SGLT2 inhibitors provide an effective therapeutic option for diabetes complicated with insulin antibodies

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Abstract. Diabetes mellitus complicated with insulin antibodies is rare in clinical practice but usually difficult to control. A high amount of insulin antibodies, especially with low affinity and high binding capacity, leads to unstable glycemic control characterized by hyperglycemia unresponsive to large volume of insulin and unanticipated hypoglycemia. There are several treatment options, such as changing insulin preparation, immunosuppression with glucocorticoids, and plasmapheresis, most of which are of limited efficacy. Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a novel class of drug which decrease renal glucose reabsorption and lowers plasma glucose level independent of insulin action. We report here a case with diabetes complicated with insulin antibodies who was effectively controlled by an SGLT2 inhibitor. A 47-year-old man with type 2 diabetes treated with insulin had very poor glycemic control characterized by postprandial hyperglycemia unresponsive to insulin therapy and repetitive hypoglycemia due to insulin antibodies. Treatment with ipragliflozin, an SGLT2 inhibitor, improved HbA1c from 8.4% to 6.0% and glycated albumin from 29.4% to 17.9%. Continuous glucose monitoring revealed improvement of glycemic profile (average glucose level from 212 mg/dL to 99 mg/dL and glycemic standard deviation from 92 mg/dL to 14 mg/dL) with disappearance of hypoglycemic events. This treatment further ameliorated the characteristics of insulin antibodies and resulted in reduced insulin requirement. SGLT2 inhibitors may offer an effective treatment option for managing the poor glycemic control in diabetes complicated with insulin antibodies.

Key words: Insulin antibodies, Sodium-glucose cotransporter 2 inhibitors, Ipragliflozin, Continuous glucose monitoring
until recently. In 2013, he developed anal canal carcinoma and was treated with TS-1 (tegafur, gimeracil, and oteracil potassium combination capsule) and mitomycin-C with concurrent radiotherapy. Shortly after this treatment, he started to experience frequent episodes of nocturnal hypoglycemia and daytime hyperglycemia. The addition of sitagliptin, discontinuation of insulin glargine, and use of a bedtime snack (160 kcal), did not reduce hypoglycemic attacks nor control daytime hyperglycemia. His HbA1c and glycated albumin (GA) was 7.9% and 26.0%, respectively. Continuous glucose monitoring (CGM) revealed nocturnal and predinner hypoglycemia with daytime hyperglycemia, with an average glucose level of 212 mg/dL., glycemic standard deviation (SD) of 92 mg/dL, and glucose range of 54-371 mg/dL (Fig. 1; black solid line). Other laboratory findings including blood cell count, serum albumin level, renal function, and liver function were all normal. Plasma concentrations of growth hormone, adrenocorticotropic hormone, cortisol, thyroid stimulating hormone, free T3 and T4 level were all within normal range. GAD antibody, thyroglobulin antibody and thyroperoxidase antibody were negative. His serum C-peptide level was undetectable, while fasting immunoreactive insulin (IRI) level was 41.13 µU/mL and the insulin antibody titer was extremely high (≥50.0 U/mL, 316 U/mL (assayed after 1/100 dilution); binding ratio, 78.2%). Scatchard analyses of equilibrium-binding assay of insulin antibodies revealed curvilinear response compatible with polyclonal antibodies with a higher and lower affinity binding site, one with very low affinity and high binding capacity ($K_1 = 0.00105 \times 10^8$ M$^{-1}$, $b_1 = 222 \times 10^{-8}$ M), and the other with higher affinity and lower binding capacity ($K_2 = 0.0206 \times 10^8$ M$^{-1}$, $b_2 = 80.4 \times 10^{-8}$ M) (Fig. 2). These characteristics of his insulin antibodies rather resembled that of insulin autoantibodies found in patients with insulin autoimmune syndrome (IAS). Serological typing of human leukocyte antigen (HLA) alleles demonstrated the allelic combination of A2/24, B46/61, DR8/9. While a variety of insulin preparations such as insulin aspart, lispro, and regular insulin were applied, his daytime hyperglycemia was not controlled and the frequency of hypoglycemic attacks was not decreased (HbA1c and GA were 8.4% and 29.4%, respectively). We finally added oral ipragliflozin (50 mg), an inhibitor of SGLT2, which controls blood glucose independently of insulin action [7, 8], while carefully adjusting insulin doses by CGM. One wk after the addition of ipragliflozin, his CGM showed marked improvement with lower daytime glucose level and no nocturnal hypoglycemia. His average glucose level was 151 mg/dL, glycemic SD 31 mg/dL, and the range in glucose level 81-221 mg/dL (CGM data not shown). Urinary glucose excretion was markedly increased from 3.4-4.0 g/day to 31.9-78.3 g/day, while urine volume was not significantly changed (from 1,450-2,400 mL/day to 1,280-1,650 mL/day). He stayed on once-daily oral 50 mg ipragliflozin and 50 mg sitagliptin, plus multiple insulin injections (total daily dose of 15 units) with no hypoglycemic attacks. CGM recorded 8 wk after
the addition of ipragliflozin revealed that his average glucose level improved to as low as 128 mg/dL with a glycemic SD of 38 mg/dL (CGM data not shown), even though his fasting IRI level was 8.82 µU/mL and insulin antibody titer remained high (> 50.0 U/mL), with a binding ratio of 79.1%. Thirty-two wk after the addition of ipragliflozin, his insulin dosage was further reduced to 8 units a day (insulin glulisine before each meal with no glargine) (Fig. 3). CGM showed additional improvement with average glucose level as low as 99 mg/dL with a glycemic SD of 14 mg/dL (Fig. 1; gray solid line) without hypoglycemia. Glycemic control markers also improved with HbA1c from 8.4% to 6.0% and GA from 29.4% to 17.9%, respectively. Analysis of his insulin antibodies performed 2 wk after the addition of ipragliflozin revealed marked improvement (low affinity/high capacity sites: $K_1 = 0.00224 \times 10^8$ M$^{-1}$, $b_1 = 71.8 \times 10^{-8}$ M; higher affinity/lower capacity sites: $K_2 = 0.0463 \times 10^8$ M$^{-1}$, $b_2 = 16.8 \times 10^{-8}$ M) (Fig. 2). Continuation of ipragliflozin treatment for 36 wk further reduced the number of insulin binding sites (low affinity/high capacity sites: $K_1 = 0.000905 \times 10^8$ M$^{-1}$, $b_1 = 27.5 \times 10^{-8}$ M; higher affinity/lower capacity sites: $K_2 = 0.107 \times 10^8$ M$^{-1}$, $b_2 = 4.62 \times 10^{-8}$ M). This treatment also reduced the insulin antibody titer from 316 U/mL to 116 U/mL (both assayed after 1/100 dilution).

**Discussion**

We reported here a case where an SGLT2 inhibitor effectively improved glycemic control and ameliorated the characteristics of insulin antibodies in a patient with diabetes complicated with insulin antibodies.

Presence of insulin antibodies induces high glycemic variability. When there are high amounts of insulin antibodies with low affinity and high binding-capacity, they may induce severe hyperglycemia by annihilating the effect of endogenous and injected insulin, and unexpectedly cause severe hypoglycemia by releasing a large amount of free insulin [2]. The current treatment options including alteration of insulin preparations [4], steroid administration [5, 6], plasmapheresis [6], use of anti-CD20 antibody, and combination of the above [5, 6], are often of limited benefit.

In the present case, CGM showed glucose profile with high glycemic variability and Scatchard analysis of insulin antibodies revealed similar characteris-

![Fig. 3](image-url) Change of total daily insulin dose, HbA1c, and glycated albumin (GA) during the therapeutic course.
tics as observed in IAS [9] (Fig. 2). Drugs containing the sulfhydryl group, such as methimazole, mercaptopropionyl glycine, and glutathion, and α-lipoic acid are known to be triggers of the onset of IAS. In the present case, the patient had no history of medication with these drugs, and did not have HLA-DR4, which almost all Japanese patients with IAS possess [9]. Although several standard treatment options failed to control his glycemia, administration of ipragliflozin, an SGLT2 inhibitor [7, 8], which enhanced urinary glucose excretion, remarkably improved his glycemic control with less glucose variability and almost completely eliminated his nocturnal hypoglycemia. Scatchard analysis revealed a curvilinear response suggesting polyclonal insulin antibodies with both high and low affinity sites (Fig. 2, open circle). The affinity and the binding-capacity of the high affinity site rather resembled those of the polyclonal insulin autoantibodies detected in patients with IAS rather those of insulin antibodies usually detected in patients treated with exogenous insulin injections. We speculated that the insulin antibodies with low affinity yet high binding-capacity annihilated the insulin action when bound, and induced severe hypoglycemia when free insulin was released from the insulin-antibody complex by some triggers. The immune reaction to exogenous antigen is enhanced when the expression of antigen is increased. The abrupt release of free insulin from the immune complex further stimulates immune response and increases the amount of antibodies which causes a vicious cycle. To terminate the vicious cycle it is necessary to reduce the amount of antigen that causes the immune response. When we reduced the amount of exogenous insulin by the SGLT2 inhibitor, inducing the immune response to gradually subside, this might have restored the inherent immune regulatory mechanism to reduce insulin antibodies. SGLT2 inhibitors decreases plasma glucose level independently of insulin action and have been shown to be an effective drug that control glucose fluctuations while reducing insulin requirement. In the present case, alteration of the insulin preparation did not contribute to the reduction of insulin requirement, while the addition of an SGLT2 inhibitor successfully reduced the insulin requirement. The reduction in insulin requirement may have subsequently changed the characteristics and amount of insulin antibodies, leading to the successful elimination of hypoglycemic attacks and insulin-insensitive hyperglycemia.

The limitation of this study is that this is the first case report that SGLT2 inhibitors provide an effective therapeutic option for diabetic patients complicated with insulin antibodies. Further case reports must be accumulated to conclude the efficacy of this treatment option because we cannot rule out the possibility of spontaneous remission of the disease process. We must also state that the usual precautions for the use of SGLT2 inhibitors in patients with type 2 diabetes must be exercised and careful adjustment of insulin doses by using CGM and/or frequent glucose monitoring must be applied to avoid hyperglycemic crisis and hypoglycemia, especially in patients with low insulin-secreting capacity.

**Conclusion**

This is the first reported case demonstrating a distinct benefit of ipragliflozin, an SGLT2 inhibitor, in patients with diabetes complicated with insulin antibodies. This case suggests that SGLT2 inhibitors provide an effective treatment option for managing the poor glycemic control in diabetic patients complicated with insulin antibodies.

**Disclosure**

None of the authors have any potential conflicts of interest associated with this research.

**References**


