



DOI: 10.4274/jcrpe.galenos.2025.2025-4-12

J Clin Res Pediatr Endocrinol

Diazoxide and Continuous Glucose Monitoring as Treatment in a Neonate with Hyperinsulinemic Hypoglycemia due to *HNF4A* Mutation

Georgia Sotiriou¹, Stilianos Xinias¹, Valentina Diamantidou¹, Anny Mertzanian²,
Meropi Dimitriadou¹, Amalia Sertedaki², Athanasios Christoforidis¹

¹1st Department of Pediatrics, School of Medicine, Faculty of Health Sciences, Aristotle University of Thessaloniki, Hippokratio General Hospital, Thessaloniki, Greece

²Division of Endocrinology, Diabetes and Metabolism, ENDO-ERN Center for Rare Paediatric Endocrine Diseases, 1st Department of Pediatrics, Medical School, Aghia Sophia Children's Hospital, National and Kapodistrian University of Athens, Athens, Greece

Cite this article as: Sotiriou G, Xinias S, Diamantidou V, Mertzanian A, Dimitriadou M, Sertedaki A, Christoforidis A. Diazoxide and continuous glucose monitoring as treatment in a neonate with hyperinsulinemic hypoglycemia due to *HNF4A* mutation. J Clin Res Pediatr Endocrinol. [Epub Ahead of Print]

ABSTRACT

The transcription factor hepatocyte nuclear factor 4A (HNF4A) plays a key role in insulin secretion and mutations in its encoding gene, *HNF4A*, have been associated with monogenic diabetes (MODY 1) during adolescence or early adulthood and with transient hyperinsulinemic hypoglycemia during infancy. They are inherited as an autosomal dominant trait, therefore, *HNF4A* sequencing should be considered in every neonate presenting with macrosomia or persistent hypoglycemia in the first 24 hours after birth, especially when there is a family history of early-onset diabetes. Management of hyperinsulinism includes regular feeding, intravenous glucose and diazoxide, as first-line treatments. Blood glucose levels need regular monitoring to optimally adjust treatment. Continuous glucose monitoring (CGM) systems are not validated for neonates or patients with hyperinsulinism, so finger-prick blood tests are usually used before every meal. We present a case of diazoxide use in a female infant with neonatal hypoglycemia due to *HNF4A* mutation, where CGM facilitated treatment decisions and detected hyperglycemia as an adverse event, early in the course. Notably, CGM use after hospital discharge contributed significantly to ongoing glucose monitoring and management. We recommend that further studies should be performed to validate CGM use for optimal clinical management of challenging cases, such as this example of early neonatal hyperinsulinemic hypoglycemia due to MODY 1.

Keywords: *HNF4A* mutation, MODY 1, diazoxide, continuous glucose monitoring, hyperinsulinemic hypoglycemia

Corresponding Author: Georgia Sotiriou, MD, MSc, 1st Department of Pediatrics, School of Medicine, Faculty of Health Sciences, Aristotle University of Thessaloniki, Hippokratio General Hospital, Thessaloniki, Greece

E-mail: gmsoti@gmail.com **ORCID:** orcid.org/0009-0002-4554-3116

Conflict of interest: None declared

Received: 02.05.2025 **Accepted:** 13.08.2025 **Epub:** 17.09.2025



What is already known on this topic?

Neonatal hypoglycemia due to *HNF4A* mutations is usually diazoxide-responsive. It is vital to closely monitor glucose levels in these children. However, continuous glucose monitoring systems (CGMs) are not currently approved for neonates.

What this study adds?

Use of a CGM system in a neonate with hyperinsulinemic hypoglycemia due to *HNF4A* mutation helped to identify hypoglycemia events with fewer finger pricks, and also identified diazoxide-induced hyperglycemia, facilitating improved treatment modification, both during hospitalization and after discharge. Furthermore, CGM aided in establishing a more physiological feeding pattern for this infant with exclusive breastfeeding. Further studies are warranted to establish the usefulness of CGM in this group of patients, as an adjunct in clinical care.

Introduction

Hepatocyte nuclear factor 4A (*HNF4A*) is a transcription factor that plays an important role in pancreas and liver development, function and cell metabolism (1). Mutations in the *HNF4A* gene follow autosomal dominant inheritance pattern and are most commonly associated with maturity-onset diabetes of youth type 1 (MODY 1), but also with macrosomia and hyperinsulinemic hypoglycemia at birth or in infancy (1,2,3). *HNF4A* variants are reported to be associated with wide phenotypic heterogeneity, including extra-pancreatic manifestations, such as developmental delay, Fanconi syndrome, and renal or hepatic findings (3). Hyperinsulinemic hypoglycemia has a reported incidence of 15% in *HNF4A* mutation carriers with an equal maternal and paternal inheritance, indicating that the pathogenesis of hyperinsulinism is independent of maternal glycemic control during pregnancy. *HNF4A*-associated hyperinsulinism is usually diazoxide-responsive but with substantial variability in treatment regimen and duration, as demonstrated in published case series (3,4).

Continuous glucose monitoring (CGM) systems measure interstitial glucose every 1-15 minutes. The first commercial CGM was approved by the FDA in 1999 for patients with type 1 diabetes mellitus. Since then, there has been significant technological evolution of this field. Currently, many people with diabetes mellitus type 1 use CGMs, as they improve glycemic control, reduce hypoglycemia incidents and have a substantial impact on quality of life (5,6,7). However, CGM devices are not yet approved for use in neonates with congenital hyperinsulinism. Nevertheless, there have been studies showing the benefits of CGM use in detecting hypoglycemia, blood glucose trends and improved management of medical therapy, implying that CGMs may have value as an adjunct to clinical care (8,9).

Having these potential benefits in mind, we decided to use a CGM device in a female macrosomic neonate with persistent hypoglycemia and a family history of *HNF4A* MODY, while initiating diazoxide therapy.

Case Report

A 22-day old female neonate was admitted to our pediatric department for investigation and management of persistent hypoglycemia. She was a near-term neonate, delivered by cesarian section in the 36th gestational week, due to premature onset of labor, with macrosomia (weight: 3680 gr-99th percentile, length: 51 cm-99th percentile). Her family history included her mother and maternal grandfather having a diagnosis of *HNF4A* MODY. These diagnoses were made using a MODY-targeted gene panel and Next Generation Sequencing and both were identified to be heterozygotes for the likely pathogenic variant c.956_958delTGC, p.Leu319del in exon 8 of the *HNF4A* (NM_175914.4) gene. Her mother had no need for anti-diabetic medication, but during pregnancy exhibited an elevation of glycated hemoglobin levels from 4.9% in the first trimester to 5.9% in the third trimester. The female neonate had hypoglycemia in the first hour after delivery (Dextro stick: 32 mg/dL) and was fed without improvement (Dextro stick: 29 mg/dL, 20 minutes after feeding). Therefore, she was transferred to the neonatal intensive care unit and was fed with a mixed diet with full-term formula and a glucose polymer. Concomitantly, she received intravenous glucose with a maximum flow of 7.5 mg/kg/min, in order to achieve glucose levels above 60 mg/dL. The hypoglycemic episodes persisted during the second day of life, so the full-term formula was replaced by a formula for premature neonates, which contains a higher glucose concentration. The term formula contained approximately 7.2 g of carbohydrates per 100 mL, whereas the preterm formula contained approximately 12 g per 100 mL. After the third day of life, she remained normoglycemic and was discharged from the neonatal unit with instructions for pre-prandial blood glucose measurements and frequent feeding, every two hours, with the preterm formula. However, while at home, the neonate continued to experience frequent hypoglycemic episodes, which were confirmed by capillary glucose measurements using a glucometer. The parents reported that she was noticeably drowsy during these episodes. As a result, on the 22nd day of life, she was admitted to our pediatric department.

At initial presentation, she was in a generally good condition, although mildly lethargic, but with no other notable findings on physical examination. Laboratory results showed normal thyroid function, normal insulin-like growth factor-1 and ammonia levels, whereas glycated hemoglobin could not be quantified because of elevated levels of HbF. During the first hours of hospitalization, she experienced an episode of hypoglycemia and a critical sample confirmed hyperinsulinemic hypoglycemia with no ketones (Table 1). A blood sample was also sent for *HNF4A* gene sequencing, given the family history of *HNF4A* MODY. A CGM was placed, after parents' consent, and the neonate continued receiving mixed feeding with preterm formula and breastfeeding every 2 hours. However, during the next few hours the CGM sensor showed 30% time in hypoglycemia, with hypoglycemic episodes mostly being corrected with feeding but one needing intramuscular administration of GlucaGen (synthetic glucagon) (Figure 1). The next day, intravenous infusion of dextrose was initiated with a maximum flow of 18.8 mg/kg/min and diazoxide treatment at a low dose of 5 mg/kg/day, split into two doses daily. However, her diazoxide dose was increased to 10 mg/kg/day on the fifth day of hospitalization because of persistent hypoglycemia, which produced a good metabolic response. Consequently, on the eighth day intravenous glucose administration was discontinued and breastfeeding and full-term formula, rather than preterm formula, was recommended. On the twelfth day of hospitalization, she was discharged, on diazoxide 10 mg/kg/day, split into two doses and continuous glucose monitoring. Concurrently, the result of the genetic

Table 1. Critical sample results		
		Normal range
Glucose in EDTA (mg/dL)	32	<50 mg/dL*
Ketones (mmol/L)	0.1	>2.0 mmol/L
Insulin (mIU/L)	2.16	<2 mIU/L
Cortisol (µg/dL)	15.40	>10 µg/dL
Growth hormone (ng/mL)	19.758	>6 ng/ml
Lactic acid (mmol/L)	4	0.6-2.0 mmol/L
Ammonia (µg/dL)	48	<60 µg/dL

*to consider the sample of diagnostic value

test was received, which confirmed that she had inherited the maternal *HNF4A* gene variant, c.956_958delTGC, p.Leu319del. This variant has been reported in a family with two of its members presenting with young onset diabetes, whereas another family member presented with macrosomia and neonatal hypoglycemia (10,11).

Ten days after discharge from hospital, she had episodes of diazoxide-induced hyperglycemia (maximum glucose: 262 mg/dL) (Figure 2), which were, at first, attributed to the change in the mode of diazoxide administration, as her parents had started to use a more precise insulin syringe to quantify the amount of diazoxide given, rather than the dosometric pipe accompanying the commercial diazoxide kit. Over the following days, her episodes of hyperglycemia persisted, so the dose of diazoxide was reduced until it was temporarily interrupted for two days.

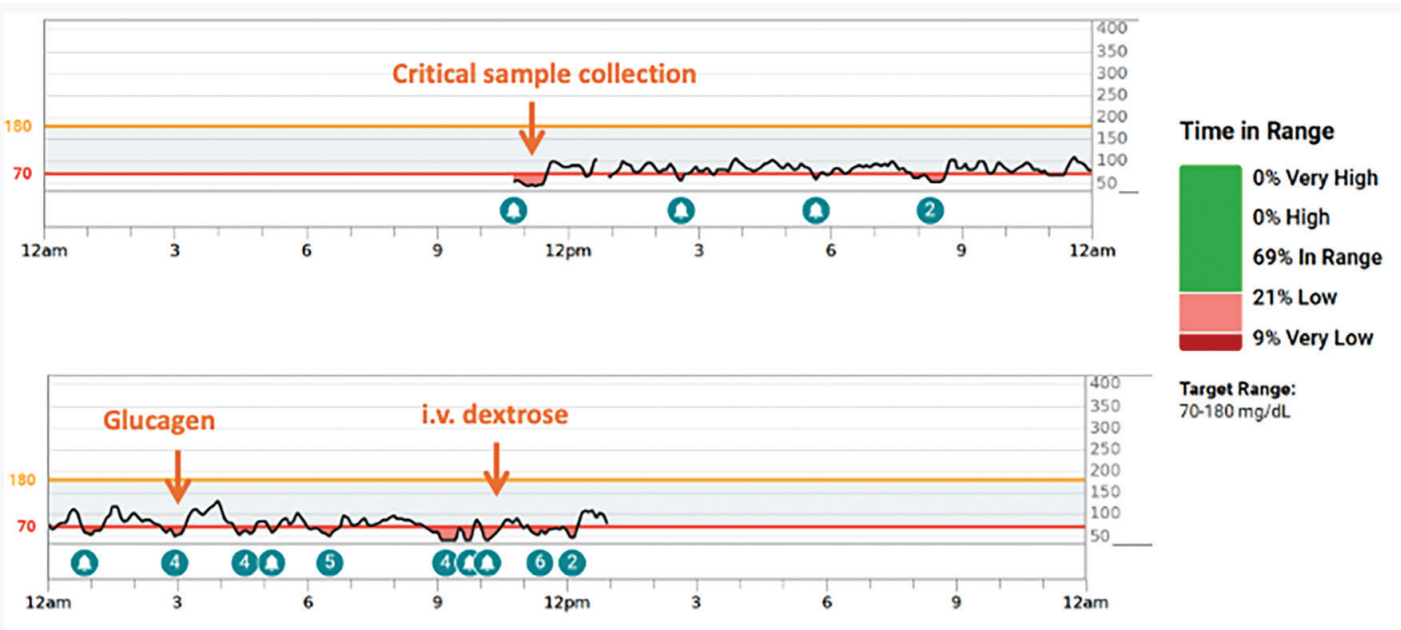


Figure 1. CGM data during the first day of application
CGM: continuous glucose monitoring

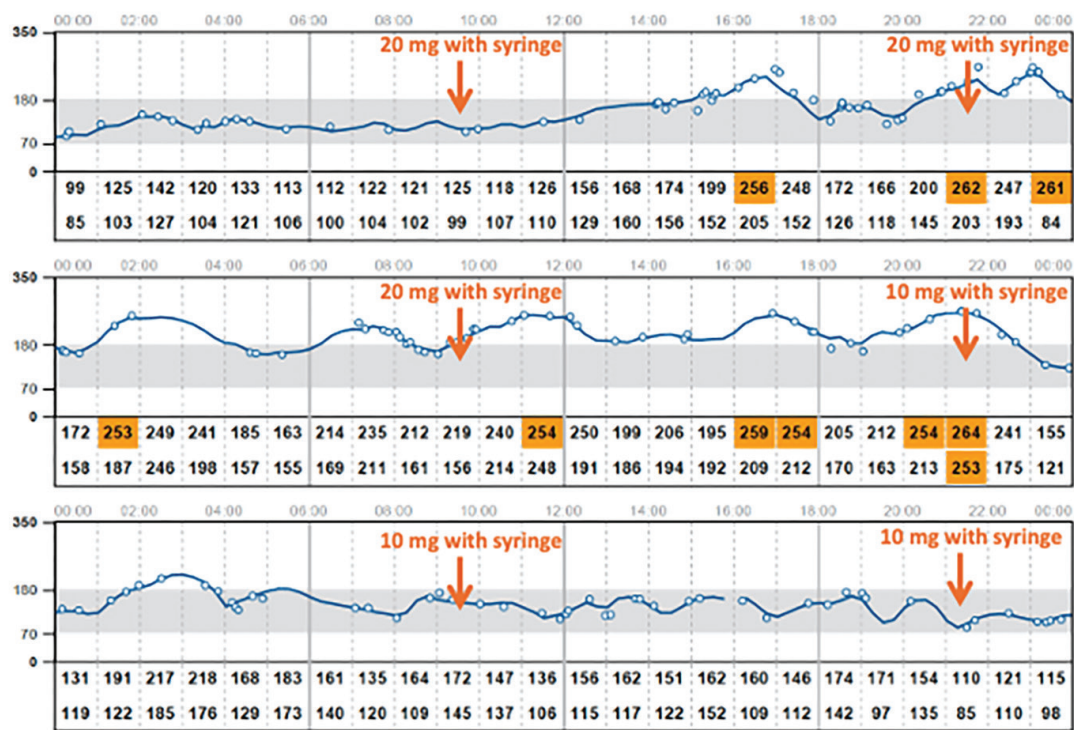


Figure 2. Diazoxide-induced hyperglycemia

However, this resulted in the reoccurrence of hypoglycemia, so diazoxide was restarted. CGM helped us managing the treatment dose, as her glucose levels appeared to be dependent on many factors. These included her first vaccination or when her mother attempted exclusive breastfeeding, during which she was continuously offered breast milk. Currently, at three months of age, her diazoxide dosing is still being adjusted once or twice per week with the aim of maintaining glucose concentrations within the normal range of 70-140 mg/dL, as her hyperinsulinism has not yet resolved.,

Whenever extreme high or low glucose values were detected by CGM, capillary blood glucose measurements were performed to verify glucose values and guide clinical decisions, both during hospitalization and after discharge to home. Moreover, the baby girl was closely monitored throughout the entire course of diazoxide therapy for the most common adverse effects, such as fluid retention, hypertrichosis, gastrointestinal disturbances, and pulmonary hypertension. No serious adverse events were observed, with the only side effect being moderate hypertrichosis.

Discussion

The clinical manifestations in the presented case were typical of *HNFA4* gene mutations, including macrosomia, hypoglycemia

from the first day of life, need for intensive neonatal care with intravenous glucose administration and diazoxide-responsive hyperinsulinism. Moreover, there was a known family history of *HNFA4* MODY, so the diagnosis was almost certain. It is important for clinicians to consider *HNFA4* sequencing in neonatal hyperinsulinemic hypoglycemia and macrosomia, especially when there is a family history suggestive of MODY (12). Conversely, when there is a known *HNFA4* mutation in the family, it is important to screen for macrosomia and hypoglycemia at birth and during the first 24 hours (2). Given that *HNFA4* mutations are inherited in an autosomal dominant pattern (2), in cases of neonatal hypoglycemia, it is crucial to investigate both parent's history of diabetes, and not only maternal glycemic control during pregnancy.

We have no data from mother's neonatal history, so it is possible that she had no hypoglycemia, or they were too mild and transient to be identified. In a recent systematic review, Perge and Nicolino (13) highlighted that mutations in *ABCC8*, *HNFA4*, *HNFA1A* and *GCK* genes can give a biphasic phenotype in the same person with both neonatal hypoglycemia and diabetes after adolescence or a reverse phenotype in the same family, as may be present in the presented family. If we accept that the mother did not manifest neonatal hyperinsulinemic hypoglycemia, the presence of hypoglycemia in the proband could suggest a

difference in genotype-phenotype correlation with a worsening of phenotype in subsequent generations within the same family. However, this has not been extensively documented and studied to date.

Diazoxide is the first-line treatment for neonatal hyperinsulinemic hypoglycemia, as it reduces insulin secretion, and most carriers of *HNF4A* mutations are responsive (14). In the presented case, diazoxide was started orally at 5 mg/kg/day in two divided doses and was subsequently increased to 10 mg/kg/day, also in two divided doses, to achieve normoglycemia. On the 20th day of treatment, while at home, the infant weighed 4 kg and was receiving 20 mg of diazoxide orally twice daily (5 mg/kg per dose; 10 mg/kg/day). CGM revealed substantial hyperglycemia. After excluding technical problems, we decided to reduce her diazoxide dose, as diazoxide-induced hyperglycemia is a well-defined, although difficult to identify, adverse event. The main pathogenetic mechanisms behind diazoxide-induced hyperglycemia are the inhibition of insulin secretion by beta-cells and the increase of epinephrine release which results in increased glycogenolysis (14). There are also case reports of diazoxide-related hyperosmolar hyperglycemia in children with hyperinsulinism, suggesting that it is extremely important to closely monitor glucose levels in these children (15,16,17).

Although CGM is increasingly being used off-label in neonates with hyperinsulinism, its accuracy at extreme glucose values remains limited. A meta-analysis in preterm infants reported low sensitivity for detecting hypoglycemia (39%), but higher sensitivity for hyperglycemia (87%), with overall specificity exceeding 95% (18). Similarly, a study in postoperative neonates demonstrated a mean absolute relative difference (MARD) of 10.8%, with 100% sensitivity and 93.9% specificity for hyperglycemia above 150 mg/dL (19). Moreover, it is well established that CGM systems may overreport hypoglycemia on the first day of sensor insertion, because of sensor stabilization, warm-up effects or even a local inflammatory response and tissue microhaemorrhage (20). These findings highlight the need for cautious interpretation of CGM data, particularly during the initial calibration phase and in hypoglycemic ranges. In the present case, to address these limitations, all extreme glucose readings, both low and high, were verified with capillary blood glucose measurements throughout hospitalization and after discharge, ensuring accurate interpretation and safe clinical decision-making. CGM provided a reasonably reliable representation of the infant's glucose trends. However, as paired measurements were not obtained systematically at all time points, formal correlation or agreement analysis was not performed.

This case again demonstrates the usefulness of CGM in titration of diazoxide dose and in adopting a more physiological feeding pattern in a neonate with hyperinsulinemic hypoglycemia due to *HNF4A* mutation. Although off indication, Win et al. (8) used also real-time CGM in neonates with hyperinsulinemic hypoglycemia and compared glucose values (sensor and blood) giving a MARD of 11%. Gariepy et al. (9) used CGM in children with hyperinsulinism, reporting marked benefit for detecting hypoglycemic episodes and in guiding medical management. Saif et al. (21) also described a case of a neonate with hyperinsulinism, where CGM helped to identify hypoglycemic episodes, overcoming the difficulty in recognizing symptoms of hypoglycemia in such a young patient and avoiding repeated skinprick sample collections. In the present case, CGM use after hospital discharge was particularly valuable for ongoing monitoring and individualized management. It enabled early identification of diazoxide-induced hyperglycemia and supported “real-time” dose adjustments based on daily variations, such as changes in feeding routines or physiological stressors like vaccination. This real-world application of CGM outside the hospital setting provided a more comprehensive view of the patient's glucose profile, helping to optimize therapy and support safe transition to exclusive breastfeeding. This case highlights the potential of CGM as a valuable outpatient management tool in infants with hyperinsulinism.

Conclusion

Mutations in *HNF4A* gene should be considered when investigating neonatal hypoglycemia, especially when there is a family history of early onset diabetes in either the maternal or paternal medical history. CGMs appear to be of benefit in the medical care of patients with hyperinsulinemic hypoglycemia treated with diazoxide. More studies are needed to support and validate the use of CGM in preventing both insensible neonatal hypoglycemia and treatment-induced hyperglycemia, which will facilitate diazoxide dosing changes in a timely manner.

Ethics

Informed Consent: Parental consent was obtained.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Georgia Sotiriou, Stilianos Xinias, Valentina Diamantidou, Anny Mertzanian, Meropi Dimitriadou, Amalia Sertedaki, Athanasios Christoforidis, Concept: Athanasios Christoforidis, Design: Athanasios Christoforidis, Data Collection or Processing: Georgia Sotiriou, Stilianos Xinias, Valentina Diamantidou, Meropi Dimitriadou, Athanasios Christoforidis, Analysis or Interpretation: Georgia Sotiriou, Anny Mertzanian,

Meropi Dimitriadou, Amalia Sertedaki, Athanasios Christoforidis, Literature Search: Georgia Sotiriou, Stilianos Xinias, Valentina Diamantidou, Anny Mertzianian, Meropi Dimitriadou, Amalia Sertedaki, Athanasios Christoforidis, Writing: Georgia Sotiriou, Amalia Sertedaki, Athanasios Christoforidis.

Financial Disclosure: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for profit sectors.

References

1. Ng NHJ, Ghosh S, Bok CM, Ching C, Low BSJ, Chen JT, Lim E, Miserendino MC, Tan YS, Hoon S, Teo AKK. HNF4A and HNF1A exhibit tissue specific target gene regulation in pancreatic beta cells and hepatocytes. *Nat Commun*. 2024;15:4288.
2. Greeley SAW, Polak M, Njølstad PR, Barbetti F, Williams R, Castano L, Raile K, Chi DV, Habeb A, Hattersley AT, Codner E. ISPAD Clinical Practice Consensus Guidelines 2022: the diagnosis and management of monogenic diabetes in children and adolescents. *Pediatr Diabetes*. 2022;23:1188-1211.
3. McGlacken-Byrne SM, Mohammad JK, Conlon N, Gubaeva D, Siersbæk J, Schou AJ, Demirbilek H, Dastamani A, Houghton JAL, Brusgaard K, Melikyan M, Christesen H, Flanagan SE, Murphy NP, Shah P. Clinical and genetic heterogeneity of HNF4A/HNF1A mutations in a multicentre paediatric cohort with hyperinsulinaemic hypoglycaemia. *Eur J Endocrinol*. 2022;186:417-427.
4. Pearson ER, Boj SF, Steele AM, Barrett T, Stals K, Shield JP, Ellard S, Ferrer J, Hattersley AT. Macrosomia and hyperinsulinaemic hypoglycaemia in patients with heterozygous mutations in the HNF4A gene. *PLoS Med*. 2007;4:e118.
5. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group; Tamborlane WV, Beck RW, Bode BW, Buckingham B, Chase HP, Clemons R, Fiallo-Scharer R, Fox LA, Gilliam LK, Hirsch IB, Huang ES, Kollman C, Kowalski AJ, Laffel L, Lawrence JM, Lee J, Maura N, O'Grady M, Ruedy KJ, Tansey M, Tsalikian E, Weinzimer S, Wilson DM, Wolpert H, Wysocki T, Xing D. Continuous glucose monitoring and intensive treatment of type 1 diabetes. *N Engl J Med*. 2008;359:1464-1476. Epub 2008 Sep 8
6. Battelino T, Conget I, Olsen B, Schütz-Fuhrmann I, Hommel E, Hoogma R, Schierloh U, Sulli N, Bolinder J; SWITCH Study Group. The use and efficacy of continuous glucose monitoring in type 1 diabetes treated with insulin pump therapy: a randomised controlled trial. *Diabetologia*. 2012;55:3155-3162. Epub 2012 Sep 11
7. Tuminia A, Crimi S, Sciacca L, Buscema M, Frittitta L, Squatrito S, Vigneri R, Tomaselli L. Efficacy of real-time continuous glucose monitoring on glycaemic control and glucose variability in type 1 diabetic patients treated with either insulin pumps or multiple insulin injection therapy: a randomized controlled crossover trial. *Diabetes Metab Res Rev*. 2015;31:61-68.
8. Win M, Beckett R, Thomson L, Thankamony A, Beardsall K. Continuous glucose monitoring in the management of neonates with persistent hypoglycemia and congenital hyperinsulinism. *J Clin Endocrinol Metab*. 2022;107:e246-e253.
9. Garipey M, Yoosefi N, Silva C, Chanoine JP, Abdulhussein FS. The use of CGM to identify hypoglycemia and glycemic patterns in congenital hyperinsulinism. *J Pediatr Endocrinol Metab*. 2023;36:1133-1139.
10. Carette C, Dubois-Laforgue D, Saint-Martin C, Clauin S, Beauvils S, Larger E, Sola A, Mosnier-Pudar H, Timsit J, Bellanné-Chantelot C. Familial young-onset forms of diabetes related to HNF4A and rare HNF1A molecular aetiologies. *Diabet Med*. 2010;27:1454-1458.
11. Colclough K, Bellanne-Chantelot C, Saint-Martin C, Flanagan SE, Ellard S. Mutations in the genes encoding the transcription factors hepatocyte nuclear factor 1 alpha and 4 alpha in maturity-onset diabetes of the young and hyperinsulinemic hypoglycemia. *Hum Mutat*. 2013;34:669-685. Epub 2013 Apr 2
12. De Leon DD, Arnoux JB, Banerjee I, Bergada I, Bhatti T, Conwell LS, Fu J, Flanagan SE, Gillis D, Meissner T, Mohnike K, Pasquini TLS, Shah P, Stanley CA, Vella A, Yorifuji T, Thornton PS. International guidelines for the diagnosis and management of hyperinsulinism. *Horm Res Paediatr*. 2024;97:279-298. Epub 2023 Jul 14
13. Perge K, Nicolino M. Variable phenotypes of individual and family monogenic cases with hyperinsulinism and diabetes: a systematic review. *Rev Endocr Metab Disord*. 2022;23:1063-1078. Epub 2022 Aug 23
14. Altszuler N, Moraru E, Hampshire J. On the mechanism of diazoxide-induced hyperglycemia. *Diabetes*. 1977;26:931-935.
15. Kahlon H, Stanley JR, Lineen C, Lam C. Diazoxide-related hyperglycemic hyperosmolar state in a child with Kabuki syndrome. *JCEM Case Rep*. 2024;2:luae108.
16. Lawson JA, Schultz B. Diazoxide-associated hyperglycemia: a critical case precipitating hyperosmolar hyperglycemic state in a child. *J Med Toxicol*. 2025;21:93-96. Epub 2024 Dec 18
17. Nakazawa H, Naruse Y, Mori M, Hiramoto R. Hyperosmolar hyperglycemic syndrome induced by diazoxide and furosemide in a 5-year-old girl. *Clin Pediatr Endocrinol*. 2021;30:139-142. Epub 2021 Jul 10
18. Nava C, Modiano Hedenmalm A, Borys F, Hooft L, Bruschettini M, Jenniskens K. Accuracy of continuous glucose monitoring in preterm infants: a systematic review and meta-analysis. *BMJ Open*. 2020;10:e045335.
19. Wasiq MA, Behura SS, Sahoo S, Panda SK. Accuracy to detect neonatal hyperglycaemia using real-time continuous glucose monitoring during postoperative period. *Eur J Pediatr*. 2023;182:1083-1087. Epub 2022 Dec 27
20. Kalogeropoulou MS, Iglesias-Platas I, Beardsall K. Should continuous glucose monitoring be used to manage neonates at risk of hypoglycaemia? *Front Pediatr*. 2023;11:1115228.
21. Saif M, Kapoor A, Kochar IP, Jindal R. Continuous glucose monitoring system for congenital hyperinsulinemia. *Indian Pediatr*. 2013;50:421-422.