Trends of the Patients Hospitalized for Severe Hypoglycemia in Type 2 Diabetes

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Aim : Severe hypoglycemia remains a major complication of diabetes ; however, the background of patients with severe hypoglycemia requiring hospitalization has not been unraveled. Therefore, in this study, we examined the characteristics of patients who required hospitalization for severe hypoglycemia.

Methods : We included 330 patients with severe hypoglycemia who had type 2 diabetes and who visited the Aizawa Hospital Emergency and Critical Care Center during a 12-year period. Furthermore, we divided the patients into two groups : patients treated with insulin (INS-group) and those treated with oral hypoglycemic agents without insulin (OHA-group). We examined the time of hospital visits and the proportion of patients requiring hospitalization.

Results : The proportion of patients requiring hospitalization was significantly lower in the INS-group than in the OHA-group. The proportion of patients who visited the hospital because of severe hypoglycemia between 12 : 00 and 17 : 59 was significantly higher in the INS-group than in the OHA-group. There was no significant difference in the proportion of patients who were hospitalized and those who could return home across all periods in the INS-group. The proportion of hospitalized patients was low between 0 : 00 and 5 : 59 and high between 18 : 00 and 23 : 59 in the OHA-group.

Conclusions : In insulin-treated patients, there is a risk of severe hypoglycemia, even with poor glycemic control. However, patients treated with OHA alone were at increased risk of hospitalization for severe hypoglycemia in cases of excessively good control and the visit time between 18 : 00 and 23 : 59.These findings suggest strategies that can reduce the risk of severe hypoglycemia and hospitalization. *Shinshu Med J 73 : 139—146, 2025*

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Key words : hypoglycemia, insulin, oral hypoglycemic agent

I Introduction

Severe hypoglycemia is an acute complication of diabetes that can lead to cardiovascular diseases and dementia[1)2)] ; therefore, it should be avoided during diabetes treatment. With the launch of dipeptidyl peptidase-4 inhibitors in 2009, glucagon-like polypeptide-1 receptor agonists in 2010, and sodium glucose cotransporter-2 inhibitors in 2014, drugs with a low risk of hypoglycemia[3)4)] have become available for the treatment of type 2 diabetes. However, several patients tend to develop severe hypoglycemia, some of whom require hospitalization, suggesting that the widespread use of drugs with a low risk of hypoglycemia alone cannot completely prevent severe hypoglycemia.

To date, severe hypoglycemia has not been examined in detail, and the background of patients with severe hypoglycemia requiring hospitalization has also not been sufficiently examined. Therefore, in this study, we examined the background of patients who required hospitalization for severe hypoglycemia and

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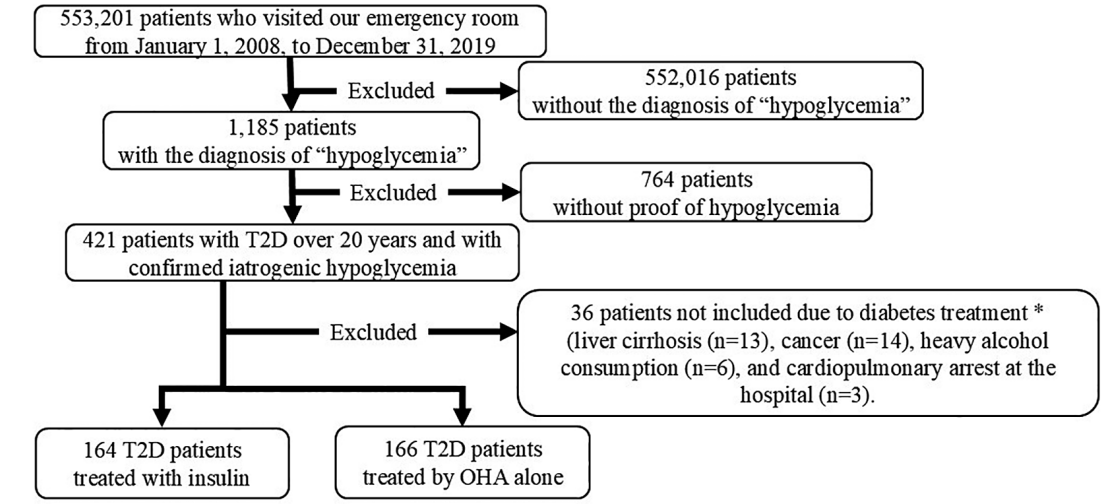

Fig. 1　Patient selection process.

determined the indications to avoid hospitalization.

Ⅱ　Patients and Methods

A　Patients

The patient selection method is illustrated in **Fig. 1**. From the 553,201 patients who visited the Aizawa Hospital Emergency and Critical Care Center during a 12-year period, January 1, 2008, to December 31, 2019, we included a total of 1,185 patients with a diagnosis of hypoglycemia. We excluded 764 who did not have type 2 diabetes, those under the age of 20 years, and those whose glucose concentration could not be confirmed to be < 70 mg/dL. Overall, 36 patients were excluded from the study, including those with decompensated cirrhosis (n = 13), advanced cancer (n = 14), heavy alcohol consumption (n = 6), and cardiopulmonary arrest at the hospital (n = 3). Additionally, for patients who visited multiple times for severe hypoglycemia, only the data from the first visit were included in the study, and a total of 55 other patients were excluded. Therefore, a total of 330 patients were finally included in this study. Furthermore, we divided the patients into two groups : patients treated with insulin (INS group) and those treated with oral hypoglycemic agents without insulin (OHA group).

This study was approved by the Ethics Review Committee of Aizawa Hospital Clinical Research (approval date : January 5, 2021 ; registry number : #2020-057). Patients could opt out of the study via the hospital's website and postings. In addition to the research methodology, the opt-out option indicated that we strictly adhered to ethical guidelines and anonymized the data. If the applicants did not express their intention to withdraw from the study, their consent to participate was implied.

B　Severe hypoglycemia

In this study, we defined patients with severe hypoglycemia as those with pretreatment blood glucose levels < 70 mg/dL and in whom recovery was difficult owing to symptoms such as impaired consciousness ; however, the symptoms in these patients could be improved by glucose administration.

C　Physical and laboratory data

Data on physical findings, such as state of consciousness and blood pressure, were extracted from the patients' electronic records. In addition, the results of the blood examination, such as the blood glucose levels, were extracted from the electronic records.

The estimated glomerular filtration rate (eGFR) was determined using a formula developed for Japanese people[5].

Males : $eGFR = 194 \times \text{serum creatinine (mg/dL.)}^{-1.094}$

Table 1 Baseline characteristics of the patients

	Total	INS group	OHA group	p-value
Number of patients	330	164	166	
Males (number, %)	188, 57.0	100, 61.0	88, 53.0	0.150
Age (years, mean (SD))	76.4 (10.1)	73.7 (10.3)	79.1 (9.2)	＜0.001 *
Transfer by ambulance (number, mean (SD))	272, 82.4	134, 81.7	138, 83.1	0.774
Hospitalization (number, %)	142, 43.0	46, 28.0	96, 57.8	＜0.001 *
Blood glucose levels (mg/dL., mean (SD))	35.9 (12.9)	36.0 (13.0)	35.7 (12.8)	0.854
HbA1c (%, mean (SD))	6.79 (1.28)	7.54 (1.38)	6.25 (0.87)	＜0.001 *
eGFR (ml/min/1.73 m^2, mean (SD))	53.82 (27.87)	55.05 (25.26)	52.52 (30.40)	0.331
FIB-4 index (mean (SD))	3.320 (3.117)	2.934 (2.487)	3.689 (3.589)	＜0.001 *
Time of visit				
00 : 00-05 : 59 (number, %)	40, 12.1	23, 14.0	17, 10.2	0.315
06 : 00-11 : 59 (number, %)	99, 30.0	45, 27.4	54, 32.5	p = 0.338
12 : 00-17 : 59 (number, %)	72, 21.8	45, 27.4	27, 16.3	p = 0.016 *
18 : 00-23 : 59 (number, %)	119, 36.1	51, 31.1	68, 41.0	p = 0.067

INS : patients treated with insulin, OHA : patients treated without insulin, HbA1c : hemoglobin A1c
eGFR : estimated glomerular filtration rate, FIB-4 index : fibrosis-4 index
* : statistical significance (p＜0.05)

$\times age^{-0.287}$

Females : $eGFR = 194 \times serum\ creatinine\ (mg/dL.)^{-1.094} \times age^{-0.287} \times 0.739$

The fibrosis-4 index (FIB-4 index), an index of liver fibrosis, was calculated using the following formula : [6]

$FIB\text{-}4\ index = (age \times AST\ (IU/L))/(Platelet\ (10^9/L) \times ALT\ (IU/L)^{0.5})$

AST : aspartate aminotransferase ; ALT : alanine aminotransferase

D Statistical analysis

Descriptive statistical analysis was performed using Wilcoxon rank sum, χ^2, or Fisher's exact test. JMP ver. 17 was used for statistical analysis. The p-value of less than 0.05 was considered statistically significant.

Ⅲ Results

A Baseline characteristics of the patients

The baseline characteristics of the patients are listed in **Table 1**. The overall proportion of males was 57.0 %. There was no significant difference between the two groups, with 61.0 % of patients in the INS group and 53.0 % of patients in the OHA group. The mean age was 76.4 years, with patients in the OHA group (79.1 years) being significantly older than those in the INS group (73.7 years) (p＜0.001). The number of patients transported by ambulance was 134 (81.7 %) in the INS group, which was not significantly different from 138 (83.1 %) in OHA group (p = 0.7735) ; however, the number of patients admitted to the hospital after transport was 46 (28.0 %) in the INS group, which was significantly lower than 96 (57.8 %) in OHA group (p＜0.001).

The mean blood glucose level during severe hypoglycemia was 36.0 mg/dL in the INS group, which was not significantly different from 35.7 mg/dL in the OHA group. In contrast, the mean hemoglobin A1c (HbA1c) level was significantly higher in the INS group (7.54 %) than in the OHA group (6.25 %).

The number of patients according to the type of drug used is shown in **Table 2**. None of the patients in this study received glucagon-like polypeptide-1 recep-

Table 2　Number of patients treated with each medication

	Total	INS group	OHA group	p-value
BG (number, %)	58, 17.6	12, 7.3	46, 27.7	p＜0.001 *
SU (number, %)	173, 52.4	13, 7.9	160, 96.4	p＜0.001 *
TZD (number, %)	43, 13.0	10, 6.1	33, 19.9	p＜0.001 *
αGI (number, %)	64, 19.4	17, 10.4	47, 28.3	p＜0.001 *
DPP4i (number, %)	80, 24.2	28, 17.1	52, 31.3	p＝0.003 *
Glinide (number, %)	6, 1.8	2, 1.2	4, 2.4	p＝0.685
SGLT2i (number, %)	1, 0.3	1, 0.6	0, 0.0	p＝0.497
GLP-1 RA (number, %)	0, 0.0	0, 0.0	0, 0.0	NA

BG : biguanide, SU : sulfonylurea, TZD : thiazolidinedione, αGI : alpha glucosidase inhibitor
DPP4i : dipeptidyl peptidase-4 inhibitor, Glinide : insulin secretagogue
SGLT2i : sodium-glucose co-transporter 2 inhibitor, GLP-1 RA : glucagon-like polypeptide-1 receptor agonist
* : statistical significance (p＜0.05)

tor agonist (GLP-1 RA). There was no significant difference in the number of patients using insulin secretagogue (Glinide) and sodium glucose co-transporter 2 inhibitor ; however, biguanide (BG), sulfonylurea (SU), thiazolidinedione (TZD), alpha-glucosidase inhibitor (αGI), and dipeptidyl peptidase-4 inhibitor (DPP4i) were used in the INS group by significantly fewer patients.

Fig. 2 shows the number of patients admitted to the hospital after transport examined by time of day. There was no significant difference in the period of transport to the emergency department of our hospital from 0 : 00 to 5 : 59, 6 : 00 to 11 : 59, and 18 : 00 to 23 : 59. For the 6 hr period between 12 : 00 and 17 : 59, 45 (27.3 %) patients in the INS group were transported to the emergency department, which was significantly higher than 27 (16.3 %) observed in OHA group.

Next, we examined the factors that led to hospitalization in each group. We examined the following factors that affected hospitalization for severe hypoglycemia : sex, age, emergency transport, blood glucose level during hypoglycemia, HbA1c level, time of visit, type of oral medication, eGFR, and FIB-4 index.

Table 3 presents the results of the INS group analysis. There were no significant differences in sex or age between the groups. The proportion of patients transported by ambulance was 95.7 %, which was significantly higher than 76.3 % of patients who returned home. The mean blood glucose level was 32.1 mg/dL in patients who required hospitalization, which was significantly lower than that in patients who returned home (37.6 mg/dL) (p＝0.027) ; however, there was no significant difference in HbA1c levels (7.73 % vs. 7.40 %, p＝0.1464). Renal and liver functions were also examined as factors associated with hypoglycemia. eGFR was used as an indicator of renal function, and FIB-4 index as an indicator of liver function ; no significant difference was observed in either (53.66 ml/min/1.73 m^2 vs. 42.05 ml/min/1.73 m^2 ; p＝0.7294, 2.908 vs. 2.945 ; p＝0.8499, respectively). Regarding the time of transportation to our hospital, we examined the time zone every 6 hours and observed no significant difference in the proportion of patients requiring inpatient treatment between 0 : 00 and 5 : 59, 6 : 00 and 11 : 59, 12 : 00 and 17 : 59, and 18 : 00 and 23 : 59. Regarding oral medications, there was a significant difference only in the SU group, and the proportion of patients who required hospitalization was higher for SU drugs (17.5 % vs. 4.2 %, p＝0.0090).

Table 4 presents the results of the OHA group analysis for each element. There were no significant differences in sex or age between the groups or in the proportion of ambulances. The mean blood glucose level was 32.8 mg/dL in patients who required hospitalization, which was significantly lower than that in patients who returned home (39.7 mg/dL) (p＝0.0011). There was no significant difference in HbA1c levels

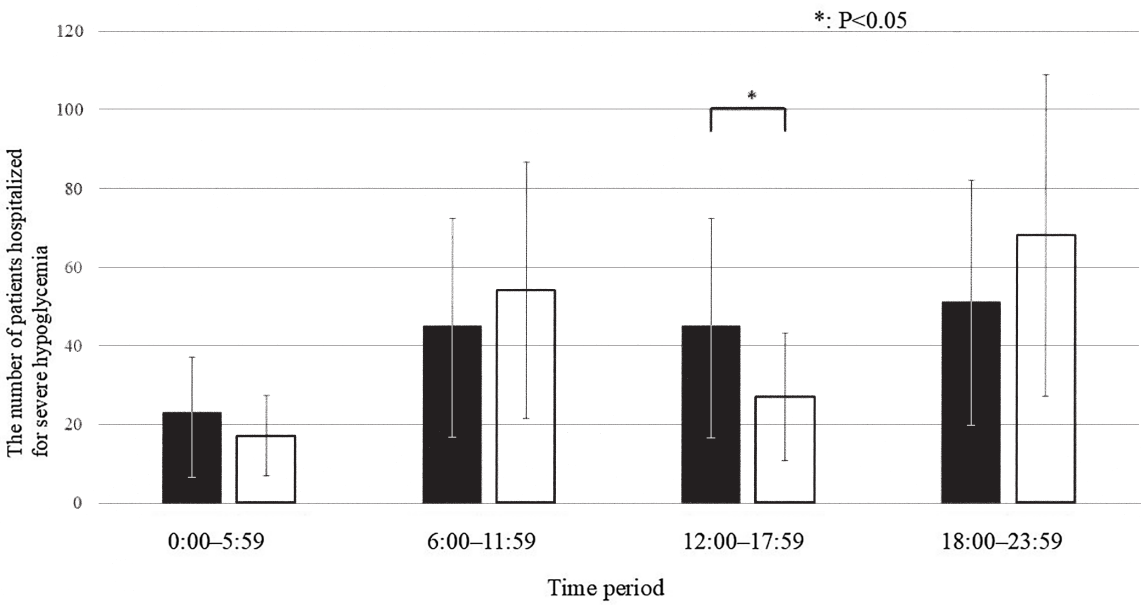

Fig. 2 Number of patients with severe hypoglycemia in each period.

The day was divided into four 6-hr periods. The number of patients with severe hypoglycemia was compared at each period. Asterisk means statistical significance ($p<0.05$). There was no significant difference in the period of transport to the emergency department of our hospital from 0 : 00 to 5 : 59, 6 : 00 to 11 : 59, and 18 : 00 to 23 : 59. For the 6 hr period between 12 : 00 and 17 : 59, 45 (27.3 %) patients in the INS group were transported to the emergency department, which was significantly higher than 27 (16.3 %) observed in OHA group.

Black bar : the number of patients with severe hypoglycemia treated with insulin

White bar : the number of patients with severe hypoglycemia treated without insulin

(6.18 % vs. 6.40 %, $p=0.1180$) or in either eGFR or FIB-4 index (54.55 ml/min/1.73 m^2 vs. 55.73 ml/min/1.73 m^2 ; $p=0.7471$, 3.887 vs. 4.422 ; $p=0.9824$, respectively). In terms of transport time, 5 patients transported between 0 : 00 and 5 : 59 required hospitalization, significantly fewer than the 12 who could return home ($p=0.0181$). Conversely, in the patients who were transported to the hospital between 18 : 00 to 23 : 59, the proportion of the patients who required hospitalization was significantly more than those who returned home (46 patients vs 22 patients, $p=0.0384$). However, there was no significant difference in the proportion of patients requiring hospitalization from 6 : 00 to 11 : 59 and from 12 : 00 to 17 : 59. For oral medications, there were no clear differences in each drug, including SU drugs.

Ⅳ Discussion

The findings of our study showed that patients in the INS group were significantly younger than those in the OHA group. In addition, as HbA1c levels were significantly higher in the INS group than in the OHA group, it was thought that the INS group included many patients with relatively poor glycemic control. In contrast, the OHA group was considered to include older patients with very good glycemic control. The proportion of patients requiring hospitalization was significantly lower in the INS group. This may have been due to the relatively young age of patients in the INS group and relatively mild complications, such as liver fibrosis. In contrast, the proportion of SU in the OHA group was extremely high. In SU-induced hypoglycemia, the risk of protracted hypoglycemia has been reported[7]. This may be due to the difficulty of rapid withdrawal from hypoglycemia, which requires hospitalization. The ratio of the number of patients who visited the hospital because of severe hypoglycemia between 12 : 00 and 17 : 59 was significantly higher in the INS group. Given that the rate of hospitalization in the INS group was relatively low over time, it is possible that the risk of hypoglycemia was relatively low during the day in the OHA group.

Table 3 Comparison of patients who required hospitalization versus those who did not in the INS group

	Hospitalization	Returning home	p-value
Number of patients	46	118	
Males (number, %)	28, 60.9	72, 61.0	1.000
Age (years, mean (SD))	75.1 (7.4)	73.2 (11.2)	0.409
Transfer by ambulance (number, %)	44, 95.7	90, 76.3	0.003 *
Blood glucose levels (mg/dL, mean (SD))	32.1 (13.7)	37.6 (13.7)	0.027 *
HbA1c (%, mean (SD))	7.73 (1.46)	7.40 (1.31)	0.165
eGFR (ml/min/1.73 m^2, mean (SD))	53.66 (25.84)	52.05 (32.21)	0.729
FIB-4 index	2.908 (0.372)	2.945 (0.238)	0.850
Time of visit			
00 : 00-05 : 59 (hour, number, %)	7 (15.2)	16 (13.6)	0.805
06 : 00-11 : 59 (hour, number, %)	17 (37.0)	28 (23.7)	0.118
12 : 00-17 : 59 (hour, number, %)	11 (23.9)	34 (28.8)	0.335
18 : 00-23 : 59 (hour, number, %)	11 (23.9)	40 (33.9)	0.262
Medication type			
BG (number, %)	5 (10.9)	7 (5.9)	0.320
SU (number, %)	8 (17.4)	5 (4.2)	0.009 *
TZD (number, %)	4 (8.7)	6 (5.1)	0.469
αGI (number, %)	5 (10.4)	12 (10.2)	1.000
DPP4i (number, %)	10 (21.7)	18 (15.3)	0.358
Glinide (number, %)	0 (0.0)	2 (1.7)	1.000
SGLT2i (number, %)	0 (0.0)	1 (0.9)	1.000

INS : patients treated with insulin, HbA1c : hemoglobin A1c, eGFR : estimated glomerular filtration rate
FIB-4 index : fibrosis-4 index, BG : biguanide, SU : sulfonylurea, TZD : thiazolidinedione
αGI : alpha glucosidase inhibitor, DPP4i : dipeptidyl peptidase-4 inhibitor, Glinide : insulin secretagogue
SGLT2i : sodium-glucose co-transporter 2 inhibitor, GLP-1 RA : glucagon-like polypeptide-1 receptor agonist
* : statistical significance ($p < 0.05$)

The rate of ambulance transport was approximately the same for patients in the INS group and in the OHA group ; however, patients in the INS group were significantly less likely to be admitted to the hospital after consultation compared to those in the OHA group. The patients in the INS group had significantly lower blood glucose levels during hypoglycemia than those in the OHA group, suggesting that hypoglycemic episodes in patients who were hospitalized were more severe than those in patients who returned home. Regarding oral medications, only SU was used in a high proportion of hospitalized patients, suggesting that a combination of insulin and SU increases the risk of hypoglycemia[7].

For the OHA group, there were no significant differences in hospitalization factors in terms of sex, age, presence or absence of emergency transport, blood glucose control, or renal or hepatic function. In patients who required hospitalization, only blood glucose levels during hypoglycemia were significantly lower than in those who returned home, suggesting that they may have experienced more severe hypoglycemia. Regarding the difference by time of day, the proportion of patients who required hospitalization was

Table 4 Comparison between patients who required hospitalization and those who did not in the OHA group

	Hospitalization	Returning home	p-value
Number of patients	96	70	
Males (number, %)	56, 58.3	32, 45.7	0.118
Age (years, mean (SD))	80.5 (7.9)	77.1 (10.4)	0.058
Transfer by ambulance (number, %)	84, 87.5	54, 77.1	0.095
Blood glucose levels (mg/dL, mean (SD))	32.8 (11.6)	39.7 (13.4)	0.001 *
HbA1c (%, mean (SD))	6.18 (0.88)	6.40 (0.86)	0.118
eGFR (ml/min/1.73 m^2, mean (SD))	54.55 (27.23)	55.73 (22.51)	0.747
FIB-4 index	3.887 (4.393)	3.422 (2.063)	0.982
Time of visit			
00 : 00-05 : 59 (hour, number, %)	5 (5.2)	12 (17.1)	0.018 *
06 : 00-11 : 59 (hour, number, %)	29 (30.2)	25 (35.7)	0.504
12 : 00-17 : 59 (hour, number, %)	16 (16.7)	11 (15.7)	1.000
18 : 00-23 : 59 (hour, number, %)	46 (47.9)	22 (31.4)	0.038 *
Medication type			
BG (number, %)	24 (25.0)	22 (31.4)	0.384
SU (number, %)	94 (97.9)	66 (94.3)	0.241
TZD (number, %)	18 (18.8)	15 (21.4)	0.697
αGI (number, %)	25 (26.0)	22 (31.4)	0.488
DPP4i (number, %)	32 (33.3)	20 (28.6)	0.612
Glinide (number, %)	1 (1.0)	3 (4.3)	0.311
SGLT2i (number, %)	0 (0.0)	0 (0.0)	NA

OHA : patients treated without insulin, HbA1c : hemoglobin A1c, eGFR : estimated glomerular filtration rate
FIB-4 index : fibrosis-4 index, BG : biguanide, SU : sulfonylurea, TZD : thiazolidinedione
αGI : alpha glucosidase inhibitor, DPP4i : dipeptidyl peptidase-4 inhibitor, Glinide : insulin secretagogue
SGLT2i : sodium-glucose co-transporter 2 inhibitor, GLP-1 RA : glucagon-like polypeptide-1 receptor agonist
* : statistical significance ($p < 0.05$)

low from 0 : 00 to 5 : 00. Since there were many elderly patients in the OHA, we considered the possibility that this was a time when it was easier to obtain the cooperation of family members. From 18 : 00 to 23 : 00, the proportion of patients requiring hospitalization was significantly high. Considering the risk of protracted hypoglycemia in the evening and night, we considered the possibility that many patients required inpatient treatment.

Overall, there were a large number of relatively young patients in the INS group, and the proportion of patients taking SU was extremely high in the OHA group. In SU-induced hypoglycemia, the risk of protracted hypoglycemia has been reported[8]. This may have been due to the difficulty of rapid withdrawal from hypoglycemia, which subsequently required hospitalization.

This study has some limitations. First, it was a retrospective, observational study. Although the findings of this study can be analyzed in detail, its causes are difficult to determine. Second, this was a single-center study ; therefore, whether this phenomenon is unique to this facility or is universal remains unclear. Third, our sample size was small ; therefore, examining other

factors potentially involved in this phenomenon was difficult.

The findings of this study indicate that there are differences in the mode of hypoglycemia development based on whether the drug was administered with or without insulin. Further, differences in the background of patients requiring hospitalization must be acknowledged and considered.

V Conclusion

The findings of this study strongly suggest a reasonable risk of hypoglycemia even with poor glycemic control when insulin treatment is administered and that hospitalization may be required, especially when SU drugs are used concomitantly. However, when treated with oral hypoglycemic drugs alone, attention should be paid to the excessive lowering of HbA1c levels and the risk of hospitalization, especially in cases of hypoglycemia in the evening and late at night. By formulating a treatment strategy with this in mind, the risk of severe hypoglycemia requiring hospitalization can be reduced.

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