Startling hyperglycaemia with transient beta cell stunning in a patient with type 2 diabetes

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Abstract. A 59-year-old woman unaware of having diabetes was transferred due to coma. Upon discovery at home, her consciousness on the Glasgow Coma Scale was E1V2M4, BP 95/84 mmHg, body temperature 34.7°C. On arrival at ER, height was 1.63 m, weight 97 kg, plasma glucose (PG) 1,897 mg/dL, HbA1c 13.6%, osmolality 421 mosm/kg, arterial pH 7.185, lactate 6.34 mmol/L, β-hydroxybutyrate 7.93 mmol/L. With saline and regular insulin infusion, PG was lowered to 1,440 mg/dL at 2 hours and then to 250 mg/dL by Day 3, and consciousness normalized by Day 5. On admission, serum immunoreactive insulin (IRI) was undetectable (<0.03 U/mL), C-peptide immunoreactivity (CPR) undetectable (<0.003 ng/mL), and anti-glutamic acid decarboxylase antibody negative. Following the above-described treatment, fasting PG was 186 mg/dL and CPR 1.94 ng/mL, respectively, on Day 14; 2-h post-breakfast PG 239 mg/dL and CPR 6.28 ng/mL, respectively, on Day 18. The patient discharged on Day 18 with 1,800 kcal diet, 32 U insulin glargine and 40 mg gliclazide. Fifteen months later at outpatient clinic, her HbA1c was 6.9% and 2-h post-breakfast PG 123 mg/dL and CPR 5.30 ng/mL with 750 mg metformin, 10 mg gliclazide and 18 U insulin glargine. Transient, but total cessation of insulin secretion was documented in a patient with type 2 diabetes under severe metabolic decompensation. Swift, sustained recovery of insulin release indicated that lack of insulin at the time of emergency was due to secretory failure, i.e., unresponsive exocytotic machinery or depletion of releasable insulin, rather than loss of beta cells.

Key words: Insulin secretion in vivo, Ketoacidosis, Startling hyperglycaemia

IN TYPE 2 DIABETES MELLITUS (T2DM), serum insulin level is depressed relative to elevated plasma glucose, which is due to reduced beta cell mass and impaired insulin synthesis and secretion [1, 2]. Nonetheless, serum insulin is usually measurable at a low level even in patients with metabolic decompensation such as ketoacidosis [3, 4]. In other words, it has been unknown if total shut-off of insulin secretion takes place in type 2 diabetes under severe metabolic stress.

Case Report

Clinical course of acute-onset diabetes

A 59-year-old woman was transferred to our emergency department due to coma. Seven years ago, she had experienced a deep vein thrombosis of the lower extremities but never aware of having diabetes. She had been busy for moving and drank several litres of sugar-containing soft drink for a few days, and feeling extremely thirsty, nauseous and anorexic for 3 days before she was discovered lying unconscious at home. Emergency clue found her blood pressure 95/84 mmHg, pulse 98/min, axillary temperature 34.7°C, deep and irregular respiration (approximately 30/min) and O2 saturation 86%. Consciousness level on the Glasgow Coma Scale was E1V2M4, and finger-prick glucose was ≥600 mg/dL. She was immediately given 6 L/min oxygen via mask. On arrival at the hospital, her tongue and skin were extremely dry and her lower legs cool and oedematous. Physical examination was otherwise non-contributory. Her body weight was 97 kg, height 163 cm and body mass index 36.5 kg/m2. Plasma glucose (PG) was 1,897 mg/dL, serum sodium 157 mEq/L, potassium 3.3 mEq/L, plasma osmolality 421 mosm/kg and β-hydroxybutyrate 7.926 mmol/L. Arterial blood gas
analysis revealed pH 7.185, pO\textsubscript{2} 83.6 mmHg, pCO\textsubscript{2} 32.4 mmHg, base excess −15.0 mmol/L and lactate 6.34 mmol/L while receiving 6 L/min oxygen via mask (Table 1). Serum amylase and lipase were elevated and there was a fluid accumulation in the dorsum of pancreas. Presence of urinary ketone bodies could not be examined because of complete anuria. Antibodies against glutamic acid decarboxylase and islet antigen 2 (IA2) were negative (Table 1).

We started 0.9% intravenous saline at 1,000 mL/h followed by 500 mL/h for the rest of Day 1 (8 h) with potassium supplementation. Regarding insulin, after a 10 U regular insulin intravenous bolus, we initiated a 0.05 U/kg BW/h regular insulin infusion. The PG lowered at a rate of 210 mg/dL/h during the initial 2 h and at 128 mg/dL/h during the following 3 h (Table 1). With this treatment, her consciousness steadily improved and became normal by Day 5.

**Endocrine evaluation and the follow-up data**

Serum immunoreactive insulin (IRI) was <0.03 μU/mL (Architect®, Abbott, Tokyo) and C-peptide immunoreactivity (CPR) <0.003 ng/mL (Lumipulse®, Fujirebio, Tokyo), and proinsulin 38.2 pmol/L (Human
Total Proinsulin ELISA®, Merck Millipore, Uppsala), in the blood sample drawn immediately before starting treatment. Fasting PG was 186 mg/dL and CPR 1.94 ng/mL on Day 14 and 2-h post-breakfast PG 239 mg/dL and CPR 6.28 ng/mL on Day 18: the patient was receiving 1,800 kcal diet and 32 U insulin glargine and 40 mg gliclazide on Day 18. Fifteen months later, her BMI did not change and HbA1c was 6.9%, 2-h post-breakfast PG 123 mg/dL and CPR 5.30 ng/mL, with 750 mg metformin, 10 mg gliclazide and 18 U insulin glargine.

**Discussion**

She had a startling level of hyperglycaemia associated with hyperosmolar hyperglycaemic state (HHS), lactic acidosis and ketoacidosis [5], and even acute pancreatitis. Excessive soft drink intake may have had worked as an aggravating factor for pre-existing hyperglycaemia. We are unaware of any report on total absence of the serum insulin in a patient with T2DM at one time and subsequent robust recovery of basal and postprandial insulin secretion. The degree of beta cell suppression was complete so that not only IRI but also C-peptide was undetectable in the serum. Insulin lack may have formed a vicious circle with hyperglycaemia/ketoacidosis/lactic acidosis together with hypothermia and hypoxemia, where each can be a cause and a result of the other. Despite total cessation of insulin exocytosis on admission, beta cell regained nutrient responsiveness soon after the treatment. Namely, on Day 18, postprandial CPR index, which correlated well with the beta cell disposition index [6], was 2.36 (calculated as [100·CPR (ng/mL)/PG (mg/dL)] as in ref. 6). The value lies in the middle range for typical Japanese patients with T2DM [6] and even as high as 4.31, 15 months later, indicating sustained beta cell function. We considered this is a case of an extreme of beta cell stunning [7] because of this robust recovery of nutrient-regulated insulin secretion.

Proinsulin immunoreactivity present in the plasma upon admission may have been mostly an accumulation of proinsulin intermediates and/or the proinsulin degradation products due to severe pre-renal renal failure: the proinsulin assay kit employed in this study does cross-react with these proinsulin-related peptides. Nonetheless, the possibility of preferential exhaustion of readily releasable insulin due to the extreme hyperglycaemia remained. Importantly, the assay used for CPR measurement was totally devoid of cross-reaction with proinsulin intermediates and the degradation products.

In *in vitro* experiment, exposure of the mouse islet beta cell to 400 mmol/L sucrose for a relatively short period (60 min) was shown to cause near-total inhibition of insulin exocytosis [8]. Of note, the similar level of hyperosmolality may have been present for *hours* in this patient. Additionally, beta cell insulin from acute pancreatitis, and hyperthermia- and hypoxemia [2]-induced inhibition of beta cell metabolism might have impeded insulin exocytosis. However, caution is needed to extrapolate these data obtained in rodents’ beta cell to human diabetes. Regarding management of hyperglycaemia, we rigorously corrected hyperglycaemia considering that the mitigation of extreme hyperglycaemia and ketonaemia is a life-saving priority [9].

**Conclusion**

Complete shut-off of insulin secretion by the islet beta cell was documented in a patient with T2DM upon extreme hyperglycaemia. Our finding is exemplifying fragility on one hand and plasticity on the other of beta cell exocytotic machinery in human diabetes. We hypothesise that the total beta cell stunning* is not so rare but has been overlooked: future studies are needed to prove or disprove the hypothesis.

**Acknowledgements**

The patient signed a written informed consent, and this study was performed in accordance with the Declaration of Helsinki.

Authors thank Drs. Shoichiro Nagasaka, Masakazu Obayashi, Tomomichi Koshi, Hiroyuki Sagesaka, Atsuki Imai, Kei Asada and Keishi Yamauchi for invaluable comments.

**Conflict of Interest**

The authors declare that there is no duality of interest associated with this manuscript.

**Funding**

None.

**Notes**

*Beta cell stunning is conceptualized by Ferrannini as follows [7]. “... the stunned β cell: a cell that is temporarily unable to appropriately sense its primary stimulus but may recover competence, at least in part.”*
References


