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Case Report

A Woman With *HNF1A*-Associated Monogenic Diabetes Treated Successfully With Repaglinide Monotherapy

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ABSTRACT

Background/Objective: Monogenic diabetes is a rare type of diabetes that is commonly misdiagnosed as type 1 or 2 diabetes mellitus, which adversely impacts patient care. Such cases are particularly challenging given the heterogeneity in presentation and overlap with other types of diabetes. As the sole use of meglitinides, especially repaglinide, to treat *HNF1A*-associated monogenic diabetes has been rarely reported in a few other observational studies, we describe a patient who was treated successfully with repaglinide.

Case Report: A 38-year-old woman with type 1 diabetes mellitus, congenital deafness, chronic kidney disease, and retinopathy presented with difficulty controlling her blood glucose levels. Although initially treated with insulin, she had periods of noncompliance with insulin without experiencing diabetic ketoacidosis. Although on insulin therapy, she experienced multiple episodes of hypoglycemia. The laboratory tests showed a hemoglobin A1c level of 10.8%, c-peptide level of 2.7 ng/mL (1.1-4.4 ng/mL), glucose level of 192 mg/dL, creatinine level of 1.23 ng/dL, and severely increased microalbumin-to-creatinine ratio of 638 mg/g (normal range, 0-29 mg/g). Pancreatic autoantibodies were negative. Genetic testing revealed a diagnosis of *HNF1A*-associated monogenic diabetes (c.1340C>T (p.P447L)). She was ultimately treated with repaglinide after trials of sulfonylureas and dipeptidyl peptidase 4 inhibitors led to frequent hypoglycemia and a significant increase in the hemoglobin A1c level, respectively.

Discussion: This case highlights the importance of correctly diagnosing monogenic diabetes and reports the successful use of repaglinide to treat *HNF1A*-associated monogenic diabetes.

Conclusion: Patients with *HNF1A*-associated monogenic diabetes who do not achieve euglycemia with sulfonylureas and insulin may be successfully treated with repaglinide monotherapy.

Introduction

Monogenic forms of diabetes are clinically heterogeneous subtypes of diabetes caused by mutations to genes important in beta cell function, which cause impaired glucose sensitivity and insulin secretion without affecting the action of insulin (with the exception of monogenic diabetes caused by mutations in the *INSR* gene).[1] Autosomal dominant forms of monogenic diabetes (formerly known as maturity-onset diabetes of the young) are classically characterized by early-onset diabetes in an individual with obesity and no dependence on insulin. Because of overlapping features with other types of diabetes, such as type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus, monogenic diabetes can be difficult to diagnose clinically. Accurate diagnosis requires genetic testing and is essential because there are implications for management. Mutations in the hepatocyte nuclear factor 1 homeobox A (*HNF1A*) gene account for 30% to 60% of cases of monogenic diabetes, making it the most common genetic (or gene) cause of monogenic diabetes.[2] Sulfonylureas are considered first-line therapy for *HNF1A*-associated monogenic diabetes.[3,4] The efficacy of

Abbreviations: ATP, adenosine triphosphate; DPP-4, dipeptidyl peptidase 4; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, hemoglobin A1c; T1DM, type 1 diabetes mellitus.

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other antihyperglycemics has been reported, including glucagon-like peptide-1 receptor agonists (GLP-1RAs) and meglitinides as monotherapy and dipeptidyl peptidase 4 (DPP-4) inhibitors as augmentative therapy. However, data to support the use of meglitinides are limited. This report presents a case that highlights the difficulty in arriving at a correct diagnosis of *HNF1A*-associated monogenic diabetes (formerly MODY3) and the subsequent successful treatment of a woman with this disease with repaglinide monotherapy.

Case Report

A 38-year-old woman with T1DM, congenital deafness, and chronic kidney disease presented to our endocrinology clinic with concerns for difficulty controlling her blood glucose levels. She was diagnosed with diabetes at the age of 21 years that was classified as T1DM based on age and a normal body habitus. Her medical history was notable for muscle weakness with walking upstairs and left-sided vision loss, which led to a diagnosis of nondiabetic retinopathy in her early 20s. Her family medical history could not be obtained. She conceived a son via an anonymous sperm donor through in vitro fertilization who has autism spectrum disorder but no other known health concerns.

She was initially treated with insulin; however, because of insurance issues, she discontinued its use for several years. During this period, she had poor glycemic control but did not experience diabetic ketoacidosis. Although off insulin, she managed to keep her hemoglobin A1c (HbA1c) between 7% and 8% by removing all carbohydrate intake from her diet. Upon resuming insulin, she had multiple unpredictable episodes of hypoglycemia and subsequently self-discontinued insulin until presenting 8 months later for further care at the age of 38 years. At this time, her physical examination was notable for a normal body mass index of 24 kg/m^2. The laboratory tests showed an HbA1c of 10.8% and detectable c-peptide level of 2.7 ng/mL (1.1-4.4 ng/mL), with a glucose level of 192 mg/dL. The results of glutamic acid decarboxylase, zinc transporter 8, islet antigen-2, and islet-cell antibodies were all negative. Her creatinine level was 1.23 ng/dL, with a severely increased microalbumin-to-creatinine ratio (638 mg/g; normal range, 0-29 mg/g). A subsequent brief trial of low-dose glipizide, a sulfonylurea, resulted in precipitous decreases in the blood glucose level; therefore, it was discontinued. She was next prescribed alogliptin alone, a DPP-4 inhibitor, which resulted in inadequate control with an increase in the HbA1c level to 11.4%.

The patient was then prescribed repaglinide twice a day. She chose to take it once a day while tightly controlling her carbohydrate intake for fear of further hypoglycemic episodes. On this regimen, hypoglycemia did not recur, and her HbA1c improved to 8.6% 2 months after starting repaglinide (Table). Genetic testing, including a monogenic diabetes panel, was negative for mitochondrial diabetes and positive for a heterozygous pathogenic variant in HNF1A (c.1340C>T (p.P447L)) previously described as consistent with a diagnosis of *HNF1A*-associated monogenic diabetes.[5] The testing did not reveal an underlying cause for the patient's congenital deafness. She was recommended to continue taking repaglinide or consider a GLP-1RA, and she chose to continue repaglinide. She also continued statin therapy and was counseled on surveillance for microvascular complications of diabetes and arranged to have targeted genetic testing for her son.

Discussion

We describe the case of a patient with *HNF1A*-associated monogenic diabetes who did not tolerate insulin, sulfonylureas, or DPP-4 inhibitors but achieved improved glycemic control with a meglitinide analog.

Highlights

- *HNF1A*-associated monogenic diabetes is rare and often misdiagnosed
- Proper diagnosis of *HNF1A*-associated monogenic diabetes impacts its management
- Repaglinide can be used to treat *HNF1A*-associated monogenic diabetes

Clinical Relevance

This case report highlights an adult patient diagnosed with *HNF1A*-associated monogenic diabetes years after the diagnosis of type 1 diabetes mellitus, who responded to repaglinide monotherapy after administration of insulin and sulfonylureas caused hypoglycemia. Limited studies exist on meglitinides as an alternative to sulfonylureas. Our report supports their use, especially for hypoglycemia-sensitive patients with *HNF1A*-associated monogenic diabetes.

Monogenic diabetes is a rare type of diabetes, accounting for 1% to 4% of all cases of diabetes depending on the population studied.[6] Genetic testing to achieve a correct diagnosis has important clinical implications allowing for better care of patients and their respective at-risk families. Barriers to making a diagnosis of monogenic diabetes include the lack of clinical awareness and recognition of atypical features and that of access to quality genetic testing services.

Treatment approaches to each subtype of monogenic diabetes are based predominantly on observational data and a few controlled experimental studies so far because rarity of their diagnosis limits randomized multicenter trials. The primary defect in patients with *HNF1A* mutations is a failure to secrete insulin because of alterations in glucose metabolism in pancreatic beta cells. These mutations interfere with glucose uptake, glycolysis, and mitochondrial adenosine triphosphate (ATP) production, which are all necessary steps for insulin secretion.[7] The change in the ATP/adenosine triphosphate ratio results in closure of the ATP-sensitive potassium channels (KATP), which then suppresses membrane depolarization and the activation of voltage-dependent calcium channels that are responsible for exocytosis of insulin-containing granules.[7] The KATP channels have regulatory sulfonylurea receptors where sulfonylurea drugs can bind to and inhibit the

Table
Timeline of Events and Corresponding Glycemic Control

Diabetes management	Glycemic control
Age of 21 y: patient diagnosed with T1DM and started on insulin	Not obtained
Patient self-discontinued and switched to diet modification only	HbA1c level of 7%-8%
Patient resumed insulin	Recurrent hypoglycemia
Age of 38 y: presentation to our clinic while off antiglycemic agents	HbA1c level of 10.8%
Glipizide monotherapy initiated	Recurrent hypoglycemia
Glipizide discontinued and alogliptin started	HbA1c level of 11.4%
Alogliptin discontinued and repaglinide started	HbA1c level of 8.6%

Abbreviations: HbA1c = hemoglobin A1c; T1DM = type 1 diabetes mellitus.

channels, thus altering the resting membrane potential and enabling insulin secretion.[8] As such, the use of low-dose sulfonylureas in *HNF1A*-associated monogenic diabetes has been well established as a first-line treatment.[3,4] However, even at low doses, patients with *HNF1A*-associated monogenic diabetes frequently experience hypoglycemia because of marked hypersensitivity to sulfonylureas.[9,10]

Meglitinides, another class of insulin secretagogues, have been infrequently reported for use in *HNF1A*-associated monogenic diabetes despite their similar mechanism of action to sulfonylureas. They are structurally different from sulfonylureas and have distinct binding sites but have also been shown to inhibit the KATP channels involved in insulin secretion.[11] Their rapid onset of action and shorter duration of action than those of sulfonylureas have been previously shown to prevent an increase in the prandial glucose level more efficiently and cause less of a hypoglycemic effect, specifically with nateglinide.[12] Repaglinide, in contrast with nateglinide, has a slightly slower onset and longer duration of action; however, given its overall similar characteristics, it was theorized that it could also be used in patients with a tendency for hypoglycemia. The successful use of repaglinide has been demonstrated in pediatric patients.[13] Our case also reports the successful use of repaglinide, specifically in an adult patient with *HNF1A*-associated monogenic diabetes, who previously could not tolerate sulfonylureas or insulin because of frequent hypoglycemia.

Other observational studies have reported optimal glycemic control without hypoglycemia with GLP-1RA monotherapy or with the addition of DPP-4 inhibitors to a regimen with a sulfonylurea.[14-16] Our patient was unable to achieve adequate glycemic control with DPP-4 inhibitors as monotherapy. It is important to note that over time, the glycemic effect of oral agents may deteriorate, after which insulin therapy may be appropriate. Therefore, we suggest the consideration of meglitinides as the primary oral treatment for adult patients with *HNF1A*-associated monogenic diabetes who have been shown to have a tendency for hypoglycemia.

Conclusion

This case is an example of the importance of raising clinical awareness for the diagnostic approach to monogenic diabetes and reports on the successful and well-tolerated use of repaglinide monotherapy for an adult woman with *HNF1A*-associated monogenic diabetes. Such cases are particularly challenging given the heterogeneity in presentation and overlap with other types of diabetes; however, correct diagnosis has significant implications on the choice of antihyperglycemic and overall care of the patient and their families.

Disclosure

The authors have no conflicts of interest to disclose.

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