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GLP-1 RA and dual GIP/GLP-1 RA treatment in MODY: a descriptive case series

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ABSTRACT

Introduction Glucagon-like peptide-1 receptor agonists (GLP-1 RA) and dual glucose insulinotropic polypeptide (GIP)/GLP-1 RA are widely prescribed, but their effectiveness in different subtypes of maturity-onset diabetes of the young (MODY) is unknown.

Research design and methods We present a descriptive case series of individuals from two MODY cohorts who used GLP-1 RA or dual GIP/GLP-1 RA. Paired *t* tests were used to compare HbA1c, body mass index (BMI), and sulfonylurea (SU) dose before and after GLP-1 RA or dual GIP/GLP-1 RA therapy.

Results 10 individuals (4 hepatocyte nuclear factor-1α (HNF1A)-MODY, 4 hepatocyte nuclear factor-4α (HNF4A)-MODY, 1 ATP-binding cassette transporter subfamily C member 8 (ABCC8)-MODY, 1 hepatocyte nuclear factor-1β (HNF1B)-MODY) were identified who used GLP-1 RA or dual GIP/GLP-1 RA. In patients with HNF1A-MODY and HNF4A-MODY, GLP-1 RA reduced HbA1c by 1.3% (p=0.010), BMI by 2.90 kg/m^2 (p=0.008), and total daily dose of SU by 66.6% (p=0.005). Dual GIP/GLP-1 RA treatment led to a non-statistically significant decrease in HbA1c of 1.8% (p=0.104), a statistically significant reduction in BMI of 8.73 kg/m^2 (p=0.010), and all patients discontinued SU (n=2) and one discontinued insulin. In patients with ABCC8-MODY and HNF1B-MODY, GLP-1 RA reduced HbA1c by 1.2% and 1.8%, BMI by 1.1 kg/m^2 and 1.2 kg/m^2, and the patients no longer required treatment with SU or insulin, respectively.

Conclusions GLP-1 RA and dual GIP/GLP-1 RA lowered HbA1c, BMI, and SU dose in patients with MODY.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Patients with maturity-onset diabetes of the young (MODY) often fail sulfonylurea (SU) treatment, and it remains unknown how effective glucagon-like peptide-1 receptor agonist (GLP-1 RA) or dual glucose insulinotropic polypeptide (GIP)/GLP-1 RA are in reducing HbA1c, weight, SU dose, and insulin dose.

WHAT THIS STUDY ADDS

⇒ We provide a descriptive case series of patients with MODY (hepatocyte nuclear factor-1α (HNF1A)-MODY, hepatocyte nuclear factor-4α (HNF4A)-MODY, ATP-binding cassette transporter subfamily C member 8 (ABCC8)-MODY, and hepatocyte nuclear factor-1β (HNF1B)-MODY) who were treated with GLP-1 RA or dual GIP/GLP-1 RA from two large academic medical centers.

⇒ In HNF1A-MODY and HNF4A-MODY: GLP-1 RA lowered HbA1c by 1.3%, SU dose by 66.6%, and weight by 2.90 kg/m^2, and dual GIP/GLP-1 RA treatment led to a non-statistically significant reduction in HbA1c by 1.8%, a statistically significant reduction in SU dose of 100%, and statistically significant body mass index reduction of 8.73 kg/m^2.

⇒ GLP-1 RA lowered HbA1c by 1.2% in ABCC8-MODY and 1.8% in HNF1B-MODY and eliminated the need for SU.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings suggest that GLP-1 RA and dual GIP/GLP-1 RA are potential effective treatments for HNF1A-MODY, HNF4A-MODY, ABCC8-MODY, and HNF1B-MODY.

INTRODUCTION

Maturity-onset diabetes of the young (MODY) is a monogenic and non-autoimmune form of diabetes mellitus that accounts for 1%–5% of all diabetes.[1 2] Hepatocyte nuclear factor-4α MODY (HNF4A-MODY), hepatocyte nuclear factor-1α MODY (HNF1A-MODY), and hepatocyte nuclear factor-1β MODY (HNF1B-MODY) are inherited in an autosomal dominant pattern and are among the common treatment-requiring forms of MODY. ATP-binding cassette transporter subfamily C member 8 MODY (ABCC8-MODY) is a less common, but still treatment-requiring form of MODY, with the best approach to treatment being unclear. In the most common treatment-requiring forms of MODY (HNF1A-MODY and HNF4A-MODY), sulfonylureas (SUs) are recognized as first-line therapy, and insulin as second-line therapy. In HNF1B-MODY, insulin is often required early in therapy because of reduced β cell function due to pancreatic hypoplasia and increased

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hepatic insulin resistance. However, there are limited real-world clinical data addressing alternative therapies.

MODY arises from variants in genes encoding transcription factors affecting the pancreatic β cell. For patients with HNF1A-MODY, HNF4A-MODY, and ABCC8-MODY, SUs stimulate insulin secretion by enhancing ATP-independent closure of the K_{ATP} channels, and therefore, bypass the low level of ATP in the pancreatic β cells or decreased sensitivity to ATP.[3–7] Although the transcription factor Hnf1b has a very similar structure to the transcription factor Hnf1a and shares a DNA-binding site, mutations in *HNF1B* result in reduced β cell function due to pancreatic hypoplasia and increased hepatic insulin resistance. Patients with HNF1A-MODY and HNF4A-MODY are initially sensitive to SU treatment, but glucose-stimulated insulin secretion in response to SUs decreases over time (at a rate of 1%–4% per year), and patients often become unresponsive to SU treatment after 3–25 years.[8 9] Although some patients remain responsive to SUs for more than 30 years, insulin treatment is frequently used for patients who become unresponsive to SUs. The latter is problematic due to the risk of hypoglycemia. As a result, there has been interest in the use of insulin-sparing agents: glucagon-like peptide-1 receptor agonists (GLP-1 RA) in HNF1A-MODY,[10–12] GLP-1 RA in HNF4A-MODY,[13] and dual glucose insulinotropic polypeptide (GIP)/GLP-1 RA in HNF1A-MODY and HNF4A-MODY.[14]

Despite the previous case reports, there has been a lack of statistical comparisons in larger cohorts of MODY describing the glycemic and weight-lowering effect of GLP-1 RA and dual GIP/GLP-1 RA. In this study, we compiled MODY cases from two tertiary academic medical centers in a descriptive case series to study the effectiveness of GLP-1 RA and dual GIP/GLP-1 RA in patients with HNF1A-MODY, HNF4A-MODY, HNF1B-MODY, and ABCC8-MODY.

METHODS

This is a descriptive case series of patients with MODY from two large tertiary care referral centers enrolled in the Long-Term Study of MODY-Monogenic Diabetes at the University of Michigan and the Study of MODY at Cincinnati Children's Hospital Medical Center. We included patients with MODY who were treated with GLP-1 RA or GIP/GLP-1 RA.

Among the 176 patients with MODY, 10 were identified from the electronic medical record and as having been prescribed a GLP-1 RA or dual GIP/GLP-1 RA. Data collected included demographics (age, sex, race/ethnicity, MODY type), type of GLP-1 RA or dual GIP/GLP-1 RA, dose and route of administration of GLP-1 RA or dual GIP/GLP-1 RA, duration of use of GLP-1 RA or dual GIP/GLP-1 RA, weight, body mass index (BMI), HbA1c, and change in total daily dose of SU and total daily dose of insulin from the visit when the GLP-1 RA or GIP/GLP-1 RA was initiated to the most recent visit after initiation.

Means and SDs were used to summarize continuous variables, and frequencies and percentages were used for categorical variables. Paired *t* tests were used to evaluate the differences in continuous variables before and after treatment. A value of $p<0.05$ was considered to be statistically significant. Analyses were completed using IBM SPSS Statistics for Windows V.27 (IBM Corp, Armonk, New York, USA) and GraphPad Prism V.10.2.1 (GraphPad Software, San Diego, California, USA).

Table 1 Demographics, duration, and type of treatment

Characteristics	N (%) or mean±SD
Age (years)	39.5±15.1
Sex	
Male	2 (20%)
Female	8 (80%)
Race and ethnicity	
Non-Hispanic white	9 (90%)
Non-Hispanic black	0
Hispanic white	1 (10%)
Asian or Pacific Islander	0
Unknown/other	0
Type of GLP-1 RA or dual GIP/GLP-1 RA	
Liraglutide (Victoza)	1 (10%)
Dulaglutide (Trulicity)	2 (20%)
Semaglutide (Ozempic, Rybelsus)	4 (40%)
Tirzepatide (Mounjaro)	3 (30%)
Months of GLP-1 RA or dual GIP/GLP-1 RA use	21.4±16.3
Metformin	6 (60%)

GIP, glucose insulinotropic polypeptide; GLP-1 RA, glucagon-like peptide-1 receptor agonist.

Data and resource availability

Deidentified data are available from the corresponding author on request with appropriate justification.

RESULTS

Baseline characteristics of the study population (n=10; 4 HNF1A-MODY, 4 HNF4A-MODY, 1 HNF1B-MODY, 1 ABCC8-MODY) are shown in table 1. The study cohort was predominantly non-Hispanic white, with BMIs mostly in the overweight or obese range. Semaglutide was the most frequently prescribed GLP-1 RA, and tirzepatide was the only dual GIP/GLP-1 RA agent prescribed.

The average age was 39.5±15.1 years, and 80% of patients were female. The mean duration of treatment with GLP-1 RA or dual GIP/GLP-1 RA was 21.4±16.3 months (table 1). Type of GLP-1 RA or dual GIP/GLP-1 RA, duration of treatment, and changes in average Hemoglobin A1c (HbA1c), Body Mass Index (BMI), and sulfonylurea

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Table 2 Patients with MODY treatment

Adult or pediatric and age range	Race/ethnicity	Gene	BMI baseline	BMI after treatment (and change)	HbA1c (baseline)	HbA1c after GLP-1 RA+SU treatment (% change)	Type of GLP-1 RA, or dual GIP/GLP-1 RA: dose, and administration	Duration of treatment	Change in SU dose in (milligrams and % change compared with baseline)	Other medications (and changes)
Adult patient in 40s	Non-Hispanic white	Heterozygous *HNF1A* pathogenic variant, c.608G>A (p.Arg203His) NM_000545.5	27.8 kg/m^2	25.5 kg/m^2 (–2.3 kg/m^2)	7.4%	5.2% (–2.2%)	Oral semaglutide 7 mg once daily (1 month at 3 mg titration dose)	29.8 months	Glimepiride 8 mg/day → 2 mg/day (75% reduction)	N/A
Adult patient in 50s	Non-Hispanic white	Heterozygous *HNF1A* pathogenic variant, c.1541del (p.His514Profs*17) NM_000545.5	30.6 kg/m^2	27.9 kg/m^2 (–2.7 kg/m^2)	7.7%	6.8% (–0.9%)	Subcutaneous dulaglutide 3 mg once weekly (3 months on 3 mg; previously on 1.5 mg for 51 months)	54.7 mos	Glipizide IR 15 mg/day to Glipizide 2.5 mg ER once daily (83.3% reduction)	Metformin 1000 mg twice daily continued, sitagliptin 100 mg daily (stopped)
Adult patient in 50s	Non-Hispanic white	Heterozygous *HNF1A* pathogenic variant, c.1108–2A>G (IVS5-2A>G) P-pedigree	20.8 kg/m^2	17.7 kg/m^{2*} (–3.1 kg/m^2)	8.2%	7.0% (–1.2%)	Subcutaneous semaglutide (0.5 mg once weekly)	18.1 months	Glipizide 15 mg/day (5 mg XR + 10 mg IR) → 10 mg/day (5 mg XR + 5 mg IR) (25% reduction)	Metformin 500 mg twice daily continued
Adult patient in 40s	Non-Hispanic white	Heterozygous *HNF4A* pathogenic variant, c.268C>T(p.Gln268Ter (Q268X))	32.3 kg/m^2	30.9 kg/m^2 (–1.6 kg/m^2)	7.6%	7.0% (–0.6%)	Subcutaneous dulaglutide (1.5 mg once weekly)	47.5 months	Glipizide 20 mg/day → Glipizide ER 10 mg/day (50% reduction)	Metformin 1000 mg twice daily continued
Pediatric patient in teens	Non-Hispanic white	Heterozygous *HNF4A* pathogenic variant, c.270C>G (p.Cys90Trp)	26.0 kg/m^2	21.0 kg/m^2 (–5.0 kg/m^2)	7.9%	6.1 (–1.8%)	Subcutaneous semaglutide (0.5 mg once weekly)	7 months	Glyburide 1.25 mg once daily → discontinued	N/A
Adult patient in 20s	Non-Hispanic white	Heterozygous *ABCC8* pathogenic variant, c.4174T>G (p.Phe1392Val)	32.7 kg/m^2	31.6 kg/m^2 (–1.1 kg/m^2)	8%	6.8% (–1.2%)	Subcutaneous liraglutide ramp up (0.6 mg daily x 1 week, 1.2 mg daily × 1 week, with final dose of 1.8 mg daily)	6 months	None	Metformin 500 mg in the AM and 1000 mg in the PM
Adult patient in 20s	Non-Hispanic white	arr17q12(32221569–33606246)x1 (hg18, NCBI36) including *HNF1B*	20.5 kg/m^2	19.3 kg/m^2 (–1.2 kg/m^2)	7.4%	5.6% (–1.8%)	Semaglutide ramp up (3 mg daily × 1 month, final dose of 7 mg daily)	10 months	N/A	N/A
Adult patient in 50s	Non-Hispanic white	Heterozygous *HNF1A* pathogenic variant, c.955+1G>A	29.8 kg/m^2	21.4 kg/m^2 (–8.4 kg/m^2)	9.5%	6.4% (–3.1%)	Subcutaneous tirzepatide 5 mg once weekly	15 months	Glipizide 5 mg/day → discontinued Insulin 19 units total daily dose (0.23 units/kg/day) → 18 units total daily dose (0.3 units/kg/day)	Metformin ER 1000 mg twice daily continued

Continued

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Table 2 Continued

Adult or pediatric and age range	Race/ethnicity	Gene	BMI baseline	BMI after treatment (and change)	HbA1c (baseline)	HbA1c after GLP-1 RA+SU treatment (% change)	Type of GLP-1 RA, or dual GIP/GLP-1 RA: dose, and administration	Duration of treatment	Change in SU dose in (milligrams and % change compared with baseline)	Other medications (and changes)
Adult patient in 30s	Hispanic white	Heterozygous *HNF4A* pathogenic variant, c.418C>T(p.Arg140X)	33.6 kg/m^2	26.2 kg/m^2 (−7.4 kg/m^2)	7.3%	5.9% (−1.4%)	Subcutaneous tirzepatide 7.5 mg once weekly	10 months	Glipizide 5 mg/day → discontinued Insulin 65 units per day (0.75 units/kg/day) → 35 units per day (0.52 units/kg/day)	N/A
Adult patient in 40s	Non-Hispanic white	Heterozygous *HNF4A* pathogenic variant, c.268C>T(p.Gln268Ter (Q268X))	37.4 kg/m^2	27.0 kg/m^2 (−10.4 kg/m^2)	6.7%	5.7% (−0.9%)	Subcutaneous tirzepatide 12.5 mg once weekly	16 months	Insulin 36 units total daily dose → discontinued Metformin 1000 mg twice daily → discontinued	N/A

*Of note: patient counseled regarding weight loss; dose of GLP-1 RA reduced, and nutrition referral discussed.
ABCC8, ATP-binding cassette transporter subfamily C member 8; BMI, body mass index; GIP, glucose insulinotropic polypeptide; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HNF1A, hepatocyte nuclear factor-1α; HNF4A, hepatocyte nuclear factor-4α; HNF1B, hepatocyte nuclear factor-1β; MODY, maturity-onset diabetes of the young; SU, sulfonylurea .

(SU) dose are shown in table 2. In patients with HNF1A-MODY and HNF4A-MODY treated with GLP-1 RA (n=5), there was a statistically significant decrease in HbA1c of 1.3% (95% CI 0.5% to 2.2%, p=0.010), in BMI of 2.9 kg/m^2 (95% CI 1.3 to 4.6, p=0.008), and a 66.6% reduction in total daily SU dose (95% CI 33.9% to 99.4%, p=0.005) (figure 1A–C). In patients with HNF1A-MODY and HNF4A-MODY treated with dual GIP/GLP-1 RA (n=3), there was a non-statistically significant decrease in HbA1c of 1.8% (95% CI −0.9% to 4.6%, p=0.104), a statistically significant reduction in BMI of 8.7 kg/m^2 (95% CI 4.9 to 12.5, p=0.010). Two patients discontinued SU, and a third patient discontinued insulin (36 units in total) (figure 2A,B). In ABCC8-MODY, GLP-1 RA led to a 1.2% reduction in HbA1c and a BMI reduction of 1.1 kg/m^2. In HNF1B-MODY, GLP-1 RA led to a 1.8% reduction in HbA1c and a BMI reduction of 1.2 kg/m^2. Notably, both the patients with ABCC8-MODY and HNF1B-MODY did not require treatment with SU or insulin.

All the patients treated with tirzepatide were able to discontinue SU, and reduce or discontinue insulin. There were mild GI adverse effects (nausea (n=1), diarrhea (n=1), and constipation (n=1)) reported in patients who were taking semaglutide 1 mg once weekly and tirzepatide 7.5 mg and 10 mg, respectively, which led to dose reductions (with return to the previous tolerated dose). No severe adverse events, pancreatitis, or hospitalizations were reported.

DISCUSSION

This descriptive case series evaluated real-world treatment response to GLP-1 RA and dual GIP/GLP-1 RA in patients with HNF1A-MODY, HNF4A-MODY, HNF1B-MODY, and ABCC8-MODY. In patients with HNF1A-MODY and HNF4A-MODY, GLP-1 RA use led to statistically significant reductions in HbA1c by an average of 1.3%, BMI by 2.9 kg/m^2, total daily SU dose by 66.6%. Dual GIP/GLP-1 RA significantly reduced BMI by 8.7 kg/m^2 and reduced HbA1c by a non-statistically significant 1.8%. Two patients discontinued SU, and one patient discontinued insulin use (36 units in total discontinued). These results expand our knowledge of the impact of GLP-1 RA and dual GIP/GLP-1 RA use in HNF1A-MODY and HNF4A-MODY.[10–14]

A previous 6-week randomized order, double-blind, cross-over trial of 16 patients with HNF1A diabetes (HNF1A-MODY) demonstrated that treatment with both liraglutide (a GLP-1 RA) and glimepiride (a SU) lowered fasting glucose levels and postprandial glycemic excursions. Liraglutide demonstrated effectiveness in comparison to glimepiride, but glimepiride was associated with more hypoglycemia than liraglutide.[11] The study did not evaluate other clinical parameters in HNF1A-MODY or HNF4A-MODY, such as HbA1c, SU dose reduction, or weight, which were later described in case reports.[12–14] The impact of dual GIP/GLP-1 use in HNF1A-MODY and HNF4A-MODY has not been investigated in a randomized

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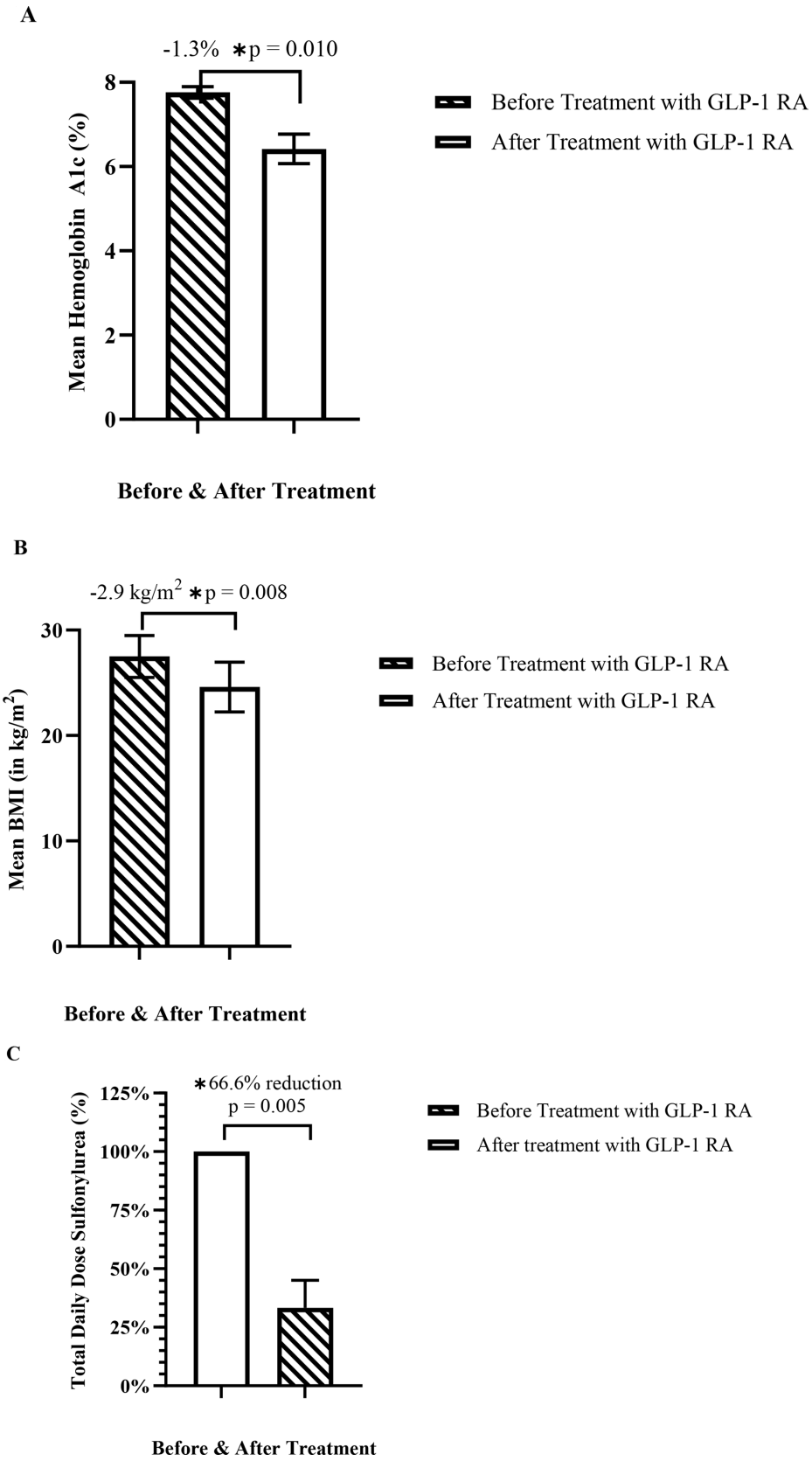


Figure 1 Change in HbA1c (A), Change in BMI (B), and Change in Percent of Total Daily Sulfonylurea Dose Before and After Treatment with GLP-1 RA in HNF1A-MODY and HNF4A-MODY. BMI, body mass index; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HNF1A, hepatocyte nuclear factor-1α; HNF4A, hepatocyte nuclear factor-4α, MODY, maturity-onset diabetes of the young.

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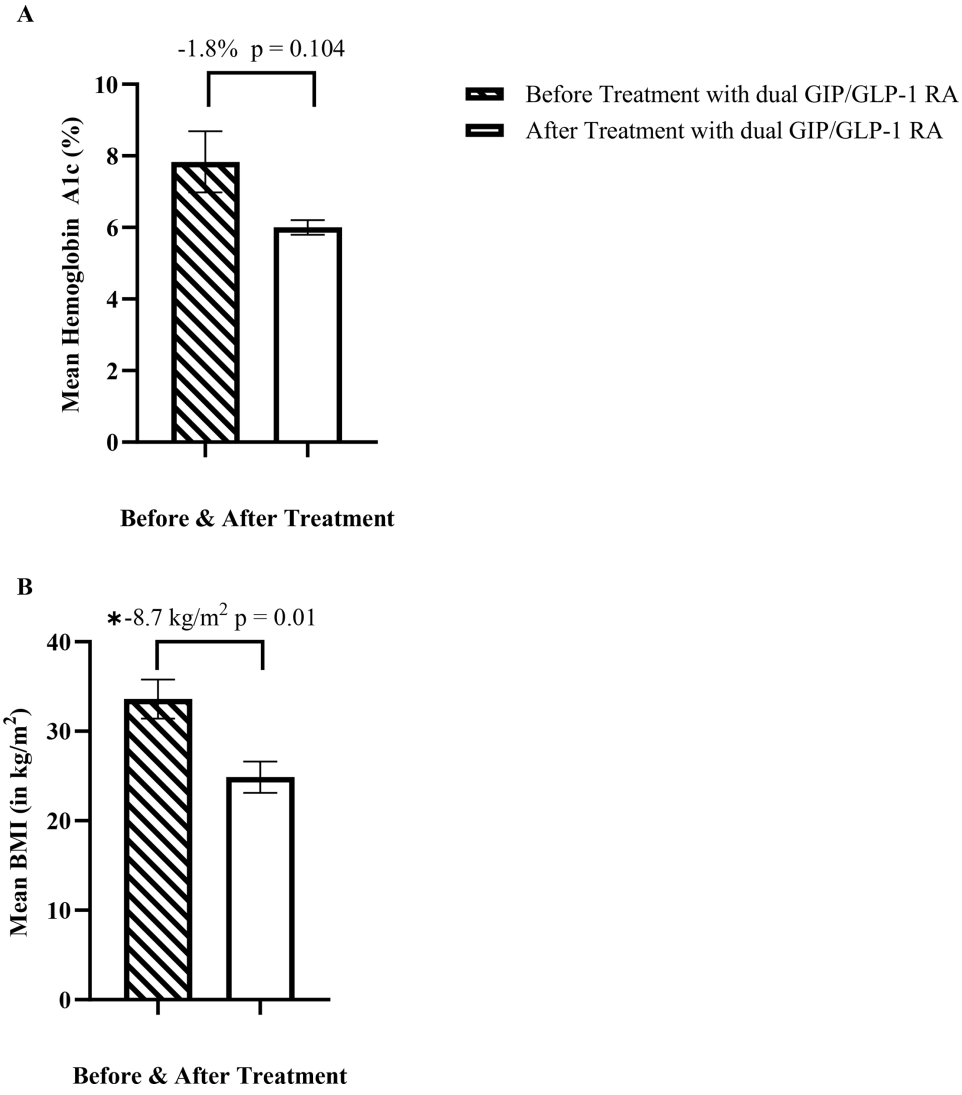


Figure 2 Change in HbA1c (A), change in BMI (B) before and after treatment with dual GIP/GLP-1 RA in HNF1A-MODY and HNF4A-MODY. BMI, body mass index; GIP, glucose insulinotropic polypeptide; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HNF1A, hepatocyte nuclear factor-1α; HNF4A, hepatocyte nuclear factor-4α; MODY, maturity-onset diabetes of the young.

controlled trial to date (except for mechanistically in HNF1A-MODY carriers).[15] Our findings suggest a potential role for these agents in this population. Previous case reports demonstrated lower HbA1c levels, weight, and insulin requirements with GLP-1 RA and dual GIP/GLP-1 RA in HNF1A-MODY and HNF4A-MODY,[12–14] but these reports did not offer comparisons across a larger cohort, nor did they have sufficient numbers for statistical analyses. Decreases or discontinuation of SUs in patients with different forms of MODY highlight the potential role of dual GIP/GLP-1 for clinical use as an alternative therapy in patients who become unresponsive to SUs and in patients with obesity.

The strengths of this study include the use of GLP-1 RAs and dual GIP/GLP-1 RAs in a real-world setting in patients with HNF1A-MODY, HNF4A-MODY, HNF1B-MODY, and ABCC8-MODY with follow-up of 21.4 months from two large academic tertiary referral centers. Weaknesses include the descriptive study design (case series), lack of controls for comparison, and the use of other antihyperglycemic medications (metformin in 60% of the cohort). Additionally, there were only three patients treated with the dual GIP/GLP-1 RA, which limited the power of analyses (HbA1c, SU dose reduction) and led to a lack of statistical significance in these findings. It is likely that the reductions in HbA1c and SU dose would have been statistically significant if more patients were studied given these large changes in comparison to the GLP-1 RA group. Other important measures, including hypoglycemia frequency, hypoglycemia severity, and lipid profiles, were not available for assessment.

In conclusion, GLP-1 RA treatment in patients with HNF1A-MODY and HNF4A-MODY has produced statistically and clinically significant reductions in HbA1c, BMI, and SU dose requirements. GLP-1 RA use also produced clinically significant reductions in HbA1c and BMI in ABCC8-MODY and HNF1B-MODY without use

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of SU or insulin in two cases. Dual GIP/GLP-1 RA treatment in patients with HNF1A-MODY and HNF4A-MODY produced statistically significant reductions in BMI and clinically meaningful reductions in HbA1c and SU doses. These findings warrant further validation in a randomized controlled trial.

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Patient consent for publication Not applicable.

Ethics approval This study involves human participants. This study was reviewed and approved by the Institutional Review Boards at the University of Michigan (IRB Med approval no. HUM#00233892) and Cincinnati Children's Hospital Medical Center (IRB approval no. 2022–0802) and performed according to the principles of the Declaration of Helsinki. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Deidentified data are available from the corresponding author upon request with appropriate justification.

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REFERENCES

1 Kavvoura FK, Owen KR. Maturity onset diabetes of the young: clinical characteristics, diagnosis and management. *Pediatr Endocrinol Rev* 2012;10:234–42.
2 Hoffman LS, Jialal I. *Diabetes, Maturity Onset in the Young (Mody)*. StatPearls:StatPearls Publishing, 2019. Available: https://www.ncbi.nlm.nih.gov/books/NBK532900/1
3 Pearson ER, Velho G, Clark P, *et al*. beta-cell genes and diabetes: quantitative and qualitative differences in the pathophysiology of hepatic nuclear factor-1alpha and glucokinase mutations. *Diabetes* 2001;50 Suppl 1:S101–7.
4 Wang H, Maechler P, Hagenfeldt KA, *et al*. Dominant-negative suppression of HNF-1alpha function results in defective insulin gene transcription and impaired metabolism-secretion coupling in a pancreatic beta-cell line. *EMBO J* 1998;17:6701–13.
5 Wollheim CB. Beta-cell mitochondria in the regulation of insulin secretion: a new culprit in type II diabetes. *Diabetologia* 2000;43:265–77.
6 Pearson ER, Starkey BJ, Powell RJ, *et al*. Genetic cause of hyperglycaemia and response to treatment in diabetes. *Lancet* 2003;362:1275–81.
7 Hansen T, Eiberg H, Rouard M, *et al*. Novel MODY3 mutations in the hepatocyte nuclear factor-1alpha gene: evidence for a hyperexcitability of pancreatic beta-cells to intravenous secretagogues in a glucose-tolerant carrier of a P447L mutation. *Diabetes* 1997;46:726–30.
8 Fajans SS, Brown MB. Administration of sulfonylureas can increase glucose-induced insulin secretion for decades in patients with maturity-onset diabetes of the young. *Diabetes Care* 1993;16:1254–61.
9 Fajans SS, Bell GI. MODY. *Diabetes Care* 2011;34:1878–84.
10 Docena MK, Faiman C, Stanley CM, *et al*. Mody-3: Novel HNF1A Mutation and the Utility of Glucagon-Like Peptide (GLP)-1 Receptor Agonist Therapy. *Endocr Pract* 2014;20:107–11.
11 Østoft SH, Bagger JI, Hansen T, *et al*. Glucose-lowering effects and low risk of hypoglycemia in patients with maturity-onset diabetes of the young when treated with a GLP-1 receptor agonist: a double-blind, randomized, crossover trial. *Diabetes Care* 2014;37:1797–805.
12 Tyler Broome D. SAT085 Oral Glucagon-like Peptide-1 Receptor Agonist As Adjuvant Treatment In HNF1A-MODY. *Journal of the Endocrine Society* 2023;7.
13 Broome DT, Tekin Z, Pantalone KM, *et al*. Novel Use of GLP-1 Receptor Agonist Therapy in HNF4A-MODY. *Diabetes Care* 2020;43:e65.
14 Broome DT, Mehdi A, Chase C, *et al*. Use of a Dual GIP/GLP-1 Receptor Agonist in HNF1A-MODY and HNF4A-MODY. *Diabetes Care* 2024;47:e65–6.
15 Christensen AS, Hædersdal S, Storgaard H, *et al*. GIP and GLP-1 Potentiate Sulfonylurea-Induced Insulin Secretion in Hepatocyte Nuclear Factor 1α Mutation Carriers. *Diabetes* 2020;69:1989–2002.

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