

# The role of intermittent continuous glucose monitoring in a successful outpatient transition from insulin to glibenclamide in a patient with transient neonatal diabetes

Arthur Lyra<sup>1</sup>

<https://orcid.org/0000-0002-4000-4853>

Fernanda Rodrigues Ferreira<sup>1</sup>

<https://orcid.org/0000-0002-3385-2870>

Regina Célia Santiago Moisés<sup>2</sup>

<https://orcid.org/0000-0002-9048-068X>

Renata Maria de Noronha<sup>1</sup>

<https://orcid.org/0000-0002-6202-6383>

Luis Eduardo Calliari<sup>1</sup>

<https://orcid.org/0000-0003-2085-5316>

<sup>1</sup> Ambulatório de Diabetes, Unidade de Endocrinologia Pediátrica, Departamento de Pediatria, Faculdade de Ciências Médicas da Santa Casa de São Paulo, São Paulo, SP, Brasil

<sup>2</sup> Divisão de Endocrinologia, Escola Paulista de Medicina, Universidade Federal de São Paulo, SP, Brasil

## SUMMARY

Neonatal diabetes mellitus (NDM) is a monogenic form of diabetes occurring mainly in the first 6 months of life. Approximately 30% of transient NDM (TNDM) cases will have an activating mutation in the  $K_{ATP}$  channel genes *ABCC8* and *KCNJ11*. The majority of the patients with *KCNJ11* mutations who are receiving insulin treatment can be transferred to treatment with sulfonylurea (SU), with an improvement in metabolic control and quality of life. Intermittent continuous glucose monitoring (iCGM) is used to assess the current and retrospective interstitial glucose, providing information such as hypo/hyperglycemia tendency and time on target. This case report describes the use of iCGM in the transition from insulin treatment to glibenclamide in a patient with TNDM caused by a pathogenic variant of *KCNJ11*. This is the first report of a successful outpatient transition from insulin to glibenclamide, in a Brazilian child with TNDM using iCGM (FreeStyle Libre®). The remote monitoring and online management allowed the patient to safely stay at home during the transition from insulin to SU, especially important in the context of the COVID-19 pandemic. We conclude that iCGM is a helpful tool in cases of NDM and should be used to increase safety and speed up dose adjustments in outpatient transition from insulin to glibenclamide. Arch Endocrinol Metab. 2022;66(3):429-35

## Correspondence to:

Luis Eduardo Calliari  
Ambulatório de Diabetes, Unidade de Endocrinologia Pediátrica, Departamento de Pediatria, Faculdade de Ciências Médicas da Santa Casa de São Paulo  
Rua Dr. Cesário Mota Jr., 112  
01238-010 – São Paulo, SP, Brasil  
lecalliari@gmail.com

Received on Oct/15/2021

Accepted on Mar/8/2022

DOI: 10.20945/2359-399700000484

## INTRODUCTION

Neonatal diabetes mellitus (NDM), a rare condition with an estimated incidence of 1:90,000-210,000 live births (1), is a monogenic disorder with onset mainly in the first six months of life (1). It can be permanent (PNDM), where lifelong treatment is required, or transient (TNDM), where remission occurs within months with recurrence in approximately half of the patients later in life (1-3).

Approximately 30% of TNDM cases will have an activating mutation in the  $K_{ATP}$  channel genes *ABCC8* and *KCNJ11*, which code, respectively, for the SUR1 and Kir6.2 subunits of the channel (4). Pathogenic gain-of-function variants in the *KCNJ11* gene cause

the permanent opening of the  $K_{ATP}$  channel, which maintains the resting state of the cell membrane of the beta-cell. Thus, there is no depolarization of the cell membrane, preventing insulin release (5)

The literature shows that most patients with *KCNJ11* pathogenic variants being treated with insulin could be transferred to treatment with sulfonylurea (SU). The transfer to SU is usually done in the hospital to guarantee the patient's safety, and the recommendation is to measure glucose before and two hours after each meal, at bedtime, and 2AM (6,7). To perform this transition at home, families require training regarding monitoring and management of hypoglycemia.

Continuous glucose monitoring (CGM) systems, either real-time or intermittent (iCGM), have recently become more widely available. The iCGM assesses current and retrospective interstitial glucose and comprises: 1. A glucose sensor attached to the patient's arm; 2. A reader, which receives data and evaluates time in target range, as well as hypo/hyperglycemia tendencies. These devices could potentially offer support in the transition from insulin to sulfonylurea therapy in NDM (8).

Here, we report the case of a patient with TDNM due to a mutation in the *KCNJ11* gene, where the use of iCGM was found to be an important tool during the transition from insulin to SU in outpatient care, during the context of the COVID-19 pandemic.

## CASE REPORT

We report a 6.8 year-old Brazilian boy, who is the second child of a non-consanguineous Caucasian couple, with no family history of diabetes mellitus. He was born at 38 weeks gestation, birth weight of 2,185 g, and birth length of 44cm (both below -2SDS).

At five months of age, he presented with respiratory symptoms (dyspnea) and was reviewed in the emergency room. He had a blood glucose of 600 mg/dL, acidosis, and ketonuria and insulin therapy was initiated. After four days, he was discharged using insulin glargine 2 IU/day and referred to our Pediatric Endocrine Unit.

Further investigation revealed glycated hemoglobin (HbA1c) of 8.4%, undetectable C-peptide, negative islet-cell antibody, glutamic acid decarboxylase antibody and insulin auto-antibody. The diagnosis of NDM was suspected and molecular genetic evaluation was performed. A missense heterozygous mutation p.Glu227Lys (c.679G>A) was found in the *KCNJ11* gene, on chromosome 11p15.1. The E227K mutation was previously reported as a pathogenic variant (6). The parents are asymptomatic and were not tested for this mutation.

During follow-up, his insulin requirements gradually decreased, and insulin therapy ceased at the age of 1.2 years. In the following five years after insulin discontinuation, the patient remained asymptomatic, his HbA1c levels ranged from 6.1-6.5% and C-peptide was 0.8 ng/mL.

At 6.5-years-old, polydipsia and polyuria were noticed by his parents. He was brought in for an evaluation, his weight was 25.6 kg (+1.2 SDS), height

112.5 cm (-1.2 SDS), and BMI 20.2 kg/m<sup>2</sup> (+2.5 SDS). Laboratory tests showed HbA1c: 8.5%, fasting blood glucose: 177 mg/dL and C-peptide: 1.1 ng/mL, indicating a relapse of diabetes.

He was therefore re-started on insulin, on November 28<sup>th</sup> 2020. The initial dose was degludec 1 IU/day and fast-acting insulin lispro 0.5IU before meals if hyperglycemic.

After insulin was initiated, the use of iCGM (FreeStyle Libre®) was proposed and accepted by the family. This system is approved by the National Health Surveillance Agency for children aged 4 years and over. During insulin therapy, the device's 14-day analysis revealed a glucose management index (GMI) of 7.2%, 72% of the time in range (70-180 mg/dL), 28% above target, and 0% hypoglycemia (Figure 1).

After glucose stabilization it was decided to switch therapy from insulin to a SU (glibenclamide). This switch is done in the hospital in the majority of patients (7) to ensure a safe transition, but given the restrictions due to the COVID-19 pandemic, it was decided that the patient should undertake the transition as an outpatient. During transition data from iCGM was uploaded using an online platform (LibreView platform®). Access to this website allowed the medical team to perform remote daily checks on glucose levels variations and suggest treatment changes.

Oral glibenclamide was started at a dose of 2.5 mg every 12 hours (0.2 mg/kg/day) on December 17<sup>th</sup> 2020. The patient's glucose profile improved rapidly, and insulin therapy was discontinued on the second day (Figure 2).

Sensor data guided changes in glibenclamide dose, which was gradually reduced to a final dose of 1.25 mg once daily (0.05 mg/kg/day). After 44 days of SU treatment, sensor data showed a time in range of 87%, GMI of 5.6% (Figure 3) and a decrease of HbA1c to 7.1%.

After four months of SU treatment, HbA1C level was 6.1% and iCGM showed that the patient had low glycemic variability, GMI of 6.2%, 93% of the time in the target range, 3% of the time in hyperglycemia, 4% hypoglycemia (54-69 mg/dL) (Figure 4).

## DISCUSSION

We present a case where the use of precision medicine and technology support allowed a successful transition from insulin to glibenclamide without hospitalization

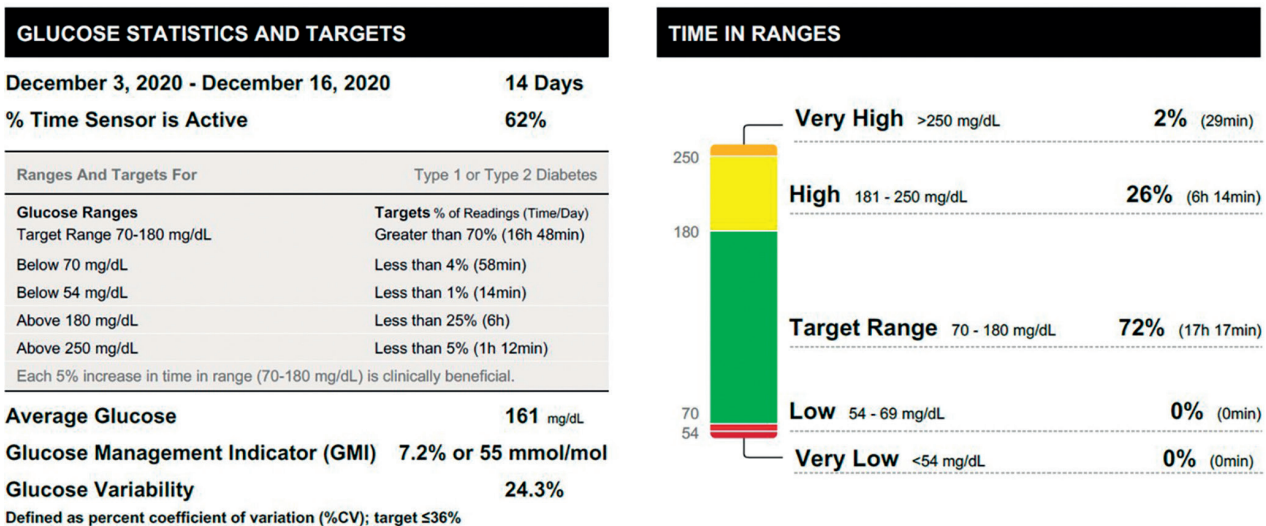
in a challenging period during COVID-19 pandemic. Our patient had a diagnosis of NDM and absence of autoantibodies (2). He was born small for gestational age, which is found in 62% of cases of NDM (2). Genetic testing is strongly recommended for neonates with persistent hyperglycemia (9). The pathogenic variant found in the *KCNJ11* gene, E227K is a gain-of-function mutation that decreases sensitivity to ATP in the  $K_{ATP}$  channel, causing reduction in insulin secretion that evolves with TNDM (9). Our patient had a remission of diabetes at 30 weeks of age and a relapse around six years old. These periods are consistent with the published data on TNDM, where remission occurred with a mean age of 35 weeks (5-208) and relapse at 4.7 years (3-15) (10). A systematic review of

103 articles analyzed the transfer from insulin treatment to sulfonylurea in 502 cases of NDM, 82.3% as a result of mutations of the *KCNJ11* gene, and found a success rate of 91%. The average dose of SU required for the treatment of NDM was 0.48 mg/kg/day (0.017-2.8 mg/kg/day). The pathogenic variant E227K was described in 13 cases and was classified as being sensitive to treatment with SU since all cases responded to glibenclamide (6). In our patient, we reached a dose of 0.05 mg/kg/day, which is lower than the dose described in a meta-analysis with 81 patients with *KCNJ11* mutations (0.12-0.45 mg/kg/day). Bowman and cols. enrolled 81 NDM carriers of *KCNJ11* gene mutations and reported 93% effectiveness of SU as a long-term monotherapy, with an average follow-up

## AGP Report

December 3, 2020 - December 16, 2020 (14 Days)

LibreView



## AMBULATORY GLUCOSE PROFILE (AGP)

AGP is a summary of glucose values from the report period, with median (50%) and other percentiles shown as if occurring in a single day.

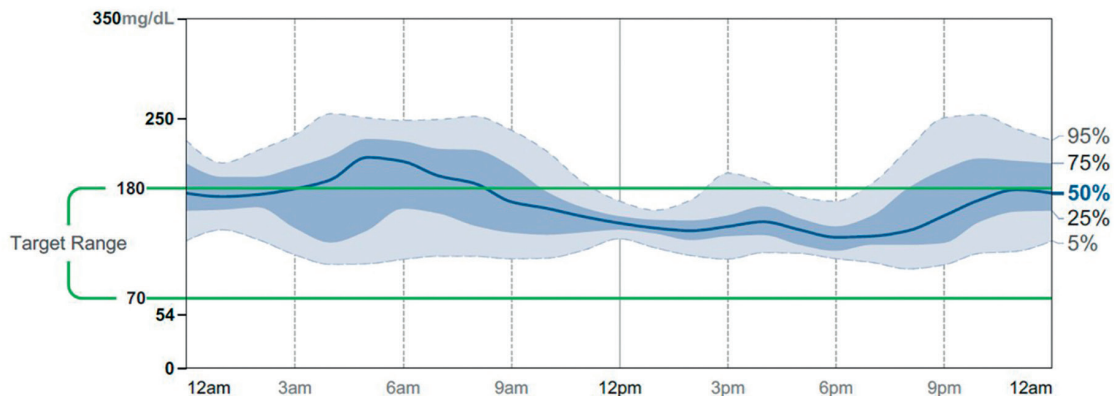


Figure 1. Two-week iCGM report using insulin.

duration of 10.2 years. In addition, the safety of SU is highlighted in the study, with no reports of seizures or loss of consciousness caused by hypoglycemia (11). The 0.05 mg/kg/day dose is equivalent to ¼ of a tablet that the parents have to crush and dilute with water since there is no other option available in Brazil at present. The use of a SU suspension like Amglicia®, recently authorized in France, could, theoretically, enable the delivery of more accurate dosages (12). This medication is still not approved by the Brazilian Health Surveillance Agency.

To the best of our knowledge, this is the first report of a successful outpatient transition from insulin to glibenclamide with iCGM in a Brazilian child with T1DM. Two articles reported Brazilian patients with *KCNJ11* mutations where a transition to glibenclamide was attempted, the first in a child with PNDM without response (13), and the second in an adult patient with a PNDM who successfully transitioned (14).

The outpatient protocol published by Pearson and cols. (7) proposes that capillary blood glucose, performed using blood from lancet finger pricks, should be tested before all meals and at bedtime. As an

alternative, we used iCGM for the measurement of interstitial glucose. With CGM, there was an increase in the number of glucose measurements to an average of 15 iCGM scans/day. This increase in measurements without invasive procedures helped to improve the distress caused by finger pricks and also gave more information regarding glucose variations during the transition phase.

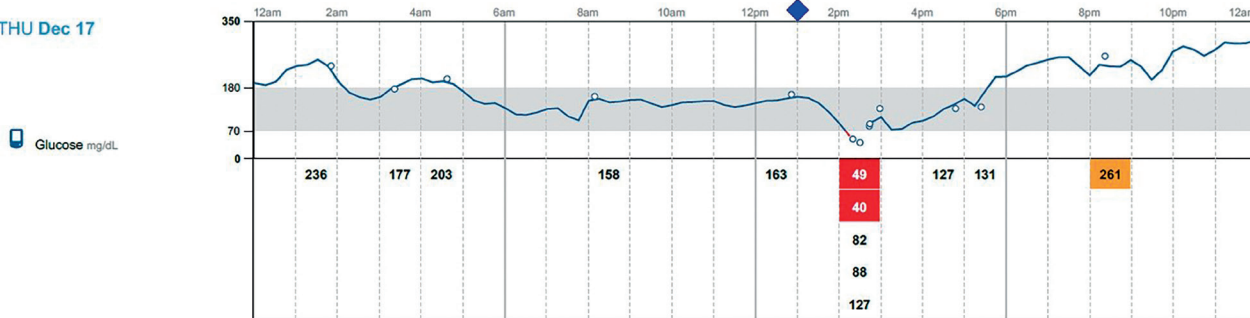
The use of iCGM had another important role in this case. Due to the COVID-19 pandemic, hospitalizations were restricted to severe cases. The use of a system with an automatic real-time transmission of interstitial glucose values from the sensor to the LibreView platform@ allowed the medical team to monitor glucose every day during the transition period. This analysis enabled the identification of patterns of hyper/hypoglycemia daily, thus accelerating therapeutic decisions to optimize treatment and reduce risks for the patient. Dahl and Kumar also mention the importance of using CGM, especially due to the risk of hypoglycemia in children with NDM, whose signs can be difficult to recognize, as the infant can present nonspecific signs such as behavioral changes and irritability (9).

### Daily Log

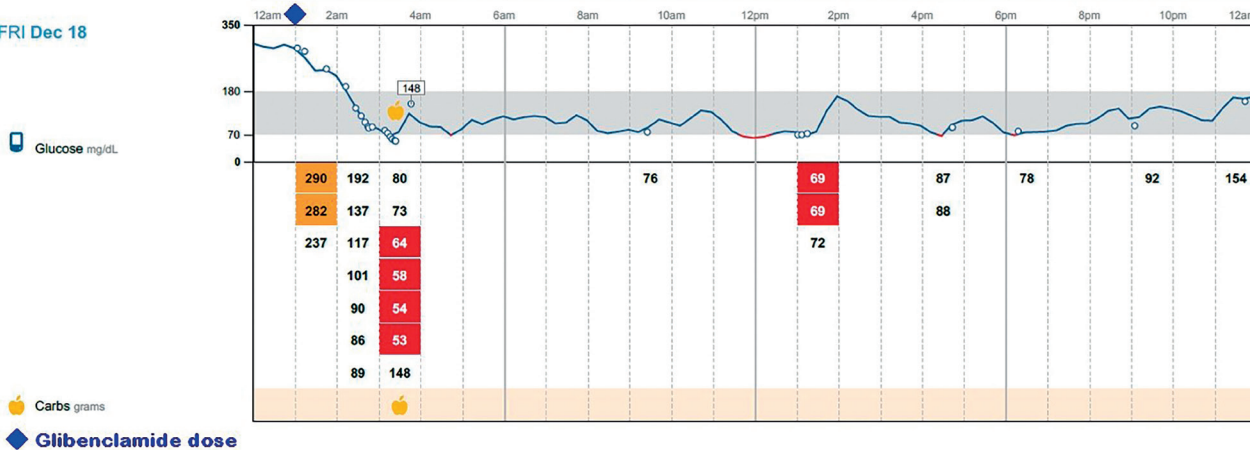
December 9, 2020 - December 22, 2020 (14 Days)

LibreView

THU Dec 17



FRI Dec 18



Copyright © AEGM all rights reserved.

Figure 2. First two days of therapy with glibenclamide (SU) at 1 pm and 1 am.

The advantages of using CGM associated with online data-sharing become more obvious when comparing this new method with the outpatient protocol proposition in which the physician should see the patient every week and be accessible by phone every day during the transfer (8).

Therefore, access to the iCGM information allowed the switch to SU to occur without hospitalization, minimizing the exposure of the family to in-hospital contamination, yet assuring safety by giving the medical team real-time results that were used to monitor and promptly adjust SU dosages (15). Rabbone and cols. describe the use of CGM (Medtronic Enlite/Dexcom

G4) integrated with continuous subcutaneous insulin infusion pumps (CSII) therapy, which allows for more precise glycemic control. This article mainly focuses on how the use of CSII allows the gradual and safe substitution of insulin therapy for glibenclamide, reducing the risk of diabetic ketoacidosis (DKA) (16). The use of CSII may be considered the gold standard in infants with neonatal diabetes, but is still not widely available. The use of iCGM in patients on MDI could be both safe and affordable when CSII is not an option.

The use of the iCGM has its limitations – the device may suffer damage with use, fall from the

## AGP Report

December 31, 2020 - January 13, 2021 (14 Days)

LibreView

### GLUCOSE STATISTICS AND TARGETS

December 31, 2020 - January 13, 2021 **14 Days**

**% Time Sensor is Active** **100%**

Ranges And Targets For	Type 1 or Type 2 Diabetes
<b>Glucose Ranges</b>	<b>Targets % of Readings (Time/Day)</b>
Target Range 70-180 mg/dL	Greater than 70% (16h 48min)
Below 70 mg/dL	Less than 4% (58min)
Below 54 mg/dL	Less than 1% (14min)
Above 180 mg/dL	Less than 25% (6h)
Above 250 mg/dL	Less than 5% (1h 12min)

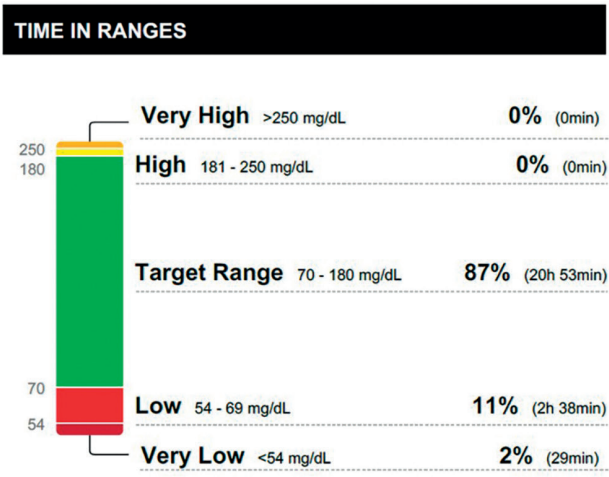
Each 5% increase in time in range (70-180 mg/dL) is clinically beneficial.

**Average Glucose** **94 mg/dL**

**Glucose Management Indicator (GMI)** **5.6% or 37 mmol/mol**

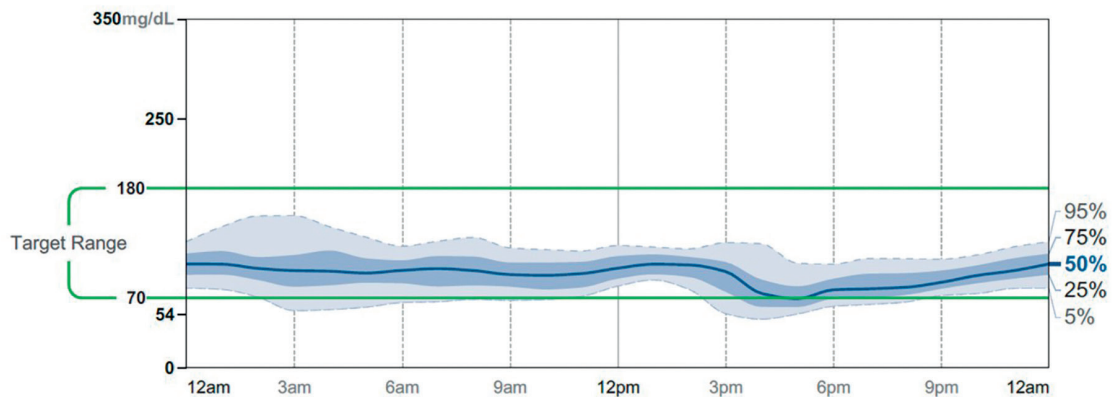
**Glucose Variability** **22.0%**

Defined as percent coefficient of variation (%CV); target ≤36%



### AMBULATORY GLUCOSE PROFILE (AGP)

AGP is a summary of glucose values from the report period, with median (50%) and other percentiles shown as if occurring in a single day.



### DAILY GLUCOSE PROFILES

Figure 3. Ambulatory glucose profile (AGP) report during the first days of starting treatment with SU.

patient’s arm or contain a calibration error. If any of these occurrences happen, the recommendation is to replace the sensor or start capillary blood glucose measurements. In addition, the family was instructed to confirm hypoglycemia identified by the iCGM through capillary blood glucose, as sensor displacement could generate low glucose values. In the case described none of these problems occurred.

The strengths of our report rely on the importance of the genetic diagnosis of TDM to define the best therapeutic option and the use of technological support (iCGM) to increase safety and convenience for the patient. The weakness is that this is just one case, not enough to generalize the indication of iCGM to help transition from insulin to SU to be done at home.

Nonetheless, we believe that this experience can be used as an example and eventually replicated in other settings.

We conclude that neonatal diabetes is a model of a genetic disease that can benefit from precision medicine, where treatment is defined after molecular diagnosis, and that iCGM is a valuable tool that should be considered to monitor glucose during the process of SU introduction to these patients.

Informed consent: written informed consent was obtained from the mother and followed the principles of the Declaration of Helsinki.

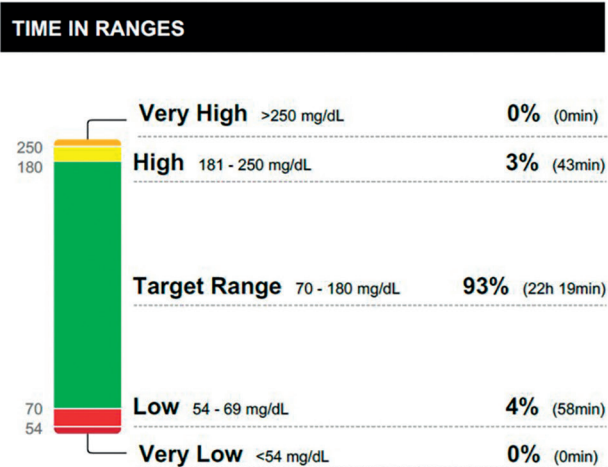
Study approval statement: this study protocol was reviewed and approved by *Instituto de Pesquisa Clínica da Santa Casa de São Paulo Brasil*, approval number 42854621.2.0000.5479.

## AGP Report

April 4, 2021 - April 17, 2021 (14 Days)

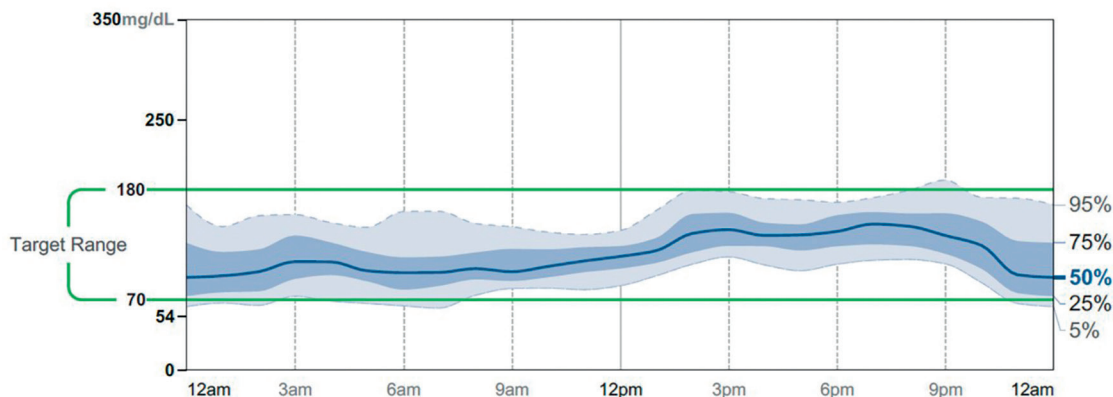
LibreView

GLUCOSE STATISTICS AND TARGETS	
<b>April 4, 2021 - April 17, 2021</b>	
<b>14 Days</b>	
<b>% Time Sensor is Active</b>	<b>70%</b>
Ranges And Targets For Type 1 or Type 2 Diabetes	
<b>Glucose Ranges</b>	<b>Targets % of Readings (Time/Day)</b>
Target Range 70-180 mg/dL	Greater than 70% (16h 48min)
Below 70 mg/dL	Less than 4% (58min)
Below 54 mg/dL	Less than 1% (14min)
Above 180 mg/dL	Less than 25% (6h)
Above 250 mg/dL	Less than 5% (1h 12min)
Each 5% increase in time in range (70-180 mg/dL) is clinically beneficial.	
<b>Average Glucose</b>	<b>119 mg/dL</b>
<b>Glucose Management Indicator (GMI)</b>	<b>6.2% or 44 mmol/mol</b>
<b>Glucose Variability</b>	<b>25.8%</b>
Defined as percent coefficient of variation (%CV); target ≤36%	



## AMBULATORY GLUCOSE PROFILE (AGP)

AGP is a summary of glucose values from the report period, with median (50%) and other percentiles shown as if occurring in a single day.



Copyright © AEGM all rights reserved.

Figure 4. iCGM reports after 4 months of SU treatment.

Consent to publish statement: written informed consent was obtained from their parents for publication of the details of their medical case and any accompanying images.

Sponsorship: the authors declare that this study received no financial support.

Authorship contributions: concept – Luis Eduardo Calliari, Renata Maria de Noronha. Data collection and processing – Arthur Lyra, Fernanda Rodrigues Ferreira. Writing: Arthur Lyra, Fernanda Ferreira Rodrigues, Regina Célia Santiago Moisés, Luis Eduardo Calliari, Renata Maria de Noronha. Analysis and interpretations – Arthur Lyra, Fernanda Ferreira Rodrigues, Regina Célia Santiago Moisés, Luis Eduardo Calliari, Renata Maria de Noronha. Literature search – Arthur Lyra, Fernanda Ferreira Rodrigues, Regina Célia Santiago Moisés, Luis Eduardo Calliari, Renata Maria de Noronha.

Data availability statement: all datasets on which the conclusions of the paper are available to editors, reviewers and readers without unnecessary restriction wherever possible.

Disclosure: no potential conflict of interest relevant to this article was reported.

## REFERENCES

1. Iafusco D, Massa O, Pasquino B, Colombo C, Iughetti L, Bizzarri C, et al. Minimal incidence of neonatal/infancy onset diabetes in Italy is 1:90,000 live births. *Acta Diabetol.* 2012;49:405-8.
2. Busiah K, Drunat S, Vaivre-Douret L, Bonnefond A, Simon A, Flechtner I, et al. Neuropsychological dysfunction and neurodevelopmental defects associated with genetic changes in infants with neonatal diabetes mellitus: a prospective cohort study. *Lancet Diabetes Endocrinol.* 2013;1:199-207.
3. Polak M, Cave H. Neonatal diabetes mellitus: a disease linked to multiple mechanisms. *Orphanet J Rare Dis.* 2007;2:12.
4. Devaraja J, Elder C, Scott A. Non classic presentations of a genetic mutation typically associated with transient neonatal diabetes. *Endocrinol Diabetes Metab Case Rep.* 2020;2020:19-0121.
5. Hattersley AT, Greeley SA, Polak M, Rubio-Cabezas O, Njølstad PR, Mlynarski W, et al. ISPAD Clinical Practice Consensus Guidelines 2018: The diagnosis and management of monogenic diabetes in children and adolescents. *Pediatr Diabetes.* 2018;19:47-63.
6. Garcin L, Mericq V, Fauret-Amsellem A, Cave H, Polak M, Beltrand J. Neonatal diabetes due to potassium channel mutation: response to sulfonylurea according to the genotype. *Pediatr Diabetes.* 2020;21(6):932-41.
7. Pearson ER, Flechtner I, Njølstad PR, Malecki MT, Flanagan SE, Larkin B, et al. Switching from insulin to oral sulfonylureas in patients with diabetes due to Kir6.2 mutations. *N Engl J Med.* 2006;355(5):467-77.
8. Danne T, Nimri R, Battelino T, Bergenstal RM, Close KL, DeVries JH, et al. International consensus on use of continuous glucose monitoring. *Diabetes Care.* 2017;40(12):1631-40.
9. Dahl A, Kumar A. Recent advances in neonatal diabetes. *Metab Syndr Obes.* 2020;13:355-64.
10. Flanagan SE, Patch AM, Mackay DJ, Edghill EL, Gloyn AL, Robinson D, et al. Mutations in ATP-sensitive K<sup>+</sup> channel genes cause transient neonatal diabetes and permanent diabetes in childhood or adulthood. *Diabetes.* 2007;56(7):1930-7.
11. Bowman P, Sulen A, Barbetti F, Beltrand J, Svalastoga P, Codner E, et al. Effectiveness and safety of long-term treatment with sulfonylureas in patients with neonatal diabetes due to KCNJ11 mutations: an international cohort study. *Lancet Diabetes Endocrinol.* 2018;6:637-46.
12. Beltrand J, Baptiste A, Busiah K, Bouazza N, Godot C, Boucheron A, et al. Glibenclamide oral suspension: suitable and effective in patients with neonatal diabetes. *Pediatr Diabetes.* 2019;20:246-54.
13. Della Manna TD, Battistini C, Radonsky V, Savoldelli RD, Damiani D, Kok F, et al. Glibenclamide unresponsiveness in a Brazilian child with permanent neonatal diabetes mellitus and DEND syndrome due to a C166Y mutation in KCNJ11 (Kir6.2) gene. *Arq Bras Endocrinol Metabol.* 2008;52(8):1350-5.
14. Vendramini MF, Gurgel LC, Moisés RS. Long-term response to sulfonylurea in a patient with diabetes due to mutation in the KCNJ11 gene. *Arq Bras Endocrinol Metabol.* 2010;54(8):682-4.
15. Battelino T, Danne T, Bergenstal RM, Amiel SA, Beck R, Biester T, et al. Clinical targets for continuous glucose monitoring data interpretation: Recommendations from the international consensus on time in range. *Diabetes Care.* 2019;42(8):1593-603.
16. Rabbone I, Barbetti F, Marigliano M, Bonfanti R, Piccinno E, Ortolani F, et al. Successful treatment of young infants presenting neonatal diabetes mellitus with continuous subcutaneous insulin infusion before genetic diagnosis. *Acta Diabetol.* 2016;53(4):559-65.