

# Long-term efficacy of the sodium–glucose cotransporter 2 inhibitor, ipragliflozin, in a case of type A insulin resistance syndrome

Shuichi Nagashima\* , Tetsuji Wakabayashi, Naoko Saito, Manabu Takahashi, Kenta Okada, Ken Ebihara, Shun Ishibashi

Division of Endocrinology and Metabolism, Department of Medicine, Jichi Medical University, Shimotsuke, Japan

## Keywords

Ipragliflozin, Sodium–glucose cotransporter 2 inhibitor, Type A insulin resistance syndrome

## \*Correspondence

Shuichi Nagashima  
Tel.: +81-285-58-7355  
Fax: +81-285-40-6035  
E-mail address:  
syu1.n@jichi.ac.jp

*J Diabetes Investig* 2020; 11: 1363–1365

doi: 10.1111/jdi.13241

## ABSTRACT

Type A insulin resistance (IR) syndrome is a severe IR form caused by insulin receptor (*INSR*) gene defects. Antidiabetic drugs, including high-dose insulin and insulin-sensitizing agents, often fail to control associated hyperglycemia. Therapy with recombinant human insulin-like growth factor 1 can be more effective, but it is expensive. We report a case of type A IR syndrome with an in-frame *INSR* heterozygous deletion ( $\Delta$ Leu999) that was treated with a combination of conventional therapy and ipragliflozin, a sodium–glucose cotransporter 2 inhibitor. Treatment reduced hemoglobin A1c levels (10.0–7.5%) and induced weight loss (54.4–52.0 kg) within 2 months, and the effects were sustained for >3 years. Sodium–glucose cotransporter 2 inhibitors might be useful to normalize blood glucose in type A IR syndrome by reducing bodyweight and ameliorating glucotoxicity.

## INTRODUCTION

Insulin resistance (IR), a major cause of type 2 diabetes, is closely associated with chronic morbidities, including atherosclerosis, hepatic steatosis and polycystic ovary syndrome. Its prevalence is rapidly increasing and becoming a worldwide public health concern. Whereas IR is commonly caused by obesity, it can also occur in non-obese patients with rare genetic defects in insulin signaling or adipocyte development<sup>1</sup>.

There are two types of IR syndrome, type A and type B. The former is caused by insulin receptor (*INSR*) gene defects, whereas the latter is characterized by anti-*INSR* antibodies<sup>1</sup>. Disease severity is inversely correlated with residual *INSR* activity, and both types can result in hyperglycemia when pancreatic  $\beta$ -cell hyperplasia fails to compensate for extreme IR. Treating genetically-induced IR is challenging and often unsuccessful. Herein, we report the long-term efficacy of a newer oral antidiabetic drug, ipragliflozin, in combination with conventional therapy, in a patient with type A IR syndrome.

## CASE REPORT

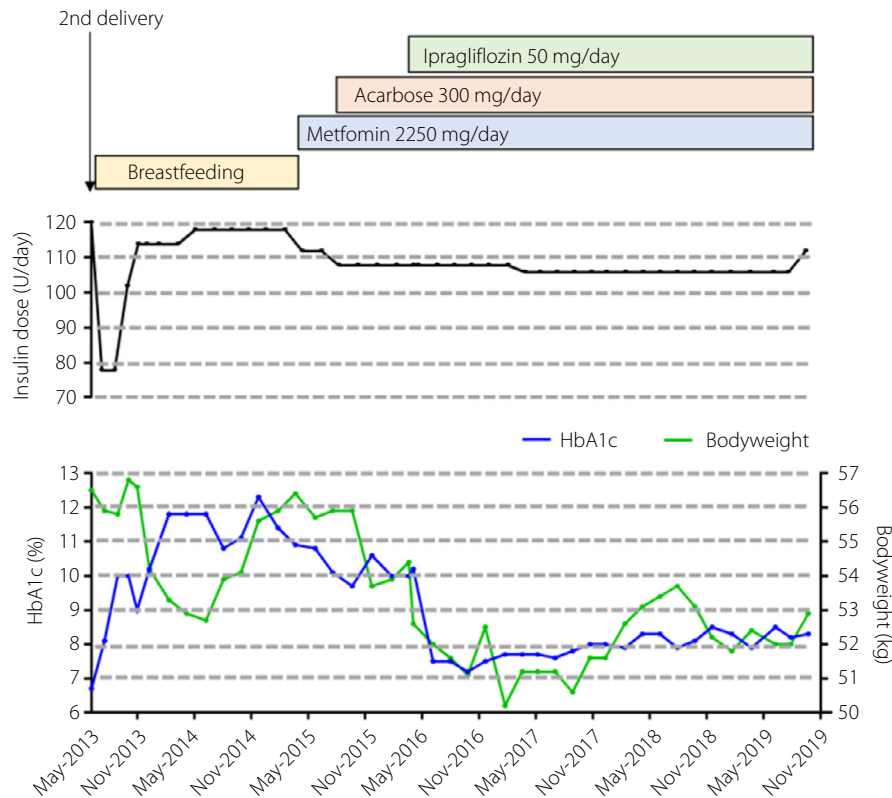
The patient was a non-obese Japanese woman diagnosed with diabetes mellitus in June 2009, at the age of 31 years (6 weeks'

gestation during first pregnancy). The clinical course of her successful pregnancy and delivery was reported previously<sup>2</sup>. Before delivery, large insulin doses (up to 480 units/day) were required to sufficiently control blood glucose levels. Genetic analysis showed an in-frame heterozygous *INSR* deletion mutation ( $\Delta$ Leu999). During her second pregnancy, we improved her glycemic control by combining metformin (2250 mg/day) with lower doses of insulin (up to 174 units/day). Both infants, harboring the same *INSR* mutation, had no abnormalities except being slightly small for their gestational age and having transient hypoglycemia at birth<sup>2</sup>.

Figure 1 shows the patient's clinical course after the second delivery in May 2013. As metformin can enter breast milk<sup>3</sup>, its administration was discontinued during breast-feeding. The patient's diabetes, which was treated with 120 units of insulin per day, became progressively worse. After the cessation of breast-feeding, metformin therapy was re-started and acarbose was initiated. However, hemoglobin A1c (HbA1c) levels decreased only slightly. She declined therapy with recombinant human insulin-like growth factor 1 (IGF-1) or higher doses of insulin because of treatment costs.

Therefore, in March 2016, we administered ipragliflozin. Before administration, the patient's bodyweight, height, body mass index and HbA1c were 54.4 kg, 150.8 cm, 23.9 kg/m<sup>2</sup> and

Received 30 December 2019; revised 12 February 2020; accepted 24 February 2020



**Figure 1** | Clinical course of the patient before and after ipragliflozin treatment. HbA1c, hemoglobin A1c.

10.0%, respectively. After 1 month, her bodyweight and HbA1c were 52.6 kg and 10.2%, respectively. After 2 months, they were 52.0 kg and 7.2%, respectively. HbA1c content was maintained at approximately 8.0% for >3 years after first administration. Ketoacidosis and other adverse effects were not observed. The only complication was simple diabetic retinopathy.

## DISCUSSION

We describe a patient with type A IR syndrome who responded well to ipragliflozin, which significantly improved glycemic control and induced bodyweight loss. SGLT2 inhibitors comprise a newer class of antidiabetics that reduce blood glucose by inhibiting renal glucose reabsorption independently of insulin action. Their use is rapidly increasing, driven by favorable results of cardiovascular trials of type 2 diabetes mellitus<sup>4</sup>. Recently, a nationwide survey of IR syndrome was reported in Japan, including individuals with type A, type B and type A-like clinical features without *INSR* mutations and Rabson-Mendenhall/Donohue syndrome with biallelic *INSR* mutations<sup>5</sup>. In that study, SGLT2 inhibitors were used for seven of 71 study participants. However, SGLT2 inhibitor efficacy data for patients with genetically-determined severe IR are limited<sup>6,7</sup>. To our knowledge, we are the first to report the long-term efficacy of an SGLT2 inhibitor for a patient with an *INSR* mutation.

Treating type A IR syndrome is challenging. Abundant insulin or recombinant human IGF-1 can activate the IGF-1 receptor

and can be effective for type A IR syndrome, because the IGF-1 receptor shares structural homology and downstream signaling pathways with *INSR*<sup>8</sup>. However, recombinant human IGF-1 therapy is expensive, and adults with type A IR syndrome do not receive sufficient financial support in Japan. Insulin-sensitizing agents are also important to manage type A IR syndrome. Metformin is often effective, as observed with the present patient during her second pregnancy<sup>2</sup>; thiazolidinediones can also exert beneficial effects<sup>1</sup>. The present patient's hyperglycemia became resistant to metformin after restarting treatment, which might be partly explained by the discontinuation of dietary restriction and/or decreased physical activity during parenting.

Just two articles have reported the efficacy of SGLT2 inhibitors in genetically-induced severe IR<sup>6,7</sup>. Combining dapagliflozin with insulin and metformin therapy lowered bodyweight and HbA1c levels in a patient with a heterozygous mutation in the phosphatidylinositol 3-kinase, regulatory subunit 1 gene, which is involved in post-*INSR* signaling<sup>6</sup>. Furthermore, combining ipragliflozin with other oral antidiabetic drugs significantly improved severe IR in a patient with a homozygous nonsense mutation of Berardinelli-Seip congenital lipodystrophy 2 gene, which is responsible for adipocyte differentiation, as assessed by a homeostasis model<sup>7</sup>.

Generally, type A IR syndrome is characterized by the absence of obesity. However, we previously reported that obesity is a risk factor for worsening glycemic control in a family with

an *INSR* mutation<sup>9</sup>. Although the patient was not obese (body mass index 22.08–23.92 kg/m<sup>2</sup>), Pearson's correlation analysis showed that HbA1c was positively correlated with bodyweight (data from Figure 1;  $n = 44$ ,  $r = 0.255$ ,  $P = 0.0005$ ). Therefore, even if type A IR syndrome patients are not obese, adiposity can be an exacerbating factor for glycemic control.

Sodium–glucose cotransporter 2 inhibitors might act by enhancing urinary glucose excretion and shifting energy substrate utilization from carbohydrates to lipids<sup>10</sup>, which is expected to eventually reduce adiposity. Here, weight loss preceded ipragliflozin-mediated HbA1c reductions. SGLT2 inhibitor-induced weight loss might explain why glycemic control is improved in patients with defective *INSR* or post-*INSR* signaling.

Two-week dapagliflozin therapy significantly increases insulin-mediated glucose disposal, of which ~80% occurs in skeletal muscle<sup>11</sup>. SGLT2 inhibitors were speculated to indirectly improve muscle insulin sensitivity by ameliorating glucotoxicity. This indicates that SGLT2 inhibitors can even improve glycemic control in patients with lipodystrophy.

Thus, long-term ipragliflozin achieved effective glycemic control in a patient with an *INSR* mutation. This might be explained primarily by weight loss and secondarily by alleviated glucotoxicity. This will be helpful to develop more effective and affordable treatment strategies for severe IR.

## DISCLOSURE

The authors declare no conflict of interest.

## REFERENCES

1. Semple RK, Savage DB, Cochran EK, *et al.* Genetic syndromes of severe insulin resistance. *Endocr Rev* 2011; 32: 498–514.
2. Enkhtuvshin B, Nagashima S, Saito N, *et al.* Successful pregnancy outcomes in a patient with type A insulin resistance syndrome. *Diabet Med* 2015; 32: e16–e19.
3. Hale TW, Kristensen JH, Hackett LP, *et al.* Transfer of metformin into human milk. *Diabetologia* 2002; 45: 1509–1514.
4. Zelniker TA, Wiviott SD, Raz I, *et al.* SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet* 2019; 393: 31–39.
5. Takeuchi T, Ishigaki Y, Hirota Y, *et al.* Clinical characteristics of insulin resistance syndromes: a nationwide survey in Japan. *J Diabetes Investig* 2020; 11: 603–616.
6. Hamaguchi T, Hirota Y, Takeuchi T, *et al.* Treatment of a case of severe insulin resistance as a result of a *PIK3R1* mutation with a sodium-glucose cotransporter 2 inhibitor. *J Diabetes Investig* 2018; 9: 1224–1227.
7. Kawana Y, Imai J, Sawada S, *et al.* Sodium-glucose cotransporter 2 inhibitor improves complications of lipodystrophy: a case report. *Ann Intern Med* 2017; 166: 450–451.
8. McDonald A, Williams RM, Regan FM, *et al.* IGF-1 treatment of insulin resistance. *Eur J Endocrinol* 2007; 157: S51–S56.
9. Ando A, Yatagai T, Rokkaku K, *et al.* Obesity is a critical risk factor for worsening of glucose tolerance in a family with the mutant insulin receptor. *Diabetes Care* 2002; 25: 1484–1485.
10. Ferrannini E, Muscelli E, Frascerra S, *et al.* Metabolic response to sodium-glucose cotransporter 2 inhibition in type 2 diabetic patients. *J Clin Invest* 2014; 124: 499–508.
11. Merovci A, Solis-Herrera C, Daniele G, *et al.* Dapagliflozin improves muscle insulin sensitivity but enhances endogenous glucose production. *J Clin Invest* 2014; 124: 509–514.