# Use of a Dual GIP/GLP-1 Receptor Agonist in HNF1A-MODY and HNF4A-MODY

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Maturity-onset diabetes of the young (MODY) is a type of monogenic diabetes with an estimated prevalence of 1 of 10,000 in adults and 1 of 23,000 in children (1). HNF1A-MODY (52%) and HNF4A-MODY (10%), caused by pathogenic variants in the respective genes encoding β-cell transcription factors, are the most common treatment-requiring forms of MODY (2). Sulfonylurea is first-line treatment for HNF1A-MODY and HNF4A-MODY, and insulin is a second-line treatment. Insulin is problematic, as it often leads to hypoglycemia and weight gain. Glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide 1 (GLP-1) have been shown to potentiate sulfonylurea-induced insulin secretion in 10 HNF1A-MODY cases (3), but the clinical use of dual GIP/GLP-1 receptor agonist (RA) treatment has not been described. By focusing on the cases of two individuals with different disease pedigrees, we aim to describe the clinical use and efficacy of tirzepatide (a dual GIP/GLP-1 RA) treatment in HNF1A-MODY and HNF4A-MODY.

A 33-year-old Hispanic White woman presented for management of HNF4A-MODY [heterozygous variant NM_000457.6 (*HNF4A*):c.418C>T(p.Arg140X)]. She was diagnosed with HNF4A-MODY at the age of 12 (by genetic testing for an established pedigree), and she was diagnosed with diabetes at age 20 at an outside hospital. At re-presentation in follow-up, she was on glipizide 2.5 mg twice daily, insulin glargine 65 units once daily (0.75 units/kg/day), and insulin lispro 5 units three times per day with meals (total daily dose 80 units/day [0.93 units/kg/day]). She gained 27.22 kg over 10 years (weight 86.2 kg, BMI 33.6 kg/m$^2$) but had no microvascular or macrovascular complications. Her $HbA_{1c}$ was 7.3%. She did not report hypoglycemia but was interested in losing weight. Tirzepatide 2.5 mg once weekly was started (with discontinuation of glipizide and prandial insulin) and titrated by 2.5 mg every 4 weeks to 7.5 mg subcutaneously once weekly. She tolerated this well, except for mild nausea. After 10 months, her $HbA_{1c}$ decreased to 5.9% and her weight decreased by 19.9 kg (weight 67.1 kg, BMI 26.2 kg/m$^2$, 23% body weight reduction) without a reported change in hypoglycemia. She did not experience significant postprandial hyperglycemia and significantly reduced her basal insulin to 35 units once daily (0.52 units/kg/day).

A 53-year-old non-Hispanic White woman presented for management of HNF1A-MODY [heterozygous variant NM_000545.5(*HNF1A*):c.955 + 1G>A]. She was diagnosed with diabetes at an outside hospital at age 24 (weight 52.1 kg, BMI 19.1 kg/m$^2$) and was initiated on glipizide extended release (ER) 5 mg once daily. At presentation to our medical center, she was on glipizide ER 5 mg once daily, metformin ER 1,000 mg once daily, and insulin glargine 19 units daily (0.23 units/kg/day). She had no reported microvascular or macrovascular complications. Her $HbA_{1c}$ was 9.5% and she was overweight (weight 81.4 kg, BMI 29.8 kg/m$^2$). An attempt was made to increase the glipizide dose, but she developed hypoglycemia (four hypoglycemic episodes, two severe, over a 30-day interval). Liraglutide was not tolerated due to nausea, and semaglutide was not tolerated due to nausea, vomiting, and diarrhea. Once-weekly subcutaneous tirzepatide was initiated and titrated to 5 mg once weekly (highest dose tolerated due to nausea) with discontinuation of glipizide. She reported no increase in postprandial hyperglycemia, a reduction in hypoglycemic events (no reported hypoglycemic events over 30 days), and a reduction in insulin glargine dose by 1 unit (0.30 units/kg/day). After 15 months of treatment, her $HbA_{1c}$ improved to 6.4% and her weight decreased by 21.3 kg (weight 60.1 kg, BMI 21.4 kg/m$^2$, 26% body weight reduction).

In these individuals, treatment with tirzepatide for HNF4A-MODY and HNF1A-MODY led to a 3.1% and 1.4% $HbA_{1c}$ reduction, 23% and 26% body weight reduction (compared with average of 14.7% reduction in patients with obesity and type 2 diabetes [4]), 45 units and 1 unit total daily insulin dose reduction, and sulfonylurea discontinuation, respectively. These cases highlight dual GIP/GLP-1 RA as adjuvant treatment and highlight a potential use of dual GIP/GLP-1 RA as monotherapy. Although it is known that GLP-1 receptor activation on β-cells leads to downstream stimulation of β-cells distal to the genetic defect (5), the mechanism of action of GIP and dual GIP/GLP-1 RA in HNF1A-MODY and HNF4A-MODY is not known. Patients with MODY may develop obesity and/or insulin resistance, which may be environmental, genetic, or a combination of the complex interplay of these



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risk factors. It is likely that the pleiotropic effects of tirzepatide will play a future role in the treatment of individuals with HNF1A-MODY and HNF4A-MODY who are overweight or obese. Given these preliminary findings, the effect of dual GIP/GLP-1 RA in HNF1A-MODY and HNF4A-MODY warrants further investigation.

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