	0	(0–1380)	<0.0001
SMBG (times)	39	(3–730)	2	(1–155)	0.0001
Minimum BG (mg/dL)	54	(46–68)	360.5	(75–1398)	<0.0001

Data are presented as the median (range) or number (%). Insulin initiation indicates the days from type 1 diabetes diagnosis to start of insulin therapy. SMBG indicates the number of SMBG done from type 1 diabetes diagnosis to the start of insulin therapy. Minimum BG indicates the lowest blood glucose level obtained before insulin therapy.

GADA: anti-GAD autoantibodies, IAA: insulin autoantibodies, IA-2A: insulinoma-2-associated autoantibodies, UCPR: 24-hour urinary C-peptide excretion, SMBG: self-monitoring of blood glucose, BG: blood glucose

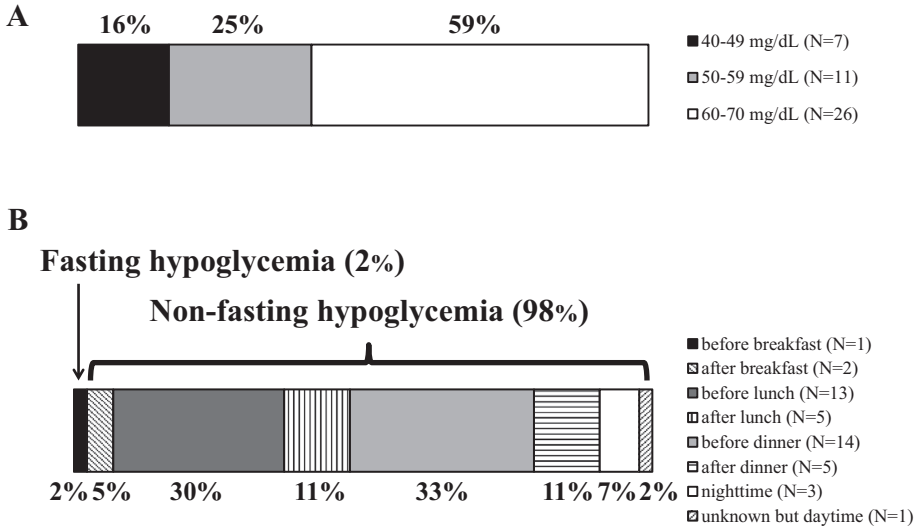

Fig. 1 – Range and timing of hypoglycemia in the hypoglycemia group. In the hypoglycemia group, 44 hypoglycemic episodes were recorded. A: Range of hypoglycemia. In the 44 recorded hypoglycemic episodes, seven were in the 40–49 mg/dL range, 11 were in the 50–59 mg/dL range, and 26 were in the 60–70 mg/dL range. B: Timing of hypoglycemia. In the 44 hypoglycemic episodes, fasting hypoglycemia before breakfast (after an overnight fasting) occurred only once (2%). 43/44 (98%) hypoglycemic episodes occurred at times other than before breakfast. 'Before breakfast,' 'before lunch,' and 'before dinner' show the timing of hypoglycemia before each meal. 'After breakfast,' 'after lunch,' and 'after dinner' show the timing of hypoglycemia two hours after each meal. 'Nighttime' shows the timing of hypoglycemia between 0 a.m. and 6 a.m. 'Unknown but daytime' indicates that the precise timing of SMBG was not documented, but that it was done sometime during the day in Case 3.

of hypoglycemia were in the low range from 40 to 49 mg/dL, and all the episodes were divided into the three classes as shown in Fig. 1A.

3.3. *Timing of hypoglycemia*

The timing of the hypoglycemic episodes was recorded in 43 instances. Insufficient information on the timing of the hypoglycemia was documented for one episode in Case 3. However, this episode clearly did not occur during an overnight fasting state (Fig. 1B). One episode in Case 5 among the 44 total hypoglycemic episodes occurred in an over-night fasting state. Neither patient experienced severe symptoms during the hypoglycemic episode; the only symptoms were hunger and irritability.

3.4. *Clinical characteristics of cases in the hypoglycemia group*

The HbA1c levels at the diagnosis of type 1 diabetes in the hypoglycemia group were lower than in the non-hypoglycemia group (Fig. 2: 7.3% (6.6–7.9%) vs. 11.9% (7.3–18.0%), 56 mmol/mol (49–63 mmol/mol) vs.107 mmol/mol (56–173 mmol/mol), $p < 0.0001$). UCPR levels in the hypoglycemia group were higher than in the non-hypoglycemia group (Fig. 2: 16.5 μg/day/m^2 (11.6–42.2 μg/day/m^2) vs. 7.0 μg/day/m^2 (0.4–86.5 μg/day/m^2), $p = 0.0075$). The number of days and SMBG measurements from the diagnosis of type 1 diabetes to the initiation of insulin was greater in the hypoglycemia group than in the non-hypoglycemia group (194 days (13–359 days) vs. 0 days (0–1380 days), $p < 0.0001$, 39 times (3–730 times) vs. 2 times (1–155 times) $p = 0.0001$) (Table 1). In short, the hypoglycemia group demonstrated greater conservation of their endogenous insulin secretion capacity.

The clinical characteristics of the six patients in the hypoglycemia group are shown in Table 2. The parents of Patient 1 were Caucasians, and the parents of the other patients were Japanese. None of the parents had a history of diabetes except the father of Patient 6, who suffered from insulin-dependent diabetes; however, the pancreatic autoantibody values for the father were unavailable. The clinical course of the six patients in the hypoglycemia group is described below.

3.5. *Clinical course of six cases in the hypoglycemia group*

Case 1. A 3-year-9-month old girl was referred to our institution due to polyuria and polydipsia of ten days' duration. Laboratory results showed elevated HbA1c (6.6%, 49 mmol/mol) and anti-GAD antibody (28.0 U/mL; reference range <1.5 U/mL) suggesting type 1A diabetes. The blood glucose profile before insulin therapy showed daytime hypoglycemia (47–51 mg/dL) alternating with hyperglycemia (203–354 mg/dL). Three episodes of hypoglycemia were recorded in the 46 SMBG done during hospitalization. Hunger was the sole symptom during these three hypoglycemic episodes. As the blood glucose levels and HbA1c gradually increased,

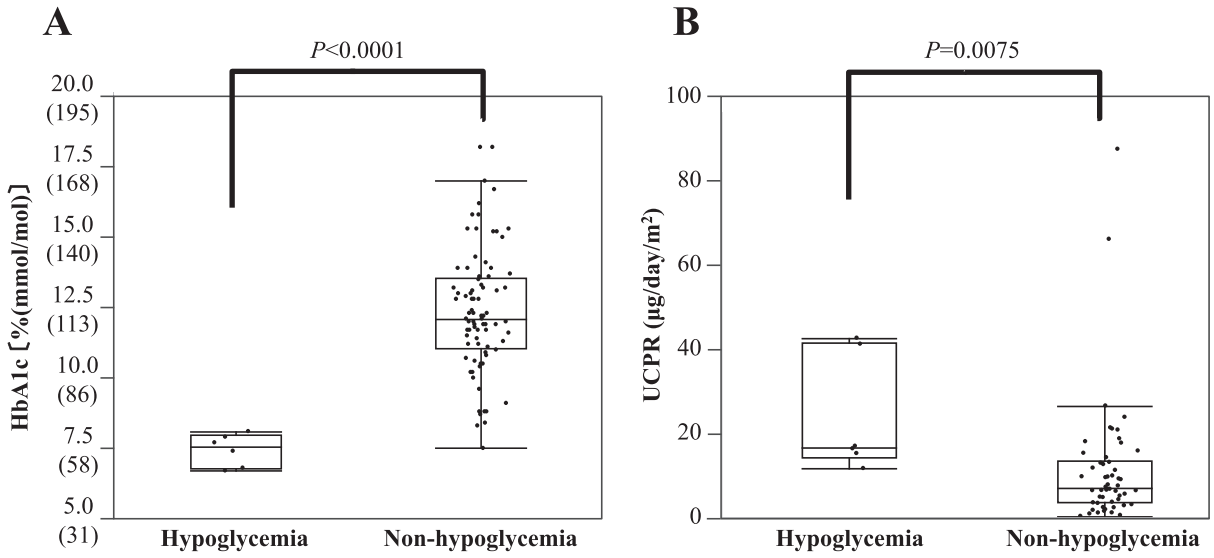

Fig. 2 – Box and whisker plot representation of HbA1c (A) and UCPR (B). HbA1c (A) and UCPR (B) at type 1A diabetes diagnosis in the hypoglycemia group (n = 6) compared with the non-hypoglycemia group (n = 81). P values for the Wilcoxon rank sum test are shown.

Table 2 – Clinical characteristics of the hypoglycemia group (n = 6).

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age (years)	3.8	6.5	9.9	10.4	12.0	14.6
Sex	Female	Female	Female	Male	Male	Male
BMI (kg/m^2)	15.3	15.7	14.4	15.3	17.0	20.3
HbA1c (%)	6.6	6.9	7.5	7.9	7.2	7.7
HbA1c (mmol/mol)	49	52	58	63	55	61
GADA (U/mL)	28.0	48.9	75.0	1.6	3.1	6.1
IAA (nU/mL)	<0.4	919.0	<0.4	<0.4	n.d.	<0.4
IA-2A (U/mL)	<0.4	3.6	6.1	<0.4	17.4	<0.4
Glycated albumin (%)	n.d.	n.d.	n.d.	23.7	37.0	n.d.
UCPR (μg/day/m^2)	16.2	40.8	15.1	42.2	11.6	16.8
Insulin initiation (days)	13	219	221	359	169	108
SMBG (times)	46	730	3	32	713	31
Hypoglycemia (times)	3	25	1	1	13	1
Minimum BG (mg/dL)	47	46	68	68	49	59

Annotations for each parameter are the same as for Table 1. n.d.: no data.

rapid-acting insulin was administered at each meal 13 days after the patient's referral to our hospital.

Case 2. A 6-year-5-month old girl presented with polydipsia of three years' duration. Type 1A diabetes was diagnosed based on hyperglycemia (as high as 347 mg/dL), elevated HbA1c (6.9%, 52 mmol/mol), and elevated an anti-GAD antibody titer (48.9 U/mL). Her blood glucose profile before insulin therapy showed hypoglycemia (46–69 mg/dL) alternating with hyperglycemia (210–347 mg/dL). During an oral glucose tolerance test (OGTT), a decrease in early insulin response and an increase in late insulin response were detected; the peak and nadir glucose values were 282 mg/dL (90 min) and 79 mg/dL (240 min), and the peak insulin and C-peptide values were 18.9 μIU/mL (120 min) and 3.92 ng/ml (120 min), respectively. Miglitol (an alpha-glucosidase inhibitor; α-GI), used to treat postprandial hyperglycemia in Japan, was administered for the first six months. The blood glucose profile was carefully monitored at home, and 25 hypoglycemic episodes were observed in the 730 SMBG records before insulin therapy. Her symptoms of hypoglycemia were hunger and irritability. As the blood glucose levels and HbA1c increased over the course of months, the hypoglycemia episodes gradually disappeared (Supplementary Fig. 1A). HbA1c increased to 9.0% (75 mmol/mol) at age 7 years, and insulin pump treatment was finally introduced.

Case 3. A 9-year-10-month old girl visited our hospital after testing positive for glycosuria on a school health screening test. The first laboratory results showed hypoglycemia (68 mg/dL) and elevated HbA1c (7.5%, 58 mmol/mol), but she was subsequently omitted from follow-up. Six months later, she presented with weight loss. She was given the diagnosis

of type 1A diabetes based on her findings for blood glucose (388 mg/dL), HbA1c (14.2%, 132 mmol/mol), anti-GAD antibody (75.0 U/mL), and anti-IA-2 antibody (6.1 U/mL). Rapid-acting and long-acting insulin preparations were initiated.

Case 4. A 10-year-4-month old boy showed glycosuria. The HbA1c (5.7%, 39 mmol/mol) was normal at the first evaluation. Two months later, the glucose and HbA1c values obtained in the outpatient clinic were 97 mg/dL and 5.9% (41 mmol/mol), respectively. However, three months later, HbA1c increased to 7.9% (63 mmol/mol), and the anti-GAD antibody was marginally high (1.6 U/mL), suggesting type 1A diabetes. During a subsequent follow-up, HbA1c temporarily improved to 6.4% (46 mmol/mol) without any treatment and daytime hypoglycemia (68 mg/dL) was detected on his blood glucose profile once. HbA1c increased to 8.7% (72 mmol/mol) at age 11 years and 3 months when rapid-acting and long-acting insulin preparations were started.

Case 5. A 12-year-old boy visited our hospital after testing positive for glycosuria on a school health screening test. Elevated HbA1c (7.2%, 55 mmol/mol) and anti-GAD antibody (3.1 U/mL) led to the diagnosis of type 1A diabetes. He was placed on a balanced diet, and his HbA1c value improved to 6.0% (42 mmol/mol). His blood glucose profile was carefully monitored at home, and 13 episodes of hypoglycemia were recorded in the 713 instances of SMBG before insulin therapy. One out of 13 hypoglycemic episodes occurred in the early morning before breakfast as explained above; the blood glucose level at that time was 53 mg/dL. In contrast, the other 12 hypoglycemic episodes occurred during the daytime or at other times except during overnight fasting. Several months after type 1A diabetes was diagnosed, the blood glucose level and HbA1c increased while the frequency of hypoglycemia gradually decreased (Supplementary Fig. 1B). HbA1c finally increased to 8.3% (67 mmol/mol) at age 12.5 years when rapid-acting and long-acting insulin preparations were begun.

Case 6. A 14-year-7-month old boy visited our hospital after testing positive for glycosuria on a school health screening test. He had elevated blood glucose (218 mg/dL), HbA1c (7.7%, 61 mmol/mol), and anti-GAD antibody (6.1 U/mL), indicating type 1A diabetes. His blood glucose profile before insulin administration revealed one episode of daytime hypoglycemia alternating with hyperglycemia; the lowest blood glucose level during the course was 59 mg/dL. As the blood glucose levels and HbA1c gradually increased during the following three months, treatment using rapid-acting and long-acting insulin was initiated.

3.6. *Two 'hypoglycemic' cases in non-hypoglycemia group*

In the non-hypoglycemia group, two patients experienced a similar 'hypoglycemic' episode. One patient received the diagnosis of type 1A diabetes at age 9 years. There were 155 SMBG records before the start of insulin therapy, and the minimum blood glucose level was 78 mg/dL. The other patient received a type 1A diabetes diagnosis at age 13 years. There was a record of 35 SMBG over six days before insulin therapy, and the minimum blood glucose level was 75 mg/dL. These two hypoglycemic episodes were also recorded in the daytime.

4. Discussion

In this retrospective study, hypoglycemia in type 1A diabetes before insulin therapy was documented in 6.9% (52 mmol/mol) of the patients. As far as we know, this is the first cohort study to show this type of hypoglycemia in type 1A diabetes.

Close monitoring of blood glucose in patients with newly diagnosed type 1A diabetes is crucial for proper management, given the possibility of hypoglycemia before insulin therapy especially in patients with a residual insulin secretion capacity. This monitoring may be critical in deciding when and how insulin therapy is started. In fact, Poon et al. reported a case of a type 1A diabetes patient who experienced a hypoglycemic seizure before insulin therapy [3].

In Cases 2 and 5, hypoglycemia before insulin therapy disappeared with the progression of diabetes. This transient course of hypoglycemia lasting months has been described elsewhere [4]. Endogenous insulin secretion is known to decline gradually over the course of months to years, with the duration of this decline varying in cases of type 1A diabetes. We therefore speculate that hypoglycemia before insulin treatment may develop only in patients with early-stage type 1A diabetes with some degree of residual endogenous insulin secretion.

While the causes of hypoglycemia documented in this study are unknown, it is noteworthy that in our cases most of the hypoglycemic episodes occurred at times other than before breakfast (Fig. 1B). We hypothesize that most episodes of this type of hypoglycemia occur postprandially and are related to delayed insulin secretion after meals. In fact, Case 2 demonstrated an improvement in hypoglycemia after starting α-GI, a delayed insulin and C-peptide peak, and a low blood glucose level at 240 min on an OGTT. A similar increase in the later C-peptide response on an OGTT was reported for the pre-diabetic state in type 1 diabetes [3,5,6]. Such delays in postprandial insulin secretion are a well-attested mechanism of postprandial hypoglycemia in early-onset, mild type 2 diabetes [7,8].

To the best of our knowledge, no clinical trials of α-GI to prevent postprandial hypoglycemic episodes in type 1A diabetes have been done. However, this type of drug theoretically mitigates the increase in blood glucose after meals, which might subsequently prevent delayed insulin secretion and related postprandial hypoglycemic episodes [9,10]. Unfortunately, the hypoglycemic episodes in our patients did not directly follow the increase in blood glucose after meals. If indeed an increase in blood glucose followed by hypoglycemia after a meal can be proved, using ultra-short acting insulin in smaller doses to ameliorate postprandial glycemic excursion may become an option for treating postprandial hypoglycemic episodes that have the potential to develop in type 1A diabetes.

This study has at least two limitations. First, the number of patients in the hypoglycemia group was small. Although

we clearly showed the presence of hypoglycemia during the early stage of type 1A diabetes, the sample size was too small to allow us to speculate about the mechanism. Further prospective studies with larger numbers of patients with untreated type 1A diabetes are necessary. Second, as the blood glucose levels were measured only several times a day, mild hypoglycemic episodes may have been overlooked in some of the subjects. Indeed, two patients in the non-hypoglycemia group showed borderline-low blood glucose in this study. If the patients had been evaluated more frequently by continuous glucose monitoring systems, more of those in the non-hypoglycemic group may have been included in the hypoglycemia group.

In conclusion, by analyzing a cohort of 87 patients we demonstrated that some type 1A diabetes patients experience hypoglycemic episodes before insulin therapy. Patients with early-stage type 1A diabetes with relatively low HbA1c or high urine C-peptide levels should have their blood glucose measured frequently so that physicians can appropriately manage this type of hypoglycemia and decide when and how insulin may be started. Further studies of the underlying mechanism are desired.

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Conflict of interest

There was no conflict of interest to disclose.

Author contributions

T.Y. and R.H. researched the data and wrote the first draft of the manuscript. S.W., K.S, and S.M. contributed to the design of this study and the analysis and interpretation of the data. A.N. and Y.H. reviewed/edited the manuscript and were responsible for all aspects of the research design and manuscript. The guarantors were A. N. and Y. H.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2018.11.011.

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