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Maturity-Onset Diabetes of the Young (MODY) With HNF1B p.Glu105Lys Mutation Achieving Significant Insulin Reduction on Tirzepatide: A Case Report

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ABSTRACT

This report describes the first case of maturity-onset diabetes in young (MODY) with HNF1B mutation started administration of the dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist, tirzepatide. A 26-year-old female with a 15-year history of diabetes mellitus was diagnosed with MODY, which is characterized by decreased insulin secretion. She was treated with tirzepatide, which significantly improved her glycemic management; insulin secretion increased the fasting serum C-peptide immunoreactivity from 0.36 to 1.09 ng/mL. The patient discontinued glimepiride, and her total daily insulin dose was reduced from 88 to 4 units. This report highlights the glucose-lowering effects of tirzepatide in a patient with MODY who has the HNF1B p.Glu105Lys mutation.

1 | Introduction

Maturity-onset diabetes of the young (MODY) is inherited in an autosomal dominant pattern and is characterized by diabetes onset in lean individuals before the age of 25 [1]. Hepatocyte nuclear factor 1 B (HNF1B) is a transcription factor involved in kidney, liver, and pancreas organogenesis. The phenotype of HNF1B mutation has extreme diversity (renal cysts, renal dysplasia, gonadal dysgenesis, pancreatic hypoplasia, and liver function abnormalities), and even family members with the same HNF1B mutation show different phenotypes [2, 3]. Japanese patients with HNF1B-MODY show early-onset pancreatic β-cell dysfunction, and therefore, they often require insulin therapy [4]. Tirzepatide is a novel glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist (RA) that enhances insulin sensitivity, beta-cell function, and glycemic management compared to selective GLP-1RAs [5]. Here, we report the first case of MODY who has the HNF1B p.Glu105Lys mutation successfully treated with tirzepatide.

2 | Case Report

A 26-year-old woman was diagnosed with diabetes mellitus at age 11 following a glucose tolerance test. At age 21, genetic analysis revealed a heterozygous missense mutation, NM_000458. 4: c.313G>A (NP_000449. 1: p. Glu105Lys), in exon 1 of *HNF1B* in both the patient and her father, consistent with MODY. Figure 1 shows the family tree. She occasionally had mildly elevated ALT levels; abdominal ultrasonography and computed

Summary

- This report describes the first known case of maturity-onset diabetes of the young (MODY) with an HNF1B mutation where treatment was initiated using the dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist, tirzepatide.

tomography (CT) scan revealed a kidney stone and a fatty liver but no other anomalies.

3 | Methods

Her treatment history before tirzepatide initiation, HbA1c levels, and glucagon stimulation test (GST) results are shown in Figure 2. Initially, her HbA1c levels remained in the 7% range until the age of 16 with glimepiride therapy but gradually worsened. At age 20, while receiving glimepiride and sitagliptin, her fasting serum C-peptide immunoreactivity (CPR) was 2.55 ng/mL, with a 6-min CPR of 2.94 ng/mL and a 6-min post-glucagon increment in CPR (ΔCPR) of 0.39 ng/mL. Liraglutide returned HbA1c levels to the 7% range, but severe nausea limited its dosage to 0.9 mg/day. At age 22, she started multiple daily insulin injections. By age 25, her insulin secretion had remarkably declined (fasting CPR 0.91 ng/mL), necessitating increased insulin doses. At age 26, a sodium-glucose cotransporter-2 inhibitor was added. Despite these measures, her glycemic management remained poor, and she declined further medications, subsequently developing retinal hemorrhages from diabetic retinopathy. Therefore, liraglutide was replaced with tirzepatide.

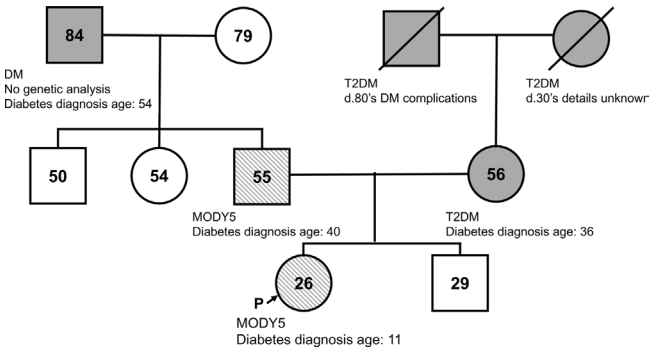

FIGURE 1 | Patient family tree. Males and females are indicated by squares and circles, respectively. Numbers inside these shapes indicate age. Diagonal line pattern symbols represent HNF1B mutation, whereas filled symbols denote diabetes mellitus. A diagonal line indicates death. DM, diabetes mellitus; MODY, maturity-onset diabetes of young; T2DM, type 2 diabetes mellitus.

4 | Conclusion and Results

Before starting tirzepatide, she was taking multiple oral hypoglycemic agents, 62 units insulin aspart, and 26 units insulin degludec per day; her ΔCPR measured by GST was 0.77 ng/mL (increasing from 0.36 to 1.13 ng/mL) (Figure 3A). A ΔCPR of 2.0 ng/mL or higher indicates preserved endogenous insulin secretion. Body composition was as follows: body weight, 55.8 kg; body mass index, 22.4 kg/m^2; body fat percentage, 29.6%; muscle mass, 36.1 kg. Thirty days prior to tirzepatide initiation, a real-time continuous glucose monitoring (rtCGM) system (Dexcom G6, TERUMO, Tokyo, Japan) revealed that the patient's average glucose level was 279 mg/dL, the time percentage in the target range (TIR, within 70–180 mg/dL) was 18%, and the time percentage above range (TAR, above 180 mg/dL) was 82% (Figure 3A). One month after tirzepatide initiation (one 2.5 mg injection per week for 4 weeks), she was also taking 10 mg dapagliflozin, 500 mg metformin, 15 units insulin aspart, and 5 units insulin degludec daily, including tirzepatide. The rtCGM revealed an average glucose level of 162 mg/dL, decreased TAR, and increased TIR (Figure 3B). The GST demonstrated an increase in fasting CPR from 0.36 to 1.00 ng/mL (Figure 3B). Body composition analysis showed that her weight was 54.8 kg, body mass index

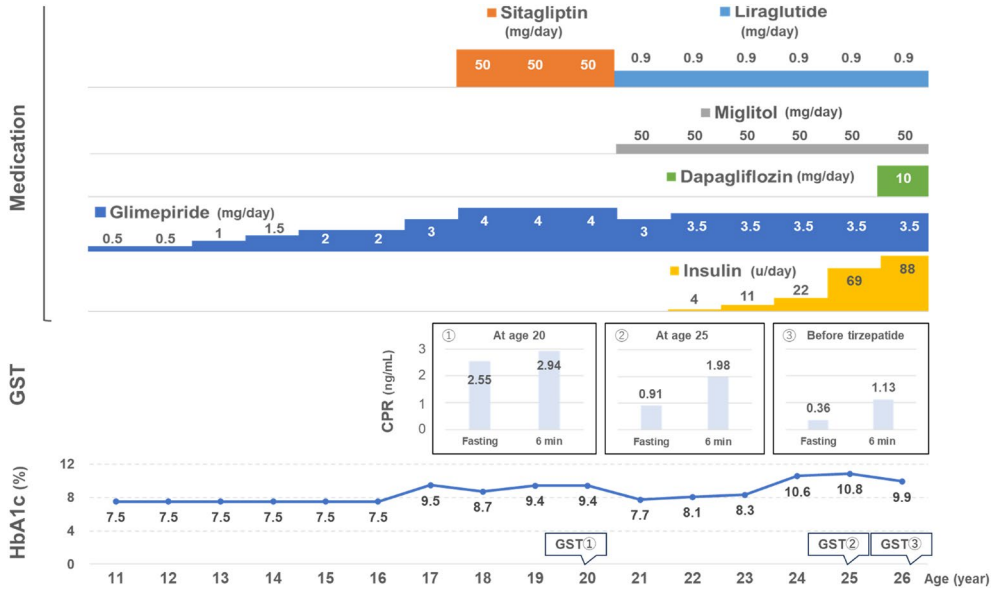

FIGURE 2 | A description of the treatment, results from the glucagon stimulation test (GST), and HbA1c levels (%).

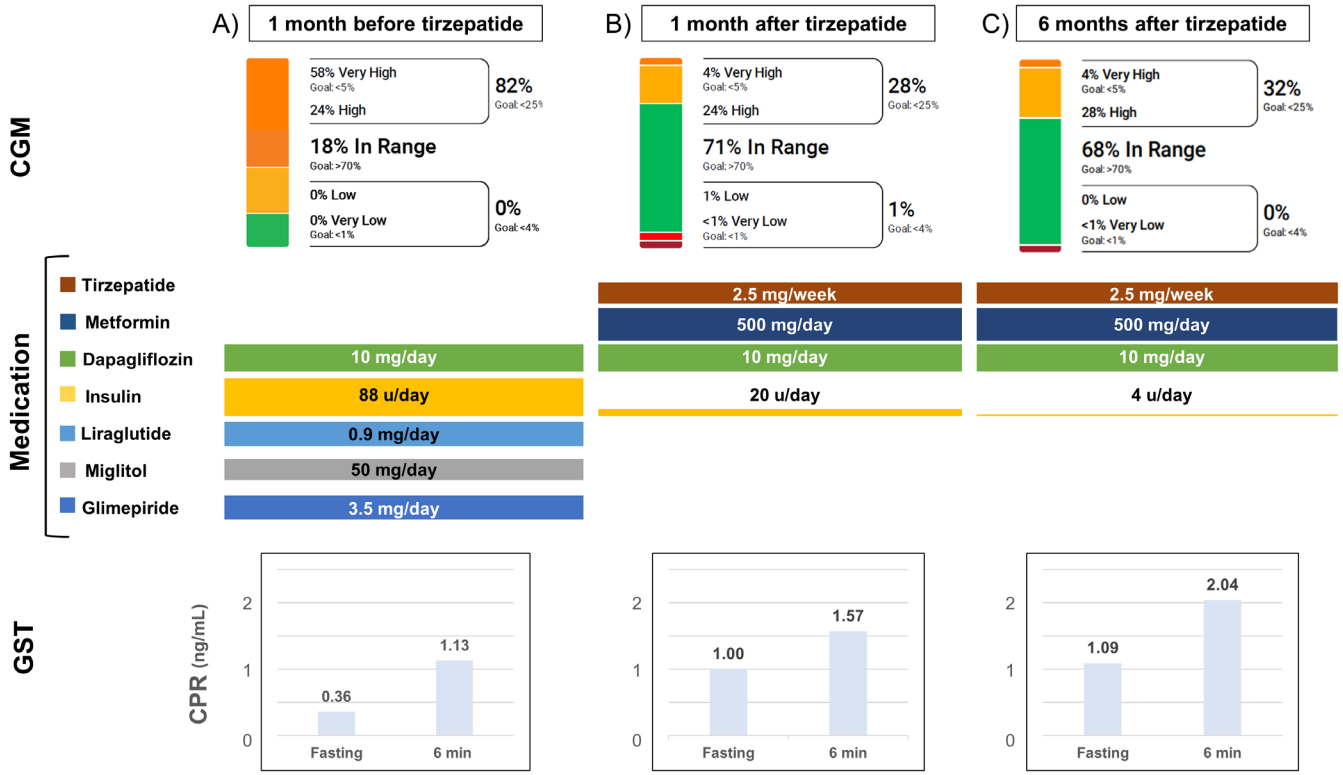

FIGURE 3 | Before and after tirzepatide administration. (A) Body weight (BW), Time in range (TIR), a description of the treatment, results from the GST prior to tirzepatide initiation. (B) BW, TIR, a description of the treatment, results from the GST 1 month after tirzepatide initiation. (C) BW, TIR, a description of the treatment, results from the GST 6 months after tirzepatide initiation.

TABLE 1 | Laboratory findings before and after tirzepatide treatment.

		Before tirzepatide	1 month after	6 months after
CPR	(ng/mL)	0.36	1.00	1.09
HbA1c	(%)	10.5	8.3	7.2
GAD Ab	(IU/mL)	< 5.0		
IAA	(IU/mL)	< 0.4		
AST	(U/L)	15	12	13
ALT	(U/L)	13	10	8
γGTP	(U/L)	20	14	15
ChE	(U/L)	448	386	393
Cr	(mg/dL)	0.58	0.54	0.47
eGFR	(mL/min/1.73 m^2)	102.1	110.4	128.55
TC	(mg/dL)	202	126	205
LDL-c	(mg/dL)	120	60	135
HDL-c	(mg/dL)	68	56	56
TG	(mg/dL)	80	80	101
Urine ketone		(–)		(–)
UACR	(mg/gCre)	8.5		

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ChE, cholinesterase; CPR, C-peptide immunoreactivity; Cr, creatinine; eGFR, epidermal growth factor receptor; GAD-Ab, glutamic acid decarboxylase antibody; GST, glucagon stimulation test; HDL-c, high-density lipoprotein-cholesterol; IAA, insulin autoantibody; LDL-c, low-density lipoprotein-cholesterol; PG, plasma glucose; TC, total cholesterol; TG, triglyceride; UACR, urine albumin-to-creatinine ratio; γGTP, γ-glutamyl transpeptidase.

was 22.0 kg/m^2, body fat percentage was 28.8%, and muscle mass was 35.9 kg. Six months after tirzepatide, she was also taking 10 mg dapagliflozin, 500 mg metformin, and 4 units insulin lispro mix 50 daily, excluding tirzepatide. The rtCGM recorded her average glucose at 162 mg/dL with TIR and TAR percentages of 68% and 32%, respectively (Figure 3C). The GST demonstrated an increase in the ΔCPR of 0.95 ng/mL (from 1.09 to 2.04 ng/mL) (Figure 3C). Body composition analysis showed that her weight was 49.4 kg, body mass index was 19.8 kg/m^2, body fat percentage was 24.7%, and muscle mass was 34.4 kg. Laboratory findings before and after tirzepatide treatment are shown in Table 1. Following treatment initiation, she experienced mild abdominal distention but no nausea or vomiting.

5 | Discussion

In this case, switching from liraglutide to tirzepatide remarkably improved glycemic management, reduced insulin requirements, and allowed for the discontinuation of glimepiride. The initiation of tirzepatide increased the fasting CPR from 0.36 to 1.09 ng/mL and the ΔCPR from 0.77 to 0.95 ng/mL, indicating enhanced insulin secretion.

This case presented with typical clinical features of MODY, including the onset of diabetes at the young age of 11 despite being non-obese and a significant reduction in insulin secretion by the age of 26 [6]. The correlation between HNF1B genotype and phenotype is unclear, but the phenotype is clinically distinct even among family members with the same variant [7]. In this case, her father, who has the same HNF1B mutation, has renal cysts; however, she does not. Cases without renal morphologic abnormalities in HNF1B-related MODY have also been reported [8]. In addition, approximately 13% of patients with normal renal function at diabetes onset show a decline in renal function after 15 years of follow-up [9], and renal function is reported to decline gradually throughout adulthood [10]. In this case, there was no evidence of abnormal renal morphology, and the renal function was in the normal range; however, the possibility of renal function deterioration in the future could not be denied. The HNF1B score for this patient was 8 points with family history (2 points), presence of diabetes (4 points), and abnormal liver function (2 points), which is the cutoff value for genetic analysis [11]. The American College of Medical Genetics (ACMG) classification [12] was based on weighted pathogenicity criteria, and the p.Glu105Lys mutation was associated with moderate evidence of pathogenicity (PM) and supporting evidence of pathogenicity (PP). Located in exon 1 of the HNF1β gene, this mutation was classified under PM1 (mutations present in hotspots or functional domains and not meeting benign criteria), as it is located in a critical and well-established functional domain. Its allele frequency in the Genome Aggregation Database (gnomAD, https://gnomad.broadinstitute.org/) is extremely low at 0.0000635229, fulfilling the PM2 criterion (absent from controls or at an extremely low frequency). In silico analysis suggests that the p.Glu105Lys mutation is likely pathogenic, meeting the PP3 criterion (multiple lines of computational evidence support a deleterious effect on the gene or gene product). In the ACMG classification, the p.Glu105Lys mutation met the criteria for PM1, PM2, and PP3 and was categorized as a Variant of Uncertain Significance (VUS). However, the p.Glu105Lys mutation co-segregated between the affected patient and the father, satisfying the PP1 criterion (co-segregation with disease in multiple affected family members in a gene definitively known to cause the disease). Additionally, the patient's phenotype and family history, which are specific for MODY, support the PP4 criterion (the patient's phenotype or family history is highly specific for a disease with a single genetic etiology). It was considered to also meet the criteria for PP1 and PP4. Furthermore, according to Horikawa et al., the p.Glu105Lys mutation in this case is a major MODY5 gene mutation [13]. Therefore, the p.Glu105Lys mutation is likely associated with the pathology of this case.

Previous reports have indicated the presence of the same genetic mutation as seen in this case, with cases of diabetes or persistent hyperglycemia being reported in patients with this mutation, ranging from 6 months to 18 years old [14]. Additionally, there is a report of an 8.9-year-old patient who developed renal cysts, vesicoureteral reflux, and significant renal function decline [15]. Another case reported bilateral polycystic kidneys, as well as elevated creatinine and uric acid levels in a patient with the same genetic mutation [16]. Even with the same HNF1B mutation, the phenotypes are diverse, and there are differences in clinical phenotypes even within the same family, suggesting the presence of other phenotype-modifying factors [6]. The mechanisms for differences in clinical phenotype even with the same HNF1B mutation have not been fully elucidated; however, genetic or environmental factors may influence these variations. In a previous report, one patient with the same HNF1B mutation had normal renal function but developed diabetes, while the other patient developed renal failure but did not develop diabetes, showing different phenotypes. One possible reason for this is that differences in the HNF1A gene may have affected the phenotype of the HNF1B mutation [17]. The cooperation between HNF1A and HNF1B is prominent in the human insulin gene promoter, and a lack of this cooperation has been observed in HNF1B mutations (H153N, E101X, R177X). This lack of cooperative action between HNF1B mutants and HNF1A at the human insulin gene promoter has been suggested as a possible cause of defective insulin secretion [18]. We cannot rule out that this lack of cooperative action may have affected the pathophysiology in this case as well.

In this patient, the ΔCPR was 0.77 ng/mL (from 0.36 to 1.13 ng/mL) on GST before tirzepatide and improved to 0.95 ng/mL (from 1.09 to 2.04 ng/mL) 6 months after treatment. The enhancement of insulin secretion by tirzepatide is reported to be mediated by both GLP-1 and GIP receptors [19]. In addition, a human study comparing insulin secretion after 28 weeks of tirzepatide and semaglutide administration showed that tirzepatide significantly increased insulin secretion compared to semaglutide. Moreover, the disposition index—a measure of the compensatory capacity of pancreatic beta cells against insulin resistance—demonstrated significant improvement in the tirzepatide group [20].

In this case, fatty liver was observed on abdominal ultrasound before tirzepatide administration. Studies have reported that GIP transgenic mice demonstrate decreased hepatic fat accumulation and reduced immune cell infiltration into adipose tissue [21]. Furthermore, in diet-induced obesity model mice,

long-term treatment with GIP significantly raised the liver pAkt/Akt ratio and improved hepatic insulin sensitivity [22]. Similarly, tirzepatide has been shown to reduce liver fat content [23] and improve hepatic insulin resistance in humans. The effect of tirzepatide on the liver may have contributed to improved glycemic management in this case.

In this case, TIR improved from 18% to 71%, and the daily insulin dose was reduced from 88 to 20 units (Figure 3A,B). The weight of the patient gradually decreased during the first 4 months after starting tirzepatide, resulting in a weight loss of 6.4 kg (11%). However, no further reduction was observed after the fifth month. This weight loss may have been due, in part, to the decrease in daily insulin dosage from 88 to 4 units, as long-term administration of tirzepatide has been reported to gradually cause moderate weight changes [24]. In addition, even though this patient was not obese before starting tirzepatide, her glycemic management was markedly improved. The hypoglycemic effect of tirzepatide has also been observed in patients with type 2 diabetes with a BMI of less than 25 before administration [25]. Tirzepatide showed a significantly greater effect on weight loss compared to that of GLP-1 RAs, but no significant difference was found in the incidence of gastrointestinal adverse events [26]. The weight loss to a BMI < 20 is concerning and the patient will be followed for long term effects.

Treatment of MODY has been adjusted according to the identified genetic mutation, but glucose-induced insulin secretion decreased over time despite treatment with sulfonylureas [27]. Although case reports were included, previous reports have shown the therapeutic effect of GLP-1 RAs in MODY3, MODY1, and MODY5 [28–30]. In the present case, liraglutide was added when insulin secretion was maintained and showed a hypoglycemic effect, but the effect waned as insulin secretion decreased. Tirzepatide showed a hypoglycemic effect in the patient even with decreased insulin secretion and improved insulin secretion. This suggests that tirzepatide may be an alternative treatment option to insulin in patients with MODY.

A limitation of this study is that the long-term effects of tirzepatide have not been evaluated. Thus, further investigation into the efficacy of tirzepatide in multiple cases of MODY is necessary.

We report a remarkable improvement of glycemic management in a patient with MODY who has the HNF1B p.Glu105Lys mutation following treatment with tirzepatide. To our knowledge, this is the first documented instance demonstrating the efficacy of tirzepatide in a patient with MODY. Our findings suggest that tirzepatide may be effective in patients with MODY, particularly those who exhibit reduced insulin secretion.

Author Contributions

Mihiro Sue: writing – original draft. **Mayu Watanabe:** writing – original draft, writing – review and editing. **Ayumi Inoue:** data curation. **Akihiro Katayama:** data curation, supervision. **Sanae Teshigawara:** data curation. **Yuichi Matsushita:** data curation. **Masaya Takeda:** supervision. **Izumi Iseda:** supervision. **Jun Eguchi:** supervision, writing – review and editing. **Kazuyuki Hida:** supervision.

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Ethics Statement

The authors have nothing to report.

Consent

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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