EJCRIM
European Journal
of Case Reports
in Internal Medicine

GLICLAZIDE CHALLENGE TESTING AS AN ALTERNATIVE DIAGNOSTIC TOOL FOR HEPATOCYTE NUCLEAR FACTOR-1-ALPHA MATURITY ONSET DIABETES OF THE YOUNG

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Received: 08/10/2025
Accepted: 20/10/2025
Published: 04/12/2025

Conflicts of Interests: The Authors declare that there are no competing interests.
Patient Consent: Written informed consent for publication of clinical details was obtained from the patient.
Acknowledgments: The authors would like to acknowledge the late Dr Winston Crasto for his clinical expertise and involvement in the care of this patient.
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How to cite this article: Pandya S, Khairati R, Mann J, Archer L, Saravanan P, Ereneta III F, Patel V. Gliclazide challenge testing as an alternative diagnostic tool for hepatocyte nuclear factor-1-alpha maturity onset diabetes of the young. *EJCRIM* 2025;**12**:doi:10.12890/2025_005892

ABSTRACT

Background: Hepatocyte nuclear factor-1-alpha monogenic diabetes (HNF1-alpha DM), formerly known as maturity-onset diabetes of the young type 3 (MODY 3), is often misdiagnosed as type 1 or type 2 diabetes. In regions where genetic testing is unavailable, alternative diagnostic approaches are needed.

Case report: A 20-year-old woman was initially diagnosed with type 1 diabetes after an incidental finding of hyperglycaemia. Despite adherence to treatment, she experienced recurrent hypoglycaemia on basal-bolus insulin, receiving over 2600 injections in 8 years. Autoantibodies were negative, C-peptide levels were preserved, and her estimated probability of MODY exceeded 10%. While awaiting genetic testing, she underwent a "glicazide challenge test", which showed a marked stimulatory response in blood glucose and C-peptide levels. Subsequent testing confirmed HNF1-alpha MODY. Insulin was stopped, and she was started on low dose gliclazide, achieving excellent control with minimal hypoglycaemia.

Conclusion: This case demonstrates the gliclazide challenge test's potential as an alternative diagnostic and therapeutic tool in suspected maturity-onset diabetes of the young when genetic testing is limited.

KEYWORDS

Maturity-onset diabetes of the young (MODY), monogenic diabetes, HNF1A mutation, gliclazide, C-peptide

LEARNING POINTS

- Young patients with atypical diabetes (negative autoantibodies, preserved C-peptide, recurrent hypoglycaemia on insulin) should prompt consideration of monogenic diabetes, and the Exeter maturity-onset diabetes of the young calculator is a valuable screening tool for clinicians.
- A gliclazide challenge test with serial C-peptide measurement can provide a simple, functional assessment of sulfonylurea sensitivity, supporting the diagnosis of maturity-onset diabetes of the young, in centres where genetic testing is limited or delayed.
- Early recognition of maturity-onset diabetes of the young allows safe transition from insulin to sulfonylureas, preventing years of unnecessary injections, reducing hypoglycaemic episodes, and improving long-term quality of life.

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INTRODUCTION

Maturity-onset diabetes of the young (MODY) is a rare monogenic form of diabetes, accounting for less than 2% of all diabetes cases[1]. In individuals with mild, stable fasting hyperglycaemia that does not progress, genetic testing for glucokinase mutations should be prioritised. Among its subtypes, hepatocyte nuclear factor-1-alpha (HNF1-alpha) mutations are the most prevalent cause, particularly in Western populations. HNF1-alpha MODY typically presents in adolescence or early adulthood and is often misdiagnosed as either type 1 or type 2 diabetes mellitus[2,3]. Unlike autoimmune type 1 diabetes, MODY patients do not require insulin therapy and often respond exceptionally well to low-dose sulfonylureas such as gliclazide[4]. The standard for diagnosing MODY is genetic testing. However, genetic testing remains inaccessible in many regions, especially in low and middle-income countries and rural areas. In this context, tests such as the gliclazide challenge test (GCT) using gliclazide with serial C-peptide measurements to assess insulin secretory response may serve as a valuable diagnostic tool[5]. The proposed placement of the GCT within the diagnostic pathway for suspected MODY is illustrated in *Figure 1*. We present a case of a young adult initially diagnosed with type 1 diabetes who, 8 years later, was found to have HNF1-alpha MODY after a positive GCT and subsequent genetic confirmation.

CASE DESCRIPTION

A 20-year-old female medical student initially presented to a secondary care centre with symptoms of a urinary tract infection and was incidentally found to have marked hyperglycaemia. Based on her age and clinical presentation, a diagnosis of type 1 diabetes mellitus was made, and she was started on a basal-bolus regimen comprising long and short-acting insulin. Over the following 8 years, she remained on insulin therapy with regular dose titrations and reported good adherence to treatment. Despite this, she continued to experience frequent hypoglycaemic episodes, which prompted her to seek a second opinion on her diagnosis at our facility.

Repeat investigations at our centre revealed a glycosylated haemoglobin (HbA1c) of 66 mmol/mol (normal <42 mmol/mol) and random C-peptide levels of 320 pmol/l and 450 pmol/l on two separate occasions. Anti-glutamic acid decarboxylase (GAD) antibodies and islet cell antibodies were negative. The Exeter MODY calculator indicated a >10% probability of MODY, taking into account her age at diagnosis, preserved C-peptide, autoantibody negativity, and family history of diabetes (father with prediabetes; maternal great-grandmother with type 2 diabetes).

Due to the limited access to genetic testing at the time, a GCT was performed after discontinuing insulin therapy. The patient ingested 75 g of anhydrous glucose under two conditions, once with 80 mg gliclazide and once without, separated by 1 week. Fasting for 10 hours before each test was ensured, and blood samples were collected every 30 minutes over 3 hours for capillary glucose, venous glucose, and C-peptide *(Fig. 2, 3, and 4)*. To ensure consistency, the patient maintained the same dietary and activity pattern for 3 days before each test.

The test results showed significant differences in C-peptide and glucose levels. At 30 minutes post-glucose ingestion, the C-peptide level was 450 pmol/l without gliclazide and increased to 708 pmol/l with gliclazide, a 57.3% increase, demonstrating preserved beta cell function with sensitivity to sulfonylurea therapy *(Table1, Fig. 4)*. Venous glucose peaked at 19 mmol/l without gliclazide and 16.4 mmol/l with gliclazide at 120 minutes, while capillary glucose peaked at

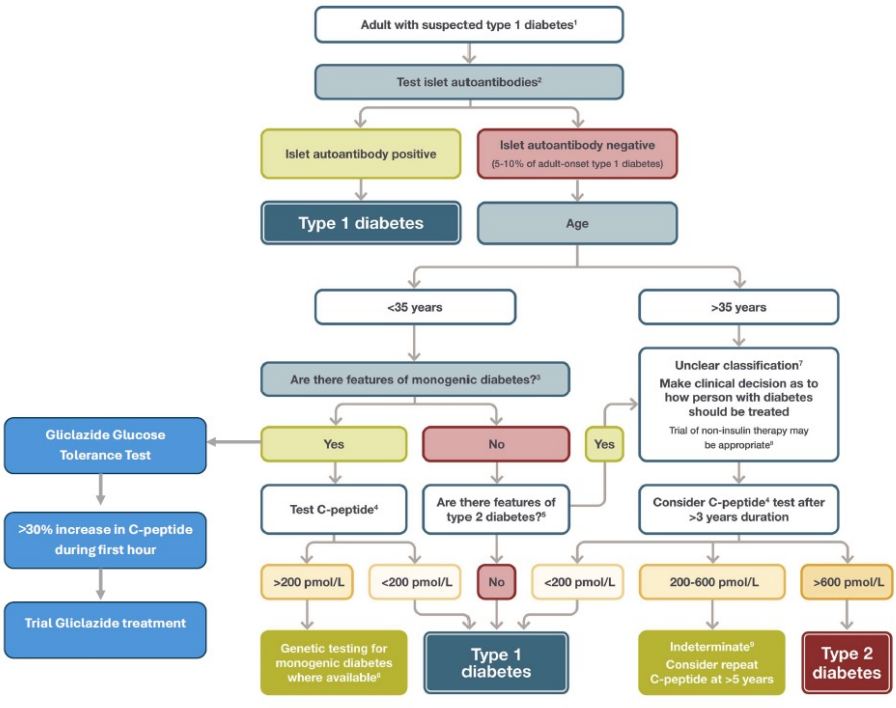


Figure 1. Adapted from "The management of type 1 diabetes in adults. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)"[10]. This figure shows where we can use the gliclazide glucose tolerance test in the diagnosis pathway in centres with no or little access to genetic testing.

C-peptide (pmol/l)				
Minutes after 75 g glucose ingestion	Without gliclazide	With 80 mg gliclazide	Difference with gliclazide	Difference with gliclazide (%)
0	361	322	-39	-12.02
30	450	708 (↑↑)	+258	57.3
60	943	939	-4	-0.4
90	1075	973	-102	-9.4
120	1178	803	-375	-31.83
150	1115	789	-326	-29.24
180	1048	725	-323	-30.82

Table 1. Blood C-peptide levels taken from venepuncture.

Blood Glucose (mmol/l)				
Minutes after 75 g glucose ingestion	Without gliclazide	With 80 mg gliclazide	Difference with gliclazide	Difference with gliclazide (%)
0	10.3	11.2	-	-
30	14.3	14.3	0	0
60	18.7	16.1	-2.6	-13.9
90	17.8	15.4	-2.4	-13.48
120	19	16.4	-2.6	-13.68
150	18.8	16	-2.8	-14.89
180	15.5	13.5	-2	-12.9

Table 2. Blood glucose measured from venepuncture.

18.3 mmol/l without and 17.1 mmol/l with gliclazide *(Table 2, Fig. 3)*. Despite higher late-phase C-peptide levels in the non-gliclazide test, glycaemic control was better with gliclazide, suggesting enhanced first-phase insulin response *(Fig. 4)*.

A few months later, funding approval was obtained, and the patient was referred to the MODY testing centre in Exeter, United Kingdom. Genetic testing confirmed a diagnosis of HNF1-alpha MODY. All insulin was discontinued, and the patient was commenced on low-dose gliclazide (20–40 mg daily). Over 2 years, her HbA1c improved from 66 to 36 mmol/mol, with a marked reduction in hypoglycaemic events. She continues on gliclazide with regular diabetes monitoring.

DISCUSSION

This case underscores the diagnostic challenges associated with MODY, particularly in low-resource healthcare systems, without ready access to genetic testing. HNF1-alpha MODY often presents with clinical features resembling both type 1 and type 2 diabetes, but its management differs significantly due to its unique pathophysiology. Gliclazides can be highly effective in these patients by stimulating residual beta-cell insulin production[4].

C-peptide is a useful marker of how much insulin a patient is producing. It is a peptide fragment cleaved from proinsulin and is secreted in equimolar amounts with endogenous insulin from pancreatic beta-cells[6]. In the context of type 1 diabetes mellitus, which is characterised by autoimmune destruction of beta-cells and absolute insulin deficiency, C-peptide levels are typically low or undetectable, reflecting minimal or absent endogenous insulin secretion. Conversely, in type 2 diabetes mellitus, where insulin resistance predominates, C-peptide levels are often normal or elevated, due to compensatory hypersecretion by functioning beta-cells. C-peptide levels in individuals with monogenic diabetes may resemble those of type 2 diabetes, which can make accurate classification more challenging without further investigation[4]. Importantly, HNF1-alpha mutations typically preserve C-peptide levels and lack autoimmunity. HNF1-alpha MODY is associated with a blunted early-phase insulin and C-peptide response to glucose due to impaired beta-cell glucose sensing and transcriptional regulation[7]. Sulfonylureas such as gliclazide enhance insulin secretion

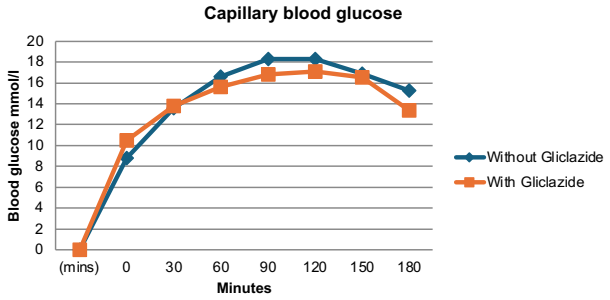


Figure 2. A graph comparing the effect on capillary blood glucose over time with and without the ingestion of 80 mg gliclazide.

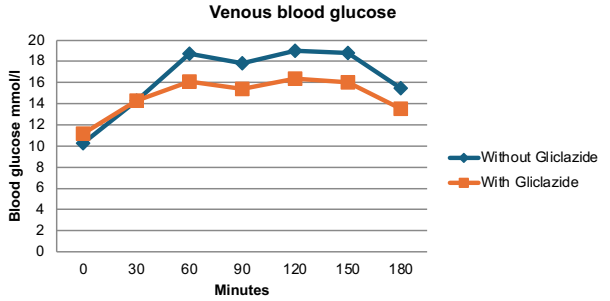


Figure 3. A graph comparing the effect on venous blood glucose over time with and without the ingestion of 80 mg gliclazide.

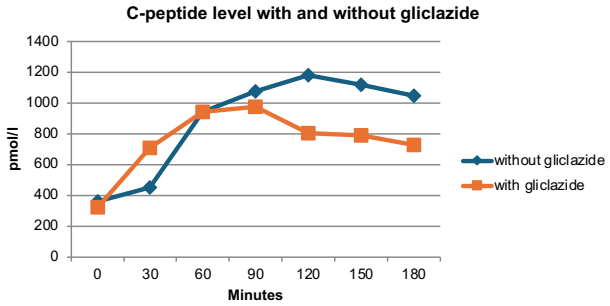


Figure 4. A graph comparing the effect on C-peptide over time with and without the ingestion of 80 mg gliclazide.

in MODY by directly closing adenosine triphosphate (ATP)-sensitive potassium channels (K-ATP), thus bypassing the defective ATP-dependent signalling pathway. The utility of biomarkers, including C-reactive protein and glycan profiling, in supporting the diagnosis of HNF1-alpha MODY was previously highlighted by Owen (2013) as a step towards earlier identification of monogenic diabetes[8]. We performed a GCT using oral gliclazide with serial C-peptide measurements to assess the endogenous insulin secretory response in a young adult with longstanding diabetes by evaluating beta-cell function. In our patient, a >50% increase in C-peptide at 30 minutes post-gliclazide confirmed sulfonylurea sensitivity and enhanced early-phase response *(Table 1, Fig. 4)*. Notably, while the peak C-peptide level was higher without gliclazide *(Table 1)*, the early-phase response was better with gliclazide. This discrepancy may reflect delayed insulin secretion kinetics common in MODY patients[9]. This simple functional test supported a diagnosis of MODY before genetic confirmation. Although genetic testing remains the definitive diagnostic approach, its accessibility is limited in many healthcare systems due to cost, availability, or long waiting periods. In such contexts, the GCT may provide a practical interim strategy to guide clinical decision-making. Further large-scale, standardised studies are warranted to validate its broader clinical applicability.

CONCLUSION

This case demonstrates the utility of the GCT in identifying patients with HNF1-alpha MODY. While definitive diagnosis relies on genetic testing, a gliclazide challenge may act as a pragmatic initial step to support decision-making in selected patients with suspected monogenic diabetes. Early identification of MODY can facilitate a switch from insulin to sulfonylureas, improving glycaemic control and patients' quality of life. Functional tests like GCT can bridge the diagnostic gap while awaiting genetic confirmation and should be considered in young patients with atypical diabetes profiles.

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