Novel Use of GLP-1 Receptor Agonist Therapy in HNF4A-MODY

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Maturity-onset diabetes of the young (MODY) is an inherited form of diabetes caused by a mutation in a single gene. The frequency of mutation carriers for HNF4A-MODY has been reported to be 1.2% (1). Our group has previously published on the successful use of glucagon-like peptide 1 receptor agonist (GLP-1 RA) therapy in three consecutive generations of a family with an HNF1A-MODY (2). Although GLP-1 RA therapy has been studied in patients with HNF1A-MODY (3), it has not been studied in patients with HNF4A-MODY. In this father-son cohort, we demonstrate successful use of GLP-1 RA therapy in two patients with c.790:1 bp deletion of G; codon:264 mutations of HNF4A.

The son first presented with neonatal hypoglycemia, then later developed diabetes and presented to our clinic at age 20, when genetic testing was performed and confirmatory for an HNF4A-MODY. He was prescribed glimepiride and titrated to 4 mg twice daily, and 2 years later his hemoglobin A_{1c} (HbA_{1c}) rose to 8.7%. He was switched to semaglutide 0.25 mg once weekly, which was titrated to a maximum dose of 1 mg weekly over 8 weeks. The patient's HbA_{1c} improved to 6.2% after 6 months of GLP-1 RA therapy and he reported fewer hypoglycemic events. The father had been diagnosed with monogenic diabetes in his early 20s and had been on sulfonylurea therapy until age 40, at which time he was transitioned to a regimen of long- and short-acting insulin therapy. Thereafter, he presented to our clinic with an HbA_{1c} of 9.6% and was transitioned to once-daily long-acting insulin in combination with once-daily liraglutide, initiated at 0.6 mg and subsequently titrated to 1.8 mg over 3 weeks. The patient tolerated this therapy well and has been off short-acting insulin for more than 1 year, with notable improvement in his HbA_{1c} to 5.9% and fewer hypoglycemic events.

To our knowledge, this is the first report demonstrating the benefits of GLP-1 RA therapy in patients with the HNF4A-MODY. GLP-1 receptor activation on β-cells results in stimulation of adenylate cyclase and subsequent elevation of cAMP. Both cAMP and activated protein kinase A may influence secretory events distal to the generation of ATP by glucose metabolism (4,5). Our hypothesis is similar to that proposed by Østoft et al. (3), in which a GLP-1 RA is likely capable of bypassing the decreased concentrations of ATP associated with HNF1A-MODY and HNF4A-MODY and thereby stimulates the secretion of insulin and reduces postprandial glucose values. Based on this report, it appears that GLP-1 RA therapy could be an effective therapy to consider in patients with HNF4A-MODY.

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