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Prevalence and clinical characteristics of fulminant type 1 diabetes mellitus in Korean adults: A multi-institutional joint research

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Keywords
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ABSTRACT

Aims/Introduction: We aimed to determine the hospital-based prevalence and clinical features of fulminant type 1 diabetes mellitus in Korea.

Materials and Methods: We identified all patients with diabetes who regularly visited the Endocrinology outpatient clinics at eight centers for a period >1 year between January 2012 and June 2017. We investigated their medical records retrospectively.

Results: During this period, 76,309 patients with diabetes had been regularly followed up. Among them, 913 (1.2%) patients had type 1 diabetes mellitus . There were 462 patients with type 1 diabetes mellitus whose data at the time of the first diagnosis could be identified (359 and 103 with non-ketosis and ketosis onset, respectively). Of these, 15 (3.2% of type 1 diabetes mellitus, 14.6% of ketosis onset diabetes) patients had fulminant type 1 diabetes mellitus. The median ages at diagnosis were 40 and 27 years in the fulminant type 1 diabetes mellitus and non-fulminant type 1 diabetes mellitus groups, respectively. The patients with fulminant type 1 diabetes mellitus had higher body mass index, lower glycated hemoglobin and fasting/peak C-peptide, and lower frequent glutamic acid decarboxylase antibody-positive rate (P =0.0010) at diagnosis. Furthermore, they had lower glycated hemoglobin at the last follow-up examination than those with non-fulminant type 1 diabetes mellitus.

Conclusions: In this study, the prevalence of type 1 diabetes mellitus was 1.2% among all patients with diabetes, and that of fulminant type 1 diabetes mellitus was 3.2% among those newly diagnosed with type 1 diabetes mellitus. The glycated hemoglobin levels were lower in patients with fulminant type 1 diabetes mellitus than in those with non-fulminant type 1 diabetes mellitus at diagnosis and at the last follow-up examination.

INTRODUCTION

Type 1 diabetes mellitus results from the destruction of pancreatic β-cells and the consequent loss of insulin-secreting capacity. Type 1 diabetes mellitus is subdivided into two categories: autoimmune (type 1A) and idiopathic (type 1B) diabetes. Type 1A diabetes is caused by the destruction of β-cells by specific autoantibodies to the cytoplasm of islet cells, glutamic acid decarboxylase (GAD), insulin and tyrosine phosphatase-like protein (IA-2 or IA-2ß); nevertheless, there is limited knowledge regarding type 1B [1,2].

Fulminant type 1 diabetes mellitus was first introduced as a subtype of type 1 diabetes mellitus by Imagawa *et al.*[3] It is

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defined as a subtype of type 1B with an extremely rapid process of β-cell destruction, and progression of hyperglycemia and ketoacidosis[3]. According to the Japan Diabetes Society criteria, the diagnostic criteria for fulminant type 1 diabetes mellitus are as follows: occurrence of diabetic ketoacidosis soon (within approximately 7 days) after the onset of hyperglycemic symptoms; plasma glucose level ≥288 mg/dL and glycated hemoglobin (HbA1c) level <8.5% at first visit; and urinary C-peptide excretion <10 μg/day or fasting serum C-peptide level <0.3 ng/mL and <0.5 ng/mL after intravenous glucagon (or after meal) load at onset. The values do not depend on the presence of antibodies in most cases[4].

The clinical characteristics and epidemiology of patients with type 1 diabetes mellitus and fulminant type 1 diabetes mellitus are heterogeneous across ethnic groups. Although the incidence of type 1 diabetes mellitus is not higher in Asian countries than in Europe and the USA, the incidence of fulminant type 1 diabetes mellitus is higher in Asian than in European countries [5–7].

Several studies have focused on type 1 diabetes mellitus; however, only one hospital-based study, which was carried out in 2007, reported the prevalence of fulminant type 1 diabetes mellitus. That study reported a 7.1% prevalence of fulminant type 1 diabetes mellitus among all patients newly diagnosed with type 1 diabetes mellitus[7]. Only a few local epidemiological studies have been carried out in Korea. Few registries have reported the incidence rates of fulminant type 1 diabetes mellitus in Korean populations. Therefore, we carried out a multicenter study in eight hospitals of the Gyeonggi Province of South Korea to clarify the frequency of fulminant type 1 diabetes mellitus and its characteristics.

MATERIALS AND METHODS

Research design and methods

The present study used data from patients with type 1 diabetes mellitus from eight centers, including four tertiary university-affiliated hospitals in Gyeonggi Province of South Korea, who were admitted to the hospitals or visited the clinic regularly for a period >1 year between January 2012 and June 2017. One physician was responsible for reviewing all the data, whereas another two physicians were responsible for auditing the data according to the same criteria.

In the present study, we defined type 1 diabetes mellitus using the following criteria: fasting C-peptide levels <0.6 ng/mL or stimulated C-peptide levels <1.8 ng/mL without a history of pancreatic disease or inflammation due to drinking alcohol, trauma or other reasons. Patients with fulminant type 1 diabetes mellitus were diagnosed according to the following inclusion criteria proposed by the Committee of the Japan Diabetes Society: (i) ketosis or ketoacidosis within 1 week after the onset of hyperglycemic symptoms; (ii) fasting serum C-peptide <0.3 ng/mL or serum C-peptide <0.5 ng/mL after meal load, or after glucagon injection soon after disease onset; and (iii) HbA1c level <8.7% (National Glycohemoglobin Standardization Program value) on the first visit. These criteria were determined based on the data at the time of first fulminant type 1 diabetes mellitus diagnosis[4].

Ethics statement

The study protocol conforms to the ethical guidelines of the Declaration of Helsinki. Furthermore, it was approved by the institutional review boards of each participating hospital.

Clinical characteristics and biochemical analysis

The clinical characteristics of all patients (i.e., age at onset, sex, body mass index [BMI], date of onset of hyperglycemic symptoms, date of insulin therapy initiation, family history of diabetes, symptoms accompanying onset of diabetes) were recorded. We retrospectively reviewed the electronic medical records and extracted the relevant laboratory data at the onset of diabetes in each hospital. In particular, data regarding the fasting plasma glucose concentration, HbA1c level, diabetes ketoacidosis status at diagnosis, fasting and stimulated serum C-peptide level were collected. Next, the fasting plasma C-peptide and 2-h postprandial C-peptide levels were determined using the electrochemiluminescence immunoassay method after the resolution. Autoantibodies to GAD (GAD Ab) and islet cell antibodies (IA-2Abs antibody) were determined at the onset of diabetes. GAD Abs and IA-2Abs were measured by a radioimmunoassay or radioligand-binding assay, thyroid antimicrosomal and anti-thyroglobulin antibodies were not investigated. In addition, the daily insulin dosages and injection times were determined at the last follow-up visit along with the following laboratory data: HbA1c, fasting glucose and creatinine levels, as well as the urinary albumin-to-creatinine ratio.

Statistical analysis

Descriptive statistics were used to investigate the data expressed as numbers and frequency percentages (%). All continuous variables with a normal distribution are expressed as the mean ± standard deviation and compared using *t*-tests, whereas those with a skewed distribution are expressed as medians (ranges). The Mann–Whitney *U*-test was used for comparisons. Categorical variables are presented as numbers with percentages; the χ^2-test or Fisher's exact test was used to compare the two groups. All data were analyzed using Stata/MP, version 15.1 (Stata Corp., College Station, TX, USA). A two-sided *P*-value of <0.05 was considered to show statistical significance.

RESULTS

Number of participants in the registry according to the subtype of type 1 diabetes mellitus and time of diagnosis

In total, 76,309 patients with diabetes were identified over the study period (January 2012 to June 2017) in the eight hospitals (Figure 1). We extracted the data of 913 patients with type 1 diabetes mellitus who had visited the outpatient clinic during same period. The hospital review identified 462 patients with data of the first diagnosis of type 1 diabetes mellitus. Of the 462 patients, 359 and 103 had non-ketosis and ketosis-onset type 1 diabetes

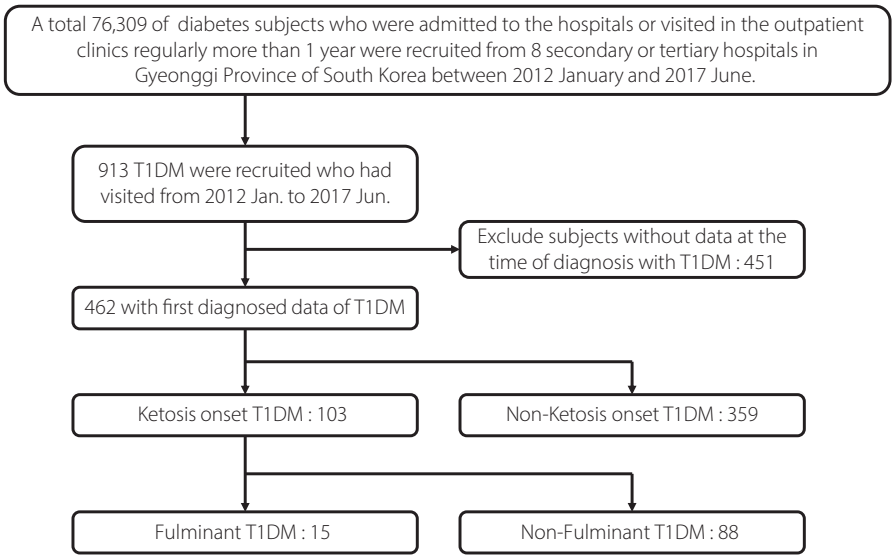

Figure 1 | Study flow diagram detailing participants. T1DM, type 1 diabetes mellitus.

Table 1 | Frequency and proportion distribution of fulminant type 1 diabetes mellitus in type 1 diabetes mellitus

	T1DM	Non-ketosis onset	Ketosis onset	FT1DM
Total				
n	**462**	359	103	**15**
Proportion for T1DM (%)		77.7	22.3	3.2
Proportion for ketosis onset (%)				14.6
Diagnosed before 2012				
n	311	253	58	**2**
Proportion for T1DM (%)		81.4	18.6	0.6
Proportion for ketosis onset (%)				3.4
Diagnosed during 2012–2017				
n	151	106	45	**13**
Proportion for T1DM (%)		70.2	29.8	8.6
Proportion for ketosis onset (%)				28.9

FT1DM, fulminant type 1 diabetes mellitus; T1DM, type 1 diabetes mellitus.

mellitus, respectively. A total of 15 patients (3.2% and 14.6% of all patients with type 1 diabetes mellitus and of those with ketosis onset, respectively) were diagnosed as having fulminant type 1 diabetes mellitus (Figure 1, Table 1) according to the criteria of the Committee of the Japan Diabetes Society[4].

Comparison of the clinical characteristics in patients with fulminant type 1 diabetes mellitus and non-fulminant type 1 diabetes mellitus

The clinical and laboratory characteristics of the participants are presented in Table 2. The characteristics were divided into fulminant type 1 diabetes mellitus and non-fulminant type 1 diabetes mellitus for description. Regarding the records at the time of diagnosis, compared with the patients in the non-fulminant type 1 diabetes mellitus group, those in the fulminant type 1 diabetes mellitus group were diagnosed at an older age ($P = 0.0018$), had lower HbA1c levels ($P < 0.0001$), lower fasting/peak C-peptide levels ($P < 0.0001$) and less frequent GAD Ab-positivity ($P = 0.0010$). There were no differences in the fasting plasma glucose or pH level at diabetic ketoacidosis. Similarly, there were no differences in the family history of diabetes between the two groups. When the patients were diagnosed with type 1 diabetes mellitus, just 19.7% of the cases of non-fulminant type 1 diabetes mellitus were accompanied by diabetic ketoacidosis, whereas 100% of fulminant type 1 diabetes mellitus cases were accompanied by diabetic ketoacidosis ($P < 0.0001$). The non-fulminant type 1 diabetes mellitus patients had lower BMI ($P < 0.0049$) at diagnosis and longer follow-up duration ($P < 0.0001$) than those with fulminant type 1 diabetes mellitus.

Table 2 | Baseline characteristics of study population stratified by FT1DM and Non-FT1DM

	Total (*N* = 462)	Fulminant T1DM (*N* = 15)	Non-fulminant T1DM (*N* = 447)	*P* value
Records at diagnosis				
Age (years)	27 (16–37)	40 (28–49)	27 (15–36)	0.0018
Male (*n*, %)	229 (49.6%)	7 (46.7%)	222 (49.7%)	0.8190
BMI (kg/m^2)	22.6 (20.8–24.8)	23.4 (20.8–26.3)	19.7 (17.4–22.0)	0.0049
Family history of diabetes (*n*, %)†	77/248 (31.0%)	3/12 (25.0%)	74/236 (31.4%)	0.7360
HbA1c (%)	12.2 (9.5–13.8)	6.1 (5.9–6.5)	12.3 (9.8–13.9)	<0.0001
Fasting plasma glucose (mg/dL)	295 (217–456)	274 (223–521)	296 (214–449)	0.4606
Fasting C-peptide (ng/mL)	0.49 (0.22–0.76)	0.1 (0.0–0.2)	0.5 (0.25–0.78)	<0.0001
Peak C-peptide (ng/mL)	0.69 (0.36–1.27)	0. 1 (0.0–0.2)	0.71 (0.39–1.3)	<0.0001
DKA (*n*, %)	103 (22.3%)	15 (100%)	88 (19.7%)	<0.0001
pH	7.16 (7.07–7.25)	7.12 (7.06–7.18)	7.17 (7.07–7.26)	0.4703
GAD antibody positivity (*n*, %)†	263/361 (72.8%)	3/13 (23.1%)	260/348 (74.7%)	0.0010
Anti–IA-2 antibody positivity (*n*, %)†	9/93 (9.7%)	0/5 (0.0%)	9/88 (10.2%)	0.2730
Insulin antibody positivity (*n*, %)†	5/60 (8.3%)	0/4 (0.0%)	5/56 (8.9%)	0.1880
Records at latest follow up				
Age (years)	35 (26–46)	41 (33–50)	35 (26–46)	0.0001
Follow-up after diagnosis (years)	8 (4–13)	3 (2–4)	8 (4–13)	0.0001
BMI (kg/m^2)	22.6 (20.8–24.7)	21.1 (20.0–21.3)	22.6 (20.8–24.8)	0.2194
HbA1c (%)	8.4 (7.3–9.7)	7.0 (6.5–8.8)	8.4 (7.3–9.7)	0.0366
Fasting plasma glucose (mg/dL)	156 (111–233)	141 (110–190)	157 (111–238)	0.4703
Fasting C-peptide (ng/mL)	0.11 (0.01–0.31)	0.02 (0.01–014)	0.12 (0.01–0.31)	0.4800
Total daily dose of insulin (unit)	44 (30–60)	37 (30–54)	44 (30–60)	0.2563
Total daily dose of insulin (unit/kg)	0.77 (0.58–1.00)	0.70 (0.58–1.14)	0.77 (0.58–1.00)	0.7243
Number of daily injection times	4 (3–4)	4 (3–4)	4 (3–4)	0.6778
Numbers of injection times - Basal insulin	1 (1–1)	1 (1–1)	1 (1–1)	0.5672
Unit of basal insulin	20 (8.5–27)	19 (11–30)	20 (8–27)	0.5516
Numbers of injection times - Prandial insulin	3 (1–3)	3 (2–3)	3 (1–3)	0.5525
Unit of prandial insulin	20 (5–30)	14 (5–30)	20 (5–30)	0.4463
Urinary albumin to creatinine ratio (mg/g)	7.30 (2.66–20.03)	4.04 (0.20–4.80)	7.46 (2.67–20.85)	0.0572

Data are presented as median (interquartile range) or number (%). BMI, body mass index; DKA, diabetic ketoacidosis, FT1DM, fulminant type 1 diabetes mellitus; HbA1c, glycated hemoglobin. †Only subjects with information or test results were analyzed, and their number was expressed as the denominator.

In the analysis of the latest data, the BMI and the levels of fasting plasma glucose and C-peptide showed no significant differences between the two groups; nevertheless, the patients with fulminant type 1 diabetes mellitus had significant lower HbA1c levels than the non-fulminant type 1 diabetes mellitus participants (7.0 vs 8.4%, $P = 0.0366$). The total daily insulin dose, the number of injections and the albumin-to-creatinine ratio showed a tendency of lower values in patients with fulminant type 1 diabetes mellitus than in non-fulminant type 1 diabetes mellitus; however, the differences were not significant.

Summary of individual characteristics in patients with fulminant type 1 diabetes mellitus

There were more middle-aged patients in the fulminant type 1 diabetes mellitus than in the non-fulminant type 1 diabetes mellitus group. The median random glucose level at diagnosis was 620 mg/dL (interquartile range 529–1,029 mg/dL), whereas the HbA1c levels were 6.2% (interquartile range 5.9–6.5%) in patients with fulminant type 1 diabetes mellitus. Among the 15 fulminant type 1 diabetes mellitus patients, 11 (68.8%) had HbA1c levels <6.5%. All the 15 patients with fulminant type 1 diabetes mellitus were treated with insulin at the last follow-up examination, and two patients showed improved β-cell function above the diagnostic level of fulminant type 1 diabetes mellitus (Table S1).

DISCUSSION

It has been recognized that the prevalence of type 1 diabetes mellitus is higher in white people than in Asian people[8,9]. In the present study, there were 913 type 1 diabetes mellitus cases among 76,309 cases of diabetes. The proportion of type 1 diabetes mellitus was 1.20%, which was in line with a previous report showing a prevalence of type 1 diabetes mellitus of approximately 0.22–1.19% among patients with diabetes in Korea[9]. In contrast, the incidence of fulminant type 1 diabetes mellitus was higher in Asian people than in white people.

Interestingly, the most reported cases of fulminant type 1 diabetes mellitus have been reported in Asian populations, such as Japanese, Korean, Chinese and Filipino, since 2010 [3,6,7,10–12]. The first case of a white patient with fulminant type 1 diabetes mellitus was reported in 2008, and just a few cases have been reported since then[13,14].

A relatively large size study for fulminant type 1 diabetes mellitus in the Korean population was published in 2007[7]; thereafter, individual case reports and a pooled analysis of case reports have been collected and compared with Japanese data[12]. According to previous reports from Korea, 7.1% of newly diagnosed patients with type 1 diabetes mellitus (30.4% of them with adult onset) were diagnosed as having fulminant type 1 diabetes mellitus, with 30.4% of the cases occurring during adulthood (age ≥18 years). However, it was unclear what percentage of the acute or ketosis onset type 1 diabetes mellitus cases corresponded to fulminant type 1 diabetes mellitus cases.

In the present study, we found that the cases of fulminant type 1 diabetes mellitus represented approximately 3.2 and 14.6% of newly diagnosed and ketosis-onset type 1 diabetes mellitus cases, respectively. These results were consistent with a previous nationwide survey carried out in Japan, which estimated that the prevalence of fulminant type 1 diabetes mellitus accounted for 19.4% of cases with acute onset type 1 diabetes mellitus and ketosis[6]. The previous study from Korea was carried out in a single tertiary institution[7], whereas the present work included data from secondary or tertiary institutions in the Gyeonggi-do region, which we believe is more meaningful. However, as our study could not include all type 1 diabetes mellitus cases in Korea, the present findings cannot be directly compared with those of studies carried out in different settings or in other countries.

The fulminant type 1 diabetes mellitus characteristics in the present study were not significantly different from those reported in previous studies (Korean and Japanese data compared by Kim *et al.*[12]). The mean BMI value among Japanese individuals was 20.7 kg/m^2, whereas that of Koreans was 23.4 kg/m^2, according to the present results and those of Kim *et al.*[12] We investigated all patients with type 1 diabetes mellitus diagnosed at the same time or during the follow-up period, and found that the patients with fulminant type 1 diabetes mellitus were slightly older and obese, and they had low HbA1c and antibody positivity rates. Regarding the total daily dosages of insulin for fulminant type 1 diabetes mellitus, in the present study, there were no differences in the total daily dosages of insulin between patients with fulminant type 1 diabetes mellitus and non-fulminant type 1 diabetes mellitus (0.77 vs 0.70 U/kg/day). In contrast, the total daily dosages in fulminant type 1 diabetes mellitus cases were higher than those in non-fulminant type 1 diabetes mellitus cases, as reported by Imagawa *et al.* (0.7 to 0.8 vs 0.5 to 0.6 U/kg/day) and Murase *et al.* (0.7 vs 0.6 U/kg/day), in which the clinical data were examined and recorded every 12 months after the onset of diabetes in each hospital. This difference was probably attributed to the differences in the follow-up periods or to the heterogeneity among Asians [15]. The aforementioned differences might have resulted from differences in human leukocyte antigen (HLA) genotypes in the susceptibility and resistance to type 1 diabetes mellitus, which is one of the distinctions between fulminant type 1 diabetes mellitus and autoimmune type 1 diabetes mellitus. The HLA DR4-DQ4 haplotype is common among Japanese patients, but rare in the white population; HLA DRB1*04:05-DQB1*04:01 haplotype and histidine residue at HLA-DRβ1 position 13 were associated with fulminant type 1 diabetes mellitus in Korean patients [16,17]. Indeed, even in the same fulminant type 1 diabetes mellitus, there were reports of contradictory statements regarding the lowered and maintained levels of glucagon in the Asian population [18,19]. However, we were unable to analyze data regarding HLA genotyping in the present study. We rarely identify HLA genotype in the real clinical field in Korea.

The GAD antibody-positive results in patients with fulminant type 1 diabetes mellitus observed in the present study (28.6%) were higher than those previously reported by Cho *et al.* (0%)[7]. Notably, one study reported a concordance rate of 20%, which corresponds approximately to the percentage of fulminant type 1 diabetes mellitus found in the present study, although the methods for antibody detection were different [20]. In addition, there were more cases after 2012 than before 2012. This might have resulted from the advances in the understanding of the disease and increased interest, although there were some incomplete data, and the possibility of recall bias cannot be discarded. In Korea, it is difficult to access medical records older than 10 years, because there are no obligations to preserve them; thus, they are often deleted. Hence, because of the lack of data at the time of diagnosis, we could analyze the data of just 462 out of 913 patients with type 1 diabetes mellitus. This fact significantly influenced the numerical values, such as the frequency after that.

The pathogenesis of fulminant type 1 diabetes mellitus and its clinical characteristics remain unclear. The possible causes of fulminant type 1 diabetes mellitus, which have not been fully identified yet, are related to human leukocyte antigen, viral infection and accelerated immune response[17,21]. The clinical features that distinguish fulminant type 1 diabetes mellitus from type 1 diabetes mellitus include cold symptoms (71.7 vs 26.9%), gastrointestinal symptoms (72.5 vs 26.9%) and low consciousness (45.2 vs 5.3%). Fulminant type 1 diabetes mellitus cases were often accompanied by pregnancy (20.0%).

The frequency of fulminant type 1 diabetes mellitus characteristics indicated that flu-like symptoms and lowered consciousness are less frequently observed in Korean than in Japanese individuals; however, the reasons remain unclear[12]. Probably because of the incomplete data, we failed to identify a predisposing factor, such as pregnancy, infection or specific clinical symptoms (i.e., flu-like symptoms, serum pancreatic

enzyme levels or gastrointestinal manifestations [vomiting and abdominal pain]), which were characteristic findings in previous studies. The present study included only patients from eight second or tertiary hospitals in Gyeonggi-do; the study did not include type 1 diabetes mellitus patients from all of Korea.

The present study had some limitations. Especially, patients with slowly progressive type 1 diabetes mellitus or latent autoimmune diabetes in their adulthood could have been included in our study population. We did not consider including such patients because of the retrospective nature of the study. Furthermore, old medical records of some patients could not be reviewed to verify the subtypes. However, it is a great advantage that all patients were followed up at the eight largest hospitals in Gyeonggi-do, which has approximately 26.0% of the Korea's total population (Gyeonggi-do population 13,449,499 residents; Korean population 51,821,669 residents). As these data cannot be analyzed using the claims data alone, and patients with type 1 diabetes mellitus are relatively more likely to be managed in large general hospitals, we estimate that the frequency of type 1 diabetes mellitus might not be as high as indicated by the present data.

To our knowledge, this is the first multicenter study that included a large number of patients to show the detailed clinical characteristics and prevalence of fulminant type 1 diabetes mellitus. This disease requires special attention from healthcare practitioners, as it is more vulnerable to the occurrence of acute and chronic complications, such as diabetic ketoacidosis, hypoglycemia, diabetic microangiopathy and mortality, than other types of diabetes [22,23]. Therefore, the reported results might be helpful for understanding the basic epidemiological characteristics. Indeed, the present findings provide novel information on the prevalence and clinical features of fulminant type 1 diabetes mellitus in Korea.

The present study was carried out in secondary or tertiary institutions in the region where one-quarter of the total Korean population lives. We hope that our work would serve as a basis for setting a policy on type 1 diabetes mellitus patients, and promote interest regarding type 1 diabetes mellitus heterogeneity. More epidemiological studies are required to determine whether fulminant type 1 diabetes mellitus is a subtype that must be distinguished from type 1 diabetes mellitus.

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DISCLOSURE

The authors declare no conflict of interest.
Approval of the research protocol: N/A
Informed Consent: N/A
Approval date of Registry and the Registration No. of the study/trial: N/A
Animal Studies: N/A

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | Summary of clinical characteristics of participants with fulminant type 1 diabetes mellitus.