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ORIGINAL ARTICLE

# Impaired glucagon secretion in patients with fulminant type 1 diabetes mellitus

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## Abstract

**Purpose** Fulminant type 1 diabetes mellitus (FT1DM), characterized by rapid and almost complete destruction of pancreatic β-cells, is a newly identified subtype of type 1 diabetes mellitus. Although, the pathophysiology of this condition remains still unclear, histological evidence suggests that not only β-cells but also α-cells of pancreatic islets are reduced in number in FT1DM. However, the ability of glucagon secretion in patients with this condition has remained largely uncharacterized. We therefore examined glucagon secretion in patients with FT1DM and compared that with patients with other types of diabetes mellitus.

**Methods** Fasting glucagon levels as well as glucagon secretion induced by intravenous administration of arginine were measured in hospitalized 83 patients with diabetes mellitus, including 4 with FT1DM, 18 with type 1 diabetes mellitus (T1DM), 40 with type 2 diabetes mellitus (T2DM), 5 with slowly progressive insulin-dependent diabetes mellitus (SPIDDM), and 16 with pancreatic diabetes mellitus (PDM).

**Results** The area under the curve for serum glucagon levels after arginine infusion in FT1DM patients was significantly smaller than that in T1DM, T2DM, or SPIDDM patients but was similar to that in PDM patients. The fasting serum glucagon level of FT1DM patients was lower than that of T1DM or T2DM patients but did not significantly differ from that of SPIDDM or PDM patients.

**Conclusions** These results suggest that glucagon secretion is impaired in patients with FT1DM.

**Keywords** Fulminant · Type 1 diabetes · Glucagon · Japanese

## Introduction

Fulminant type 1 diabetes mellitus (FT1DM), characterized by rapid and almost complete destruction of pancreatic β-cells in the absence of islet autoantibodies, is a newly identified subcategory of type 1 diabetes mellitus (T1DM) [1–3]. FT1DM has been described in various ethnicities, including Caucasians [4], Hispanics [5], and Southeast Asians [6, 7]. This condition however appears to be most prevalent among East Asians, accounting for 15–20% of cases of acute-onset T1DM in Japan [8] and for 7% of those in Korea [9]. Although, the pathophysiology of FT1DM remains unclear, previous reports have suggested that not only β-cells but also α-cells of pancreatic islets are reduced in number in affected individuals [10, 11]. It is thus possible that not only insulin secretion but also glucagon secretion is impaired in patents with this condition. Glucagon secretion in FT1DM has remained largely uncharacterized, however. We therefore investigated glucagon secretion in individuals with FT1DM, and compared that with those in patients with other types of diabetes mellitus given that circulating levels of glucagon appear to largely influence the pathophysiology of diabetes mellitus [12, 13].

## Materials and methods

Individuals with diabetes mellitus who were hospitalized for management of their disease and who underwent an arginine challenge test in the Division of Diabetes and

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Endocrinology, Kobe University Hospital, between August 2005 and January 2010 were studied. The patients were administered standard diet and drug therapy (including insulin and oral hypoglycemic agents) for diabetes. The arginine challenge test was performed after they had achieved a fasting plasma glucose (FPG) concentration of < 130 mg/dl. None of the patients was treated with dipeptidyl peptidase–4 inhibitors or glucagon-like peptide–1 receptor agonists. Among 95 patients who underwent the test, 12 with a clinical diagnosis of T1DM but who had tested negative for islet autoantibodies (anti-GAD, islet cell antibodies, or anti-IA2) and one with a mitochondrial DNA mutation (3243 A→G) were excluded from the study. The remaining 83 patients included 4 with FT1DM, 5 with slowly progressive insulin-dependent diabetes mellitus (SPIDDM, also known as latent autoimmune diabetes in adults), 18 with T1DM, 40 with type 2 diabetes mellitus (T2DM), and 16 with pancreatic diabetes mellitus (PDM). FT1DM [14] and SPIDDM [15] were diagnosed according to previously described criteria. The etiologies of PDM included distal pancreatectomy for pancreatic tumors, chronic pancreatitis, and pancreaticoduodenectomy for duodenal papillary carcinoma in six, nine, and one patient (s), respectively. For the arginine challenge test, arginine (30 g) was administered intravenously over 30 min after the patients had fasted overnight. Blood was collected before and 15, 30, 60, 90, and 120 min after initiation of arginine infusion for measurement of plasma glucose, serum C-peptide immunoreactivity (CPR), and plasma glucagon. The area under the curve for plasma glucose ($AUC_{PG}$), serum CPR ($AUC_{CPR}$), or plasma glucagon ($AUC_{IRG}$) from 0 to 120 min was calculated. Serum CPR levels in the undetectable range (<0.2 ng/ml) were assigned a value of 0.1 ng/ml for analysis. Glucagon was assayed with a radioimmunoassay kit (Glucagon Kit Daiichi II; TFB, Tokyo, Japan). The data are presented as means ± SD and were compared among groups by one-way ANOVA followed by Dunnett's test. A $P$-value < 0.05 was considered statistically significant.

## Results

Age, BMI, fasting serum CPR, fasting plasma glucagon, $AUC_{PG}$, $AUC_{CPR}$, and $AUC_{IRG}$ differed significantly among the patient groups, whereas disease duration and FPG did not (Table 1). The $AUC_{IRG}$ for FT1DM patients was smaller than that for SPIDDM ($P = 0.001$), T1DM ($P = 0.029$), or T2DM ($P = 0.005$) patients but did not differ significantly from that for PDM patients ($P = 0.976$). The values of the $AUC_{IRG}$ of all the FT1DM patients were lower than the value of any T1DM and SPIDDM patients whereas a small overlap was apparent between the values of FT1DM and T2DM patients (Fig. 1). F-IRG of FT1DM patients was significantly lower than that of T1DM or T2DM patients ($P = 0.028$ and 0.019, respectively) but did not differ from that of SPIDDM ($P = 0.212$) or PDM ($P = 0.451$) patients. The $AUC_{IRG}$ ($10^3$ pg ml$^{-1}$ min) of T1DM patients with undetectable ($n = 12$) or detectable ($n = 6$) F-CPR levels was 29.4 ± 9.1 and 30.4 ± 6.4, respectively, with both values being significantly higher than that of FT1DM patients ($P = 0.0052$ and 0.0067, respectively).

**Table 1** Characteristics of the diabetes patient groups

| | FT1DM | SPIDDM | T1DM | T2DM | PDM |
|---|---|---|---|---|---|
| Number | 4 | 5 | 18 | 40 | 16 |
| Sex (male/female) | 3/1 | 1/4 | 4/14 | 25/15 | 8/8 |
| Age (years)* | 53.3 ± 22.8 | 72.2 ± 9.2 | 52.9 ± 18.8 | 59.6 ± 12.8 | 65.0 ± 6.2 |
| BMI (kg/m$^2$)* | 20.2 ± 0.5 | 22.6 ± 3.3 | 21.8 ± 3.1 | 26.9 ± 5.4 | 21.3 ± 3.8 |
| Duration (years) | 3.0 ± 4.0 | 7.4 ± 7.9 | 8.3 ± 7.1 | 11.1 ± 8.9 | 6.4 ± 7.6 |
| HbA1c (%) | 7.4 ± 1.9 | 9.1 ± 2.3 | 9.0 ± 2.4 | 9.0 ± 1.3 | 8.7 ± 2.2 |
| FPG (mg/dl) | 107 ± 29 | 119 ± 35 | 129 ± 59 | 105 ± 18 | 126 ± 29 |
| F-CPR (ng/ml)* | 0.1 ± 0 | 0.8 ± 0.5 | 0.2 ± 0.2 | 1.7 ± 1.0 | 0.8 ± 0.5 |
| F-IRG (pg/ml)* | 50.3 ± 14.8 | 116.4 ± 53.8 | 131.2 ± 57.2 | 133.1 ± 67.7 | 88.6 ± 26.0 |
| $AUC_{PG}$ ($10^3$ mg dl$^{-1}$ min)* | 21.1 ± 5.8 | 18.5 ± 5.1 | 20.6 ± 7.1 | 15.6 ± 3.1 | 17.6 ± 4.2 |
| $AUC_{CPR}$ (ng ml$^{-1}$ min)* | 12 ± 0 | 165 ± 120 | 46 ± 60 | 378 ± 194 | 150 ± 133 |
| $AUC_{IRG}$ ($10^3$ pg ml$^{-1}$ min)* | 15.1 ± 3.8 | 37.5 ± 7.9 | 29.7 ± 8.2 | 31.4 ± 11.8 | 16.9 ± 6.0 |

Data are means ± SD

*$P < 0.05$. $P$-values for differences among five diabetes groups were determined by ANOVA

*FT1DM* fulminant type 1 diabetes mellitus, *T1DM* type 1 diabetes mellitus, *T2DM* type 2 diabetes mellitus, *SPIDDM* slowly progressive insulin-dependent diabetes mellitus, *PDM* pancreatic diabetes mellitus, *FPG* fasting plasma glucose, *CPR* C-peptide immunoreactivity, *IRG* plasma glucagon, $AUC_{PG}$ area under the curve for plasma glucose, $AUC_{CPR}$ area under the curve for serum CPR, $AUC_{IRG}$ area under the curve for plasma glucagon

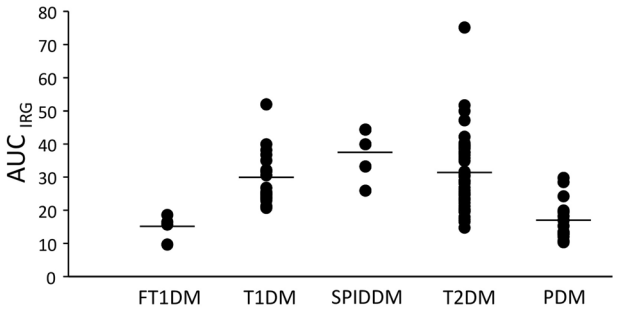


**Fig. 1** $AUC_{IRG}$ during glucagon challenge tests in patients with various type of diabetes mellitus. FT1DM fulminant type 1 diabetes mellitus;T1DM type 1 diabetes mellitus; T2DM type 2 diabetes mellitus; SPIDDM slowly progressive insulin-dependent diabetes mellitus; PDM pancreatic diabetes mellitus

## Discussion

Glucagon secretion induced by food intake or arginine administration is exaggerated in T1DM or T2DM [16, 17], likely contributing to the manifestation of hyperglycemia of these conditions. Glucagon secretion in FT1DM has remained largely uncharacterized; however, with only one study having evaluated glucagon levels during meal ingestion in a single case of FT1DM [18]. We showed here that arginine-induced glucagon secretion in individuals with FT1DM was attenuated compared with that in T1DM, T2DM, or SPIDDM patients but was similar to that in PDM patients. The fasting serum glucagon level of FT1DM patients was also lower than that of T1DM or T2DM, but was similar to SPIDDM or PDM patients. Glucagon secretion is largely influenced by circulating glucose levels [12, 17] as well as by the level of glucotoxicity [19]. We thus performed the analyses after the patients had achieved an FPG concentration of < 130 mg/dl during hospitalization, thus minimizing secondary effect of circulating glucose or glucotoxicity. Although, the level of HbA1c was lower in FT1DM patients than that of other patient's groups, FPG at the glucagon challenge test did not significantly differ among the patient groups. A marked reduction in serum CPR level is a diagnostic criterion of FT1DM [2, 14]. In this study, F-CPR was undetectable in all FT1DM patients, whereas it was detectable or undetectable in the T1DM patients. The $AUC_{IRG}$ of FT1DM patients was significantly smaller than those of both T1DM subgroups, groups with undetectable or detectable CPR levels, suggesting that the attenuated glucagon response in FT1DM patients is not related to the absolute deficiency of insulin.

The diagnosis criteria of FT1DM incudes the occurrence of diabetic ketosis or ketoacidosis soon after the onset of hyperglycemic symptoms [14]. Given that glucagon inhibits acetyl-CoA carboxylase and thereby increases carnitine palmitoyltransferase–I activity in the liver, the increase in the level of circulating glucagon is theoretically contributed to the overproduction of ketone bodies [20]. The current finding that glucagon secretion is impaired in patients with FT1DM may suggest that the ketosis-prone nature of FT1DM is possibly independent of the level of circulating glucagon. It remains to be elucidated the circulating glucagon level of FT1DM during diabetic ketosis or ketoacidosis, however.

Although a role for immunoreactions triggered by viral infection has been suggested [1–3], the pathophysiology of FT1DM is not completely understood. Histological characteristics of T1DM include lymphocytic infiltration of pancreatic islets and a reduced number of β-cells, with relative preservation of α-cells [21, 22], whereas reduced numbers of both β-cells and α-cells associated with the infiltration of $CD3^+$ T lymphocytes and macrophages both in pancreatic islets and in exocrine tissue have been described in FT1DM [10, 11]. The impaired glucagon response revealed in the present study thus likely reflects the reduced number of α-cells in FT1DM patients.

PDM patients often manifest unstable glycemia and readily develop hypoglycemia in response to a small overdose of insulin [23]. Impaired glucagon secretion in association with hypersensitivity to insulin due to weight loss and hyponutrition might be attributable to such characteristics of PDM. In FT1DM, small residual of insulin secretion has been shown to be important for the stability of glycemic control [24]. Whether the impaired glucagon secretion of FT1DM contributes to the instability of glycemic control remains to be determined. A limitation of this study is the relative small number of the studied patients with FT1DM: a study with a greater number of patients is required to further confirm these observations.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the ethics committee of Kobe University Graduate School of Medicine (approval no. 180044). All patients provided written consent to the analysis and publication of their clinical data for scientific purposes.

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