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LETTER TO THE EDITOR

Glucagon secretions are impaired in patients with fulminant type 1 diabetes

We have read with great interest the articles by Murase-Mishibe *et al.*[1] and Takahashi *et al.*[2] studying glucagon secretion in fulminant type 1 diabetes patients. Murase-Mishibe *et al.* investigated plasma glucagon levels of fulminant type 1 diabetes patients (n = 3) and acute-onset type 1 diabetes patients (n = 6) during a meal tolerance test, and stated in their study that "no defect in glucagon secretion was observed" in fulminant type 1 diabetes without providing the information for statistical analysis. Takahashi *et al.* investigated plasma glucagon levels of fulminant type 1 diabetes patients (n = 5) and age- and diabetes duration-matched type 1 diabetes patients (n = 5) during an arginine challenge test (ACT), and stated that "the curve of glucagon levels were similar between the two groups." It is again unclear how the authors analyzed the similarity between the groups.

We have recently investigated glucagon secretion during ACT in various types of diabetes patients, including four fulminant type 1 diabetes patients, five slowly progressive insulin-dependent diabetes patients, 18 type 1 diabetes patients, 40 type 2 diabetes patients and 16 pancreatic diabetes (PD) patients, and showed that the area under the curve of glucagon levels in fulminant type 1 diabetes patients was significantly smaller than those of type 1 diabetes patients, but was similar to PD patients[3]. We now show the time course of our previous data of glucagon secretion during ACT in these patients (Figure 1). The analysis of the

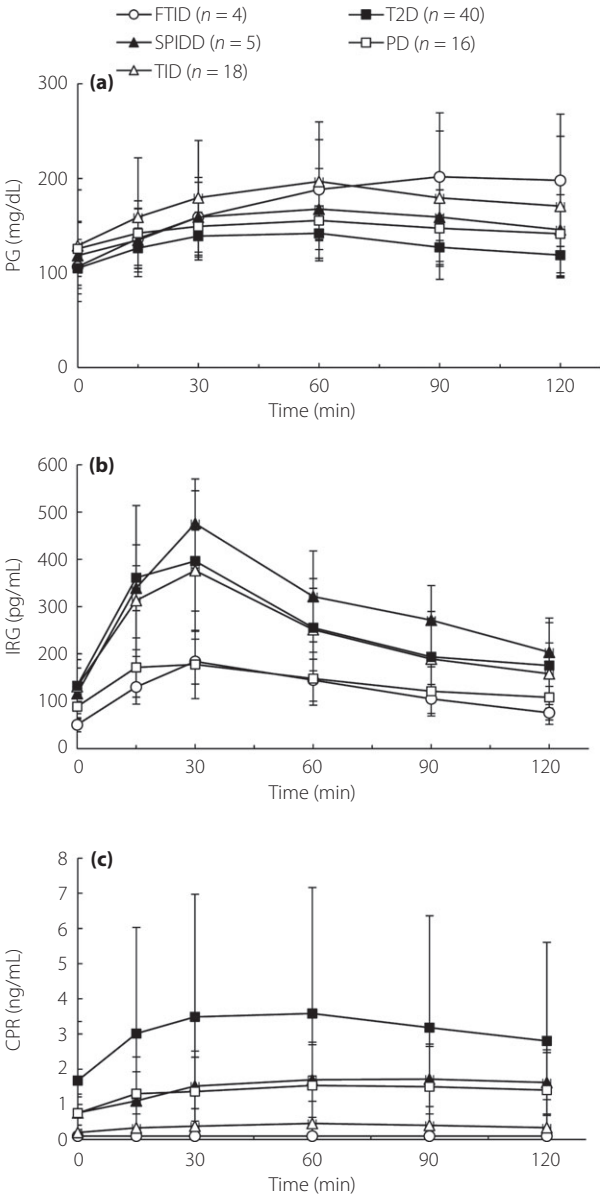

Figure 1 | Plasma glucose, serum glucagon and serum C-peptide during an arginine challenge test in various type of diabetes patients. Characteristics of the study participants and study methods were previously described[3]. Data are shown as the mean ± standard deviation. CPR, C-peptide reactivity; FT1D, fulminant type 1 diabetes; IRG, immunoreactive glucagon; PD, pancreatic diabetes; SPIDD, slowly progressive insulin-dependent diabetes; T1D, acute-onset type 1 diabetes; T2D, type 2 diabetes.

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time course data with repeated-measures ANOVA showed that the glucagon levels of fulminant type 1 patients diabetes were significantly lower than that of type 1 diabetes patients ($P = 0.003$), but similar to PD patients ($P = 0.397$), consistent with our previous analysis[3]. Given that Takahashi's group previously showed that glucagon secretion in patients with fulminant type 1 diabetes was substantially decreased within 6 months after the onset of the disease[4], the two groups of investigators discussed whether the duration of the disease could affect the ability of glucagon secretion[1,2]. The duration of the disease of our fulminant type 1 diabetes patients was 1, 6, 12 and 100 months (29.8 ± 47.0 months).

The numbers of study participants with fulminant type 1 diabetes in our (4) and the two investigator groups (3 and 5) were small. It is obvious that a study with a larger number of participants is required to obtain a definite conclusion. It is possible that the difference in assays is attributable to the apparent inconsistency of our and the other groups' results. We used a radioimmunoassay that has been used conventionally to determine the levels of glucagon, and evidence suggests that a newly launched sandwich enzyme-linked immunoassay more accurately reflects the hormone levels[5]. Takahashi *et al.* showed that whereas the absolute values determined by the radioimmunoassay and by the enzyme-linked immunoassay were different, the relative changes in these two assays were similar[4]. Metabolic testing of our study (ACT) and that of Murase-Mishibe *et al.* (a meal tolerance test) differed, which also might be attributable to the inconsistency. Furthermore, whereas Murase-Mishibe *et al.* carried out the test with healthy volunteers, we only analyzed patients with various types of diabetes.

An interesting finding in our study is that, in contrast to glucagon, secretion of C-peptide in fulminant type 1 diabetes patients is similar to that of type 1 diabetes patients ($P = 0.284$), but smaller than that of PD patients ($P = 0.020$; Figure 1). The difference in the extent of the impairment of the two pancreatic hormone secretions might be related to clinical characteristics of the three types of diabetes primarily caused by insufficient insulin secretion. Again, further analysis with a larger number of participants warrants clarifying this point.

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DISCLOSURE

The authors declare no conflict of interest.

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REFERENCES

1. Murase-Mishiba Y, Bessho-Tachibana M, Imagawa A. "Preserved" glucagon secretion in fulminant type 1 diabetes. *J Diabetes Investig* 2019; 10: 186–187.
2. Takahashi N, Chujo D. Response to "Preserved" glucagon secretion in fulminant type 1 diabetes. *J Diabetes Investig* 2019; 10: 188–189.
3. Komada H, Hirota Y, Sakaguchi K, *et al.* Impaired glucagon secretion in patients with fulminant type 1 diabetes mellitus. *Endocrine* 2019; 63: 476–479.
4. Takahashi N, Chujo D, Kajio H, *et al.* Contribution of pancreatic α-cell function to insulin sensitivity and glycemic variability in patients with type 1 diabetes. *J Diabetes Investig* 2018. https://doi.org/10.1111/jdi.12949
5. Miyachi A, Kobayashi M, Mieno E, *et al.* Accurate analytical method for human plasma glucagon levels using liquid chromatography-high resolution mass spectrometry: comparison with commercially available immunoassays. *Anal Bioanal Chem* 2017; 409: 5911–5918.

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