SGLT2i as a Useful Adjunctive Medication for HNF4A-MODY

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Maturity-onset diabetes of the young (MODY) results from heterozygous pathogenic variants of genes involved in pancreatic β-cell function (1). Typical clinical features include young onset (before 30 years of age, in which the prevalence is 3.6%) (2), absence of islet autoantibodies, and impaired insulin secretion with insulin independence. HNF4A-MODY is the third most common genetically diagnosed type of MODY, with a frequency of 14% (3). The first-line treatment for HNF4A-MODY is sulfonylurea, which is the same as that for HNF1A-MODY (1). A study on the use of sulfonylurea for HNF1A-MODY revealed that 87.5% of patients benefited from as little as 40 mg/day gliclazide, while the remaining patients benefited from 80 mg/day (4). However, several patients with HNF4A/HNF1A-MODY developed worse glycemic control after treatment with sulfonylurea, with increasing disease duration. Second-line therapy is not well studied, and insulin therapy is usually required as the disease progresses (1).

Here, we report a case of a 24-year-old patient with HNF4A-MODY who did not achieve glycemic control even with sulfonylurea treatment; however, treatment with a sodium–glucose cotransporter 2 inhibitor (SGLT2i) markedly improved his glycemic control.

The patient had no history of hypoglycemia. At 10 years of age, the patient presented with glycosuria and was diagnosed with diabetes on the basis of him having a high blood glucose (BG) level (243 mg/dL [13.5 mmol/L]) and a high HbA_{1c} level (9.9% [85 mmol/mol]). He was not obese (BMI 18.2), and islet autoantibodies (GAD 65, IA-2, and insulin autoantibody) were absent. His fasting BG (138 mg/dL [7.7 mmol/L]), insulin (6.5 μU/mL [46.6 pmol/L]), and homeostasis model assessment of insulin resistance (2.2) and β-cell function (31%) indicated insulin deficiency. The patient was treated with insulin from age 10 to 20 years. He had a family history of young-onset diabetes without obesity spanning at least three generations, including his father (age of onset 25 years) and grandfather (age of onset 30 years). At 19 years, he underwent genetic testing for *HNF1A*, *HNF4A*, and *GCK*, revealing a previously reported heterozygous variant (c.908G>A, p.Arg303His [GenBank accession no. NM_000457.3]) in *HNF4A*. At that time, his HbA_{1c} was 8.1% (65 mmol/mol) with insulin treatment (0.8 units/kg/day). The patient's medication was switched from insulin to gliclazide (Fig. 1), with an initial dose of 40 mg/day. It was then increased by 40 mg/day every month up to 160 mg/day. Insulin was tapered from the initiation of gliclazide and discontinued after 2 months. The HbA_{1c} levels during the 4 months from gliclazide initiation to its maximum dose were 8.2% (66 mmol/mol), 7.7% (61 mmol/mol), 7.7% (61 mmol/mol), and 7.6% (60 mmol/mol). Two months after the maximum dose, his HbA_{1c} dropped to 7.2% (55 mmol/mol). Although the patient adhered to this treatment plan for 1 year and 8 months, he did not achieve the targeted glycemic control of <7.0% (53 mmol/mol); conversely, his HbA_{1c} level deteriorated to 8.0% (64 mmol/mol) at 21 years of age. As his endogenous insulin secretion was preserved (serum C-peptide 1.54 nmol/L), empagliflozin at 10 mg/day was added to his treatment plan without decreasing the gliclazide dose. After 8 months, his HbA_{1c} level decreased to 6.3% (45 mmol/mol) with occasional hypoglycemic symptoms; therefore, empagliflozin was discontinued, considering residual capacity of his insulin secretion to gliclazide. However, his HbA_{1c} level gradually increased to 8.5% (69 mmol/mol) at 23 years of age while his endogenous insulin secretion was preserved (serum C-peptide 1.00 nmol/L). Therefore, empagliflozin (10 mg/day) was restarted, 5 months after which his HbA_{1c} level improved to 6.9% (51 mmol/mol) and remained stable over the next 5 months.

To our knowledge, this is the first report to demonstrate the benefits of an SGLT2i as an adjunctive medication for HNF4A-MODY. The addition of empagliflozin to gliclazide resulted in excellent glycemic control, demonstrating its glucose-lowering effect. SGLT2i induces glycosuria to lower BG levels by blocking the low-affinity, high-capacity glucose transporter located in the proximal renal tubules (5). Although the precise mechanism is unknown, we speculate that the ability of SGLT2i to work in HNF4A-MODY is actually due, at least in part, to expression of HNF4A in the kidneys (1). Patients with HNF1A-MODY, with pathogenesis similar to that of HNF4A-MODY, also report greater glycosuria with SGLT2i use compared with that associated with type 2 diabetes despite having reduced SGLT2 expression, which is positively regulated by HNF1A (6). Our patient benefited

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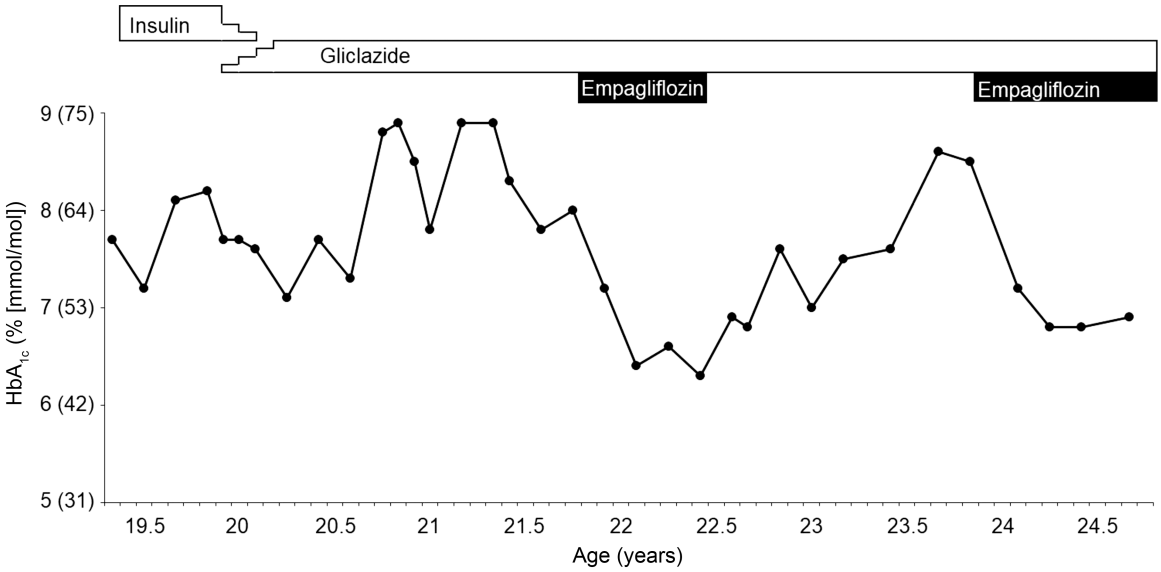

Figure 1—Clinical course of gliclazide and empagliflozin treatment after switching from insulin therapy. The treatment is shown in the upper part of the graph. The patient was switched from insulin to gliclazide at 19 years and 10 months of age. The initial dose of gliclazide was 40 mg/day. Insulin was discontinued 2 months after gliclazide initiation. Gliclazide was administered at the highest dose of 160 mg from 20 years and 1 month. Empagliflozin (10 mg/day) was added from 21 years 9 months to 22 years 5 months. Thereafter, empagliflozin at 10 mg/day was resumed at 23 years and 10 months.

from SGLT2i, as have many previous patients with type 2 diabetes (5). However, SGLT2i may increase the risk of developing ketoacidosis due to reduced endogenous insulin secretion in patients with MODY (7). Therefore, further clinical studies are required to demonstrate the efficacy of SGLT2i in patients with HNF4A-MODY. In conclusion, SGLT2i may be an effective adjunctive medication for patients with HNF4A-MODY.

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