



# The prescription rates of glucagon for hypoglycemia by pediatricians and physicians are low in Japan

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Received: 14 September 2018 / Accepted: 12 October 2018 / Published online: 26 October 2018  
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## Abstract

**Purpose** Hypoglycemia is a common and life-threatening complication in type 1 diabetes mellitus (T1DM) patients. Current guidelines recommend glucagon for treating hypoglycemia in out-of-hospital settings; however, glucagon is reportedly underused in such patients. We conducted a doctor-oriented, questionnaire-based survey of pediatricians and physicians to determine the glucagon prescription rate and identify the reason(s) for its underuse in T1DM patients.

**Methods** A questionnaire was mailed to 415 pediatricians and 200 physicians employed at 66 facilities with >100 general wards throughout Hyogo, Japan. The following variables were surveyed: doctor's specialty, glucagon prescription rate, familiarity with glucagon use guidelines, barriers to prescribing glucagon, and attitude changes after education.

**Results** After 16 doctors were found to have retired, 599 doctors were enrolled; 305 (187 pediatricians and 118 physicians) returned a completed questionnaire. In all, 45 pediatricians and 104 physicians were treating T1DM patients, of whom 24% and 28% reported prescribing glucagon, respectively. The guideline familiarity rate among pediatricians was lower than that among physicians. The major barrier to prescribing glucagon was the complex preparation procedure required by patients/caregivers. More than half of the doctors who did not prescribe glucagon began doing so after being educated about the guidelines.

**Conclusion** The glucagon prescription rate was low among both pediatricians and physicians in Japan.

**Keywords** Glucagon · Prescription · Type 1 diabetes mellitus · Guideline

## Introduction

Type 1 diabetes mellitus (T1DM) is one of the most common chronic metabolic disorders in children and adolescents worldwide. The main goals of insulin replacement therapy are to achieve optimal glycemic control and to prevent long-term complications. Modern therapeutic options include multiple daily injections and insulin pumps

that allow physiologic insulin replacement and optimal glycemic control. However, severe hypoglycemia remains a common insulin therapy-related complication that occurs in 4.1–29.7% of T1DM patients every year [1–4]. It decreases the patient's quality of life and can also be fatal [5]; therefore, it is necessary to properly treat severe hypoglycemia. Intramuscular glucagon injection is the recommended primary care method for out-of-hospital T1DM patients with severe hypoglycemia; it rapidly elevates blood glucose levels [6–8]. Therefore, patients and caregivers should have the injection readily available and be ready to administer it promptly in a non-medical environment when necessary. However, previous studies found that glucagon was underused owing to its complex preparation procedure or because of a lack of education [9, 10]. In Japan, only 15.9% of adult T1DM patients were reported to have glucagon in their homes [2]. However, since these studies were user-oriented surveys, it was unclear whether doctors' beliefs or behaviors factored into its underuse. Therefore, an

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investigation of doctors who treat T1DM patients is required to better understand the dynamics of glucagon use.

In this study, we conducted a questionnaire-based survey of both pediatricians and physicians to determine the glucagon prescription rate in Japan. To identify why glucagon is underused by these patients, we also surveyed the extent of familiarity with the guidelines on glucagon use, barriers to prescribing glucagon, and attitude changes after education about glucagon.

## Research design and methods

### Setting

This was a single-center initiated, cross-sectional survey of glucagon prescription patterns in Japan. The survey was conducted between 1 November 2017 and 31 December 2017.

### Participants

All pediatricians who were employed at Hyogo Prefectural Kobe Children's Hospital or at pediatric departments in hospitals with >100 general wards in the Hyogo prefecture of Japan were invited to this study. Furthermore, all physicians employed at diabetes/endocrinology departments in hospitals with >100 general wards in the Hyogo prefecture were also surveyed. Appropriate participants for this study were identified by examining each aforementioned hospital's website.

### Questionnaire

A self-administered questionnaire was designed and mailed to all the participants. Glucagon's product documentation and the relevant guidelines about its recommended use for hypoglycemia were also enclosed with the questionnaire. The questionnaire asked questions to delineate the following variables: department, length of practice as a doctor, sex, subspecialty certification, and the number of patients aged  $\leq 15$  years and  $\geq 16$  years being treated. The questionnaire further assessed familiarity with recommended glucagon guidelines by a polar question, and changes to glucagon prescription attitudes after receiving educational documents. Educational documents consisted of guidelines on glucagon use for hypoglycemia, glucagon product documentation including its preparation method, and information about a nasally administered glucagon product.

### Statistical analysis

Fisher's exact test was used to compare the rates of glucagon prescriptions and those of familiarity with the

guidelines between physicians and pediatricians. It was also used to compare the glucagon prescription rates among doctors who were familiar with the guidelines versus those who were not.  $P$  values  $< 0.05$  were considered statistically significant. All statistical analyses were performed using GraphPad Prism 7.02 (GraphPad Software, Inc., San Diego, CA).

## Results

### Participants and response rate

The questionnaire was mailed to 615 doctors in 66 hospitals. Sixteen mailings were not received by their addressees because they had already retired; the remaining 599 participants (402 pediatricians and 197 physicians) were enrolled in this study. In all, 305 doctors (187 pediatricians and 118 physicians) returned a completed questionnaire. Hence, the response rate was 51% (47% for pediatricians and 60% for physicians). Of these 305 doctors, 149 (45 pediatricians and 104 physicians) were treating T1DM patients; doctor characteristics are shown in Table 1. The median lengths of practice as a pediatrician and physician were 15 and 13 years, respectively. In addition, 89% of pediatricians and 75% of physicians were board-certified members of the Japanese Pediatric Society and the Japanese Society of Internal Medicine, respectively. The proportion of physicians who were board certified by the Japan Diabetes Society was greater than that of pediatricians.

### Proportion of doctors prescribing glucagon

Among doctors treating T1DM patients, 11 pediatricians (24%) and 29 physicians (28%) prescribed glucagon; there were no significant differences in glucagon prescription rates between pediatricians and physicians ( $P = 0.69$ ) (Fig. 1).

Nearly 70% of pediatricians had 1–5 patients aged  $\leq 15$  years; in contrast, 70% of physicians had 6 or more patients aged  $\geq 16$  years. Hence, pediatricians treated younger T1DM patients but also a proportion of those aged  $> 16$  years. Similarly, physicians did treat some T1DM patients who were aged  $\leq 15$  years. Interestingly, one T1DM-treating pediatrician had no patients aged  $\leq 15$  years, and one physician treated only younger patients, with none being aged  $\geq 16$  years (Table 1).

### Familiarity with guidelines

The questionnaire queried whether the doctors were familiar with glucagon use guidelines for T1DM management [11, 12], as we hypothesized that such familiarity influences the

**Table 1** Characteristics of the surveyed pediatricians and physicians

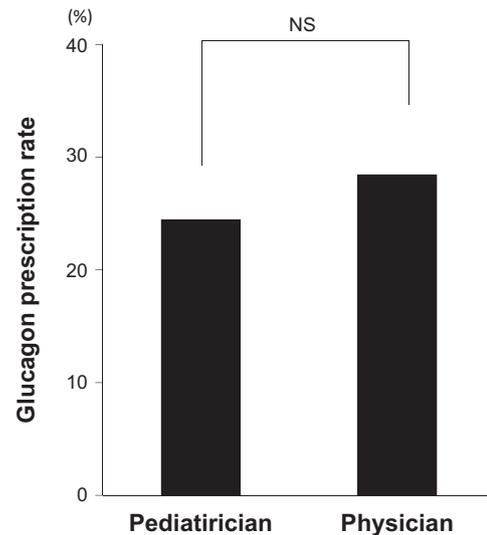
Characteristic	Pediatricians ( <i>n</i> = 45)	Physicians ( <i>n</i> = 104)
Length of service (years)	15 (3–38)	13 (3–50)
Male sex	27 (60)	73 (70)
Board certification		
Internal medicine	0 (0)	78 (75)
Pediatrics	40 (89)	0 (0)
Diabetology	2 (4)	59 (57)
Endocrinology	1 (2)	22 (21)
None	5 (11)	14 (13)
Number of treated T1DM patients		
Patients aged ≤15 years		
0	1 (2)	92 (88)
1–2	21 (47)	10 (10)
3–5	10 (22)	2 (2)
6–10	10 (22)	0 (0)
11–19	1 (2)	0 (0)
≥20	2 (4)	0 (0)
Patients aged ≥16 years		
0	29 (64)	1 (1)
1–2	7 (16)	5 (5)
3–5	5 (11)	26 (25)
6–10	3 (7)	36 (35)
11–19	1 (2)	12 (12)
≥20	0 (0)	24 (23)

Data are shown as median (range) or as *n* (%). Board-certified international medicine, pediatrics, diabetology, and endocrinology members are certified by The Japanese Society of Internal Medicine, Japan Pediatric Society, Japan Diabetes Society, and Japan Endocrine Society, respectively

T1DM type 1 diabetes mellitus

glucagon prescription rate. The rates of familiarity with the guidelines were 53% (24/45) among pediatricians and 84% (87/104) among physicians treating T1DM patients (Fig. 2a). The rate of familiarity among pediatricians was significantly lower than among physicians ( $P = 0.0004$ ).

Next, we investigated whether familiarity with the guidelines influenced the glucagon prescription rate. Of the 45 pediatricians, 24 were familiar with the guidelines. Of these, 11 (46%) prescribed glucagon (Fig. 2b). The remaining 21 pediatricians neither knew the guidelines nor prescribed glucagon. Furthermore, 26 out of the 87 physicians who knew the guidelines (30%) prescribed glucagon. Among the remaining 17 who were unfamiliar with the guidelines, 3 (18%) prescribed glucagon. These results revealed that familiarity with the guidelines was significantly associated with a higher glucagon prescription rate among pediatricians ( $P = 0.0003$ ). However, it was not related to the prescription rate among physicians ( $P = 0.55$ ).



**Fig. 1** The glucagon prescription rate among pediatricians and physicians treating patients with type 1 diabetes mellitus. NS not significant

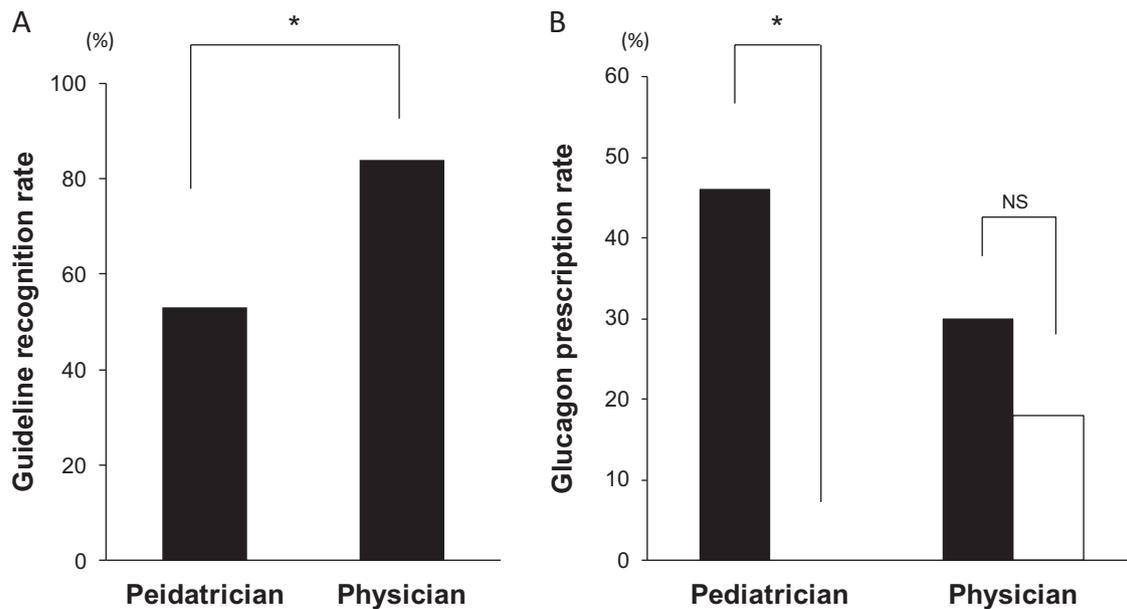
### Obstacles to prescribing glucagon

Nearly 25% of T1DM-treating doctors (both pediatricians and physicians) prescribed glucagon. To identify the factors responsible for the low glucagon prescription rate, we collected responses to multiple choice questions inquiring about: (1) the status of patient education about glucagon use, (2) the availability of glucagon at their hospitals, (3) patient/caregivers' rejection of this treatment, (4) complex preparation procedures required by the patients/caregivers, (5) non-cooperation of caregivers, and (6) others.

Among both pediatricians and physicians who did not prescribe glucagon, the most common reason given was the complex preparation procedure required by the patient/caregiver (Fig. 3). Other common barriers to prescribing glucagon were educational deficits among patients, uncooperative caregivers, and patient/caregiver rejection. Glucagon unavailability at the hospitals was not mentioned as a barrier to its prescription by any of the pediatricians; however, it was the fifth most common factor among physicians. 'Other' reasons not to prescribe glucagon included the lack of need for patients with rare episodes of hypoglycemia, no home-care support because of living alone or with no proper caregivers, bulky non-kit products, and the doctors' inexperience.

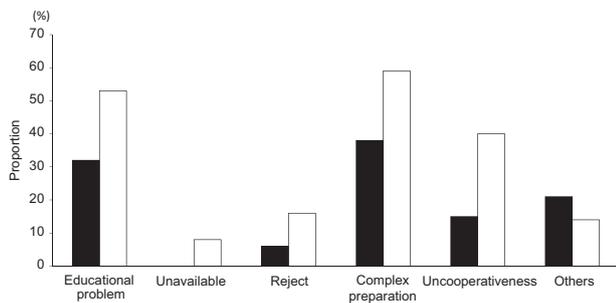
### Attitude changes among doctors after glucagon use education

We investigated whether doctors who did not prescribe glucagon to their T1DM patients changed their minds after receiving education materials containing guidelines



**Fig. 2** Glucagon use guideline's familiarity and prescription rates. **a** The rate of type 1 diabetes mellitus-treating doctors who were familiar with the guidelines on glucagon use for hypoglycemia. The rates of familiarity with the guidelines were 53% and 84% in pediatricians and physicians, respectively. **b** The glucagon prescription rate among pediatricians who were familiar with the guidelines (black bars) was

significantly higher than among those who were not (white bars) (46% vs. 0%). Among physicians, the rate of those prescribing glucagon was high among those familiar with the guidelines, but there were no significant differences compared to those who were not familiar (30% vs. 18%). \* $P < 0.001$ , NS not significant



**Fig. 3** Barriers to prescribing glucagon. The black and white bars represent the proportions of positive answers by pediatricians and physicians who did not prescribe glucagon, respectively. Questions inquired about (1) the lack of patient education about glucagon use (Educational problem), (2) unavailability of glucagon at their facility (Unavailable), (3) rejection by the patient/caregivers (Reject), (4) complexity of the glucagon preparation procedure by the patient/caregiver (Complex preparation), (5) uncooperative caregivers (Uncooperativeness), and (6) other reasons

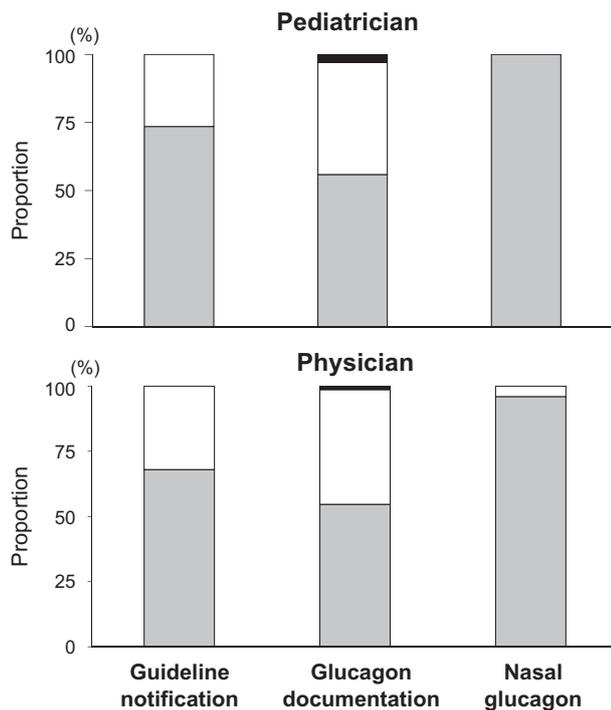
recommending its use, glucagon product documentation, and information regarding the easy-to-use intranasal glucagon administration method. After receiving information about guideline recommendations on glucagon use, 74% of physicians and 68% of pediatricians chose to prescribe it (Fig. 4). Next, after the doctors read the glucagon product documentation explaining that it is a non-ready-to-use product and requires mixing and monitoring by caregivers, the motivation for prescribing glucagon decreased among

both pediatricians and physicians. Finally, when advised that a non-invasive intranasal glucagon product was available, most doctors (100% of pediatricians and 96% of physicians) were amenable to prescribing it.

## Discussion

We determined the glucagon prescription rate in both pediatricians and physicians who treated T1DM patients in Hyogo, Japan. To the best of our knowledge, this is the first survey to investigate the proportion of doctors who prescribed glucagon to T1DM patients using a self-administered questionnaire. The glucagon prescription rates were 24% and 28% among pediatricians and physicians, respectively. This result was consistent with the low prescription rate found in a questionnaire-based study of adult T1DM patients in Japan [2]. Therefore, the lack of doctors' interest in prescribing glucagon may be responsible for its underuse in Japanese T1DM patients.

The usefulness and importance of glucagon use for hypoglycemia have been reported previously [13, 14]. According to the Japanese guidelines for pediatric T1DM [15], glucagon use is recommended for patients with severe hypoglycemia. However, our survey revealed a low rate of familiarity with glucagon use guidelines; only half of the pediatricians treating T1DM patients were familiar with the



**Fig. 4** Changes in intent to administer glucagon after receiving education on the product by pediatricians (upper panel) and physicians (lower panel) who did not prescribe glucagon. The cumulative bar chart represents the proportion of doctors' responses after receiving education on glucagon administration guidelines (Guideline notification), glucagon product documentation (Glucagon documentation), and the non-invasive intranasal glucagon product (Nasal glucagon). Gray, white, and black bars refer to positive, negative, and no response, respectively, with regard to deciding to administer glucagon

guidelines. This is critically important considering that our study showed that only pediatricians who were familiar with these guidelines prescribed glucagon. Since most pediatricians in our study were not board certified and had relatively few patients, those who responded to the questionnaire appeared to be general doctors in the pediatric department and not experts in treating T1DM. In contrast to the Japanese guidelines for pediatric T1DM, glucagon use is optional according to the Japanese guidelines for adult T1DM patients [16]. However, the physicians in our study presumably had more advanced expertise and showed a higher rate of familiarity with glucagon use guidelines.

Interestingly, pediatricians and physicians shared common obstacles to administering glucagon, including complex preparation procedures, the lack of patient education regarding glucagon use, and uncooperative caregivers. To increase the glucagon prescription rate, guidelines should be better distributed to caregivers, particularly pediatricians. However, among physicians, other factors may exist regarding the lack of glucagon use that have not yet been addressed.

In Japan, only the vial product of glucagon is currently available. Unlike ready-to-use kits, patients or caregivers must prepare the product using complicated procedures, including dissolving the glucagon powder using a diluting solution, attaching a needle to a syringe, and removing the air in the syringe. These complex glucagon preparation methods were cited as a reason why the product is not optimal for emergency use by non-medical professionals [2, 9, 10]. In our survey, the product's complex preparation procedure was revealed as the most common obstacle to glucagon prescription by both pediatricians and physicians (Fig. 3). Recently, a new user-friendly, non-invasive glucagon delivery system that is administered intranasally has been under development as an alternative [17, 18]. Accordingly, most doctors and patients would prefer the intranasal product if available.

This study had some limitations. First, it only included participants working in general hospitals with >100 wards. Because T1DM is not highly prevalent in Japan [19], it is possible that only doctors working in subspecialty departments treated these patients. The likelihood that primary care doctors tended to T1DM patients could not be ruled out. Second, this study was conducted via a self-administered, easy-to-answer questionnaire which may have biased the data while trying to increase the response rate. However, the relatively high response rate (51%) for this type of study represented a real-world assessment of glucagon prescription rates in Japan. Furthermore, the questionnaire did not determine details about treated T1DM patients. Therefore, characteristics, including onset age, educational status, disease duration, past and current treatment, frequency of hypoglycemic episodes, and HbA1c level, may affect the doctor's decision to prescribe glucagon, but this could not be investigated in this study. Additionally, the questionnaire did not determine the clinical structure of the hospital. Stable teams or patient-empowering programs improve patient education [20], and it is assumed that a lack of these structures may decrease glucagon prescription rates. Further study is necessary to elucidate whether patient factors are related to the glucagon prescription rate.

In conclusion, the glucagon prescription rate by both pediatricians and physicians is low in Japan. Wider dissemination of the guidelines on glucagon use and easy-to-prepare glucagon treatments is warranted to improve the prescription rate.

**Acknowledgements** The authors would like to thank Kanako Yokoyama and Saki Enomoto, secretaries of Department of Pediatrics, Kobe University Graduate School of Medicine, for mailing questionnaires.

**Author contributions** M.M., H.A., Y.H., M.N., R.B., A.M., T.H., T. T., and Y.N. conceptualized this study and participated in its design and coordination. M.M., M.N., and R.B. collected and analyzed the

data. M.M. and H.A. drafted the original manuscript. Y.H., A.M, T.H., and T.T. helped draft the manuscript. Y.H., W.O., and K.I. reviewed and edited the manuscript. All authors read and approved the final manuscript.

### Compliance with ethical standards

**Conflict of interest** W.O. received a research grant and lecture fees from Novo Nordisk. Y.H. received lecture fees from Novo Nordisk. The remaining authors declare that they have no conflict of interest.

**Ethical approval** All procedures performed in this study involving human participants were in accordance with the guidelines of the Declaration of Helsinki, and the study protocol was approved by the ethics committee of Kobe University Graduate School of Medicine (Approval No. 170120).

**Informed consent** Written informed consent was obtained from all the participants.

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