CASE REPORT

DOI: 10.4274/jcrpe.galenos.2023.2023-2-12

J Clin Res Pediatr Endocrinol 2025;17(1):120-125

Continuous Glucose Monitoring Systems and the Efficacy of Acarbose Treatment in Cystic Fibrosis-related Dysglycemia

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What is already known on this topic?

Dysglycemia is common in patients with cystic fibrosis (CF). Insulin is the first choice for treatment, especially in cases of hyperglycemia.

What this study adds?

In the early detection of CF related diabetes (CFRD), screening with oral glucose tolerance test after the age of 10 years may be inaccurate. Therefore, routine use of the continous or intermittant glucose monitoring systems should be considered. In CFRD with severe hypoglycemia, acarbose may be an important alternative in the high and increased dose range.

Abstract

Early detection of glycemic dysregulation and optimization of glycemic control in cystic fibrosis (CF) related diabetes (CFRD) is associated with improved pulmonary function and decreased mortality. The standard 2-hour oral glucose tolerance test (OGTT) is the current routine screening test for CFRD. However, hyperglycemia can be detected by continuous glucose monitoring systems (CGMS) in patients with normal OGTT evaluation. High-dose acarbose is an important alternative in the treatment of glycemic dysregulation especially accompanied by hypoglycemia. A 7-year-old boy with CF presented with hyperglycemia. Hypoglycemia (29 mg/dL) and hyperglycemia (400 mg/dL) were demonstrated by OGTT and intermittent CGM (iCGMS). Thickener was added to nutritional solutions and acarbose was initiated as 3x12.5 mg/dose and increased to 6x25 mg without any side effects. On the twentieth day of treatment, glycemic dysregulation resolved. In the early detection of CFRD, screening with OGTT after the age of 10 years may be inaccurate. Therefore, routine use of CGMS or iCGMS should be considered. In addition, in CFRD with severe hypoglycemia, acarbose may be an important alternative in the high and increased dose range.

Keywords: Acarbose, CFRD, CGMS, cystic fibrosis

Introduction

The incidence of cystic fibrosis (CF) related diabetes (CFRD) has increased as more effective clinical management of CF has developed and the life expectancy of patients with CF extended. The prevalence of CFRD increases markedly with age, affecting approximately 2% of children, 19% of adolescents, and 40% to 50% of adults with CF (1). Early detection of glycemic dysregulation and optimization of glycemic control is associated with improved body weight and pulmonary function, reduced frequency of pulmonary exacerbations, and decreased mortality (1). Therefore, early detection of glycemic dysregulation in patients with CF is important. The issue of how to screen for glycemic dysregulation in these patients is still contentious. The standard 2-hour oral glucose tolerance test (OGTT) is currently

Cite this article as: Arslan E, Özalp Kızılay D, Atik Altınok Y, Girgin Dündar B, Jalilova A, Demir G, Özen S, Darcan Ş, Gökşen RD. Continuous glucose monitoring systems and the efficacy of acarbose treatment in cystic fibrosis-related dysglycemia. J Clin Res Pediatr Endocrinol. 2025;17(1):120-125

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Received: 27.03.2023
Accepted: 11.09.2023
Epub: 14.09.2023
Publication date: 19.03.2025

the routine screening test for CFRD and is recommended annually after 10 years of age. However, hyperglycemia (>200 mg/dL) may be detected by continuous glucose monitoring systems (CGMS) in patients with normal OGTT evaluation (2). Therefore, CGMS has been suggested for use in follow-up. Treatment of CFRD is complicated because of the presence of both insulin deficiency and resistance, a high energy requirement, nocturnal feeding to ensure adequate energy intake, fasting and postprandial hypoglycemia as well as hyperglycemia. Insulin therapy is often required in these patients. However, different treatment methods are used in the management of early glucose dysregulation and in patient groups with prominent hypoglycemia (3,4,5).

Case Report

A 7-year-old boy with CF (homozygous c.2183AA>G variant was detected in the *CFTR* gene) and pancreatic insufficiency presented with hyperglycemia during resolution of a pulmonary exacerbation.

Since the age of four years, routine annual hemoglobin A1c (HbA1c) had remained below 6.5% (NR 5.4% to 6.4%). OGTT was performed with frequent sampling (at minutes -15, 0, 10, 20, 30, 45, 60, 90, 120, 150, 180) and symptomatic severe fasting hypoglycemia (29 mg/dL), severe hyperglycemia at 60 minutes (400 mg/dL), impaired glucose tolerance at 120 minutes (180 mg/dL) and severe hypoglycemia at 180 minutes (26 mg/dL) was detected (Table 1). He had no history of polyuria, polydipsia, or chronic glucocorticoid treatment. He had a history of frequent acute exacerbations and hospitalization, poor weight gain, and underwent a gastrostomy at the age of four years. His weight was 20 kg (-1.18 standard deviation score (SDS)], height 124 cm (-0.21 SDS) and body mass index (BMI) 13.1 (-2.39 SDS). He was on a high energy diet by oral and gastrostomy route with continuou infusion overnight and pump assisted infusion during the day.

Anti-insulin and anti-glutamic acid decarboxylase antibodies were negative. Sensor glucose readings above 350 mg/dL and below 50 mg/dL were detected with intermittent CGMS (iCGMS) (FreeStyle Libre system; Abbott Diabetes Care) (Figure 1). Due to frequent acute exacerbations, history of hospitalization, and poor weight gain, the need for gastrostomy was accepted as a symptom of CFRD for our patient. The patient was diagnosed with CFRD according to the International Society for Pediatric and Adolescent Diabetes (ISPAD) 2022 CFRD guideline with hyperglycemia exceeding 200 mg/dL, which was detected both by OGTT and CGMS data.

Glucose dysregulation was attributed to the negative effect of CF on gastric emptying and insulin-glucagon action. Postprandial hyperglycemia and reactive hypoglycemia were also associated with delayed and prolonged hyperinsulinemia.

To prevent postprandial rapid glucose rise and reactive hypoglycemia, enteral nutrition formula content was adjusted and thickener was added. Since hyper- and hypoglycemia continued after these changes, 3x12.5 mg of acarbose (alpha-glucosidase inhibitor) was added due to the effect of slowing down the hydrolysis and absorption of carbohydrates before the meal and the initial dose was gradually increased. Although glucose fluctuations decreased, hyperglycemia persisted during meals without

Table 1. Frequently sampled oral glucose tolerance test

	-15. min	0. min	10. min	20. min	30. min	45. min	60. min	90. min	120. min	150. min	180. min
Glucose (mg/dL)	29	55	65	130	208	342	415	308	181	45	26
Insulin (mU/L)	0.772	4.15	2.21	5.21	5.86	76.4	220	174	67.3	17.9	5.88
C-peptide (mg/L)	0.232	1.04	1.21	2.7	2.36	7.64	18.1	17.3	14.7	7.01	3.25

min: minutes

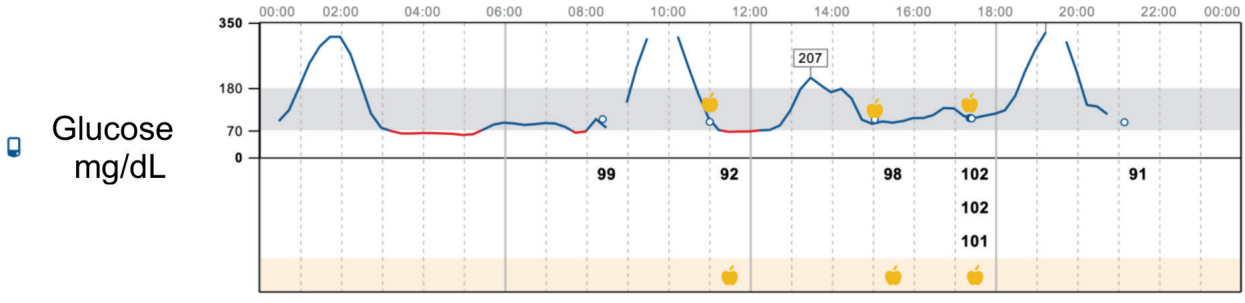

Figure 1. Pre-treatment continuous glucose monitoring systems

acarbose treatment and so treatment was increased to 6x12.5 mg and then gradually to 6x25 mg without any side effects (Figure 2). On the twentieth day of treatment, no hyper- or hypoglycemia was detected. The CGMS data of the case before and after treatment is summarized in Table 2. Weight gain improved after treatment, and at the sixth month of treatment, improvements in weight 22.5 kg (-0.62 SDS), height 127 cm (-0.14 SDS) and BMI 13.95 (-1.56) were noted.

Discussion

CFRD shares some characteristics with both type 1 and type 2 diabetes, yet also has unique pathophysiologic considerations. CFRD is not an autoimmune disease as diabetes autoantibodies and diabetes-associated HLA types are not different from the general population (6). Specific features of CFRD include partial loss or dysfunction of pancreatic islets leading to deficiency of insulin secretion, insulin resistance caused by chronic inflammation that increases and fluctuates periodically during infection, a very high energy diet in order to achieve weight gain, and disruption of the incretin system.

The incretin axis is involved in the etiology of the development of CFRD. Incretins, such as glucose-dependent insulinotropic polypeptide and glucagon-like peptide 1 (GLP-1), are intestinal hormones that are secreted after meals, primarily triggered by carbohydrates. Insulin release, inhibition of glucagon and somatostatin, preservation of β-cells, delay of gastric emptying, and suppression of appetite are important biological effects of incretins. Kuo et al. (7) showed that nondiabetic CF patients with exocrine pancreatic insufficiency had faster gastric emptying after a high-fat/high-carbohydrate meal compared with healthy controls. This was accompanied by profound disruption of GLP-1 secretion and these authors suggested that this is one of the causes of postprandial glycemic variability

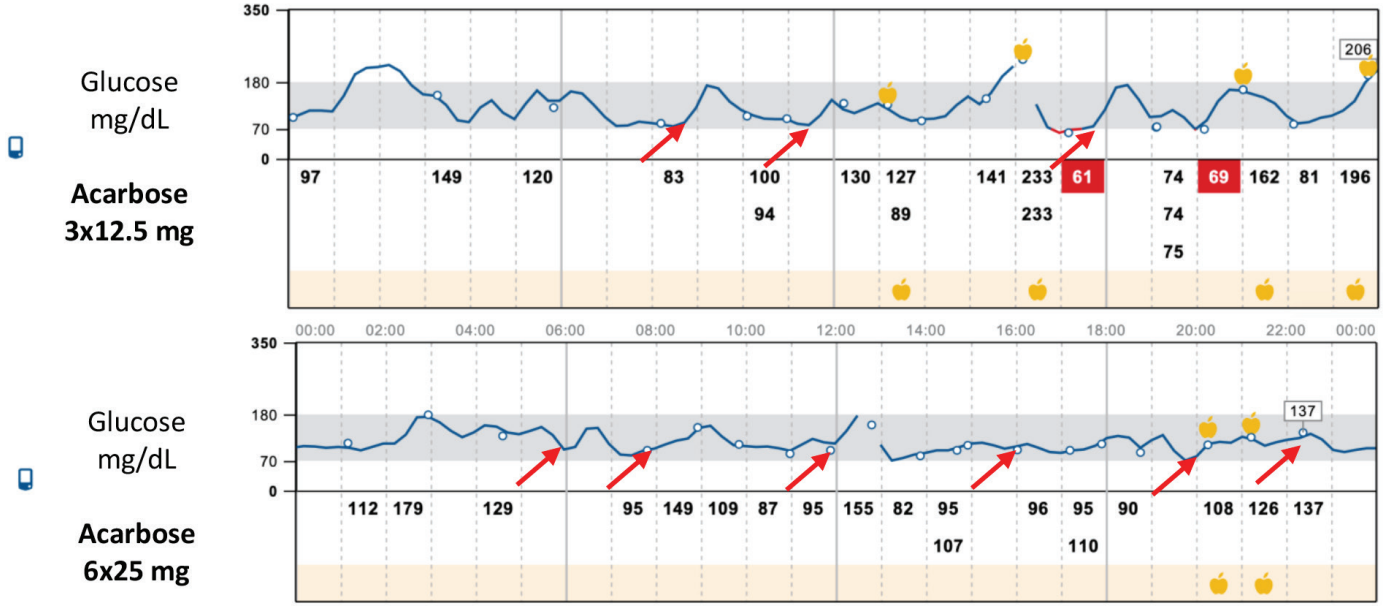

Figure 2. After adding acarbose to meals

**Red arrows indicated with meals added acarbose*

Table 2. CGMS data before and after treatment changes

	Before treatment	With thickener	Acarbose 3x12.5 mg	Acarbose 6x25 mg
GMI, %	7.2	6.8	6.8	6.0
Mean glucose, mg/dL	164	145	144	114
CV, %	40.7	38.7	36.2	22.9
Time in range, %	60	74	80	96
Low glucose*, %	6	4	2	1
Very low glucose**, %	2	1	1	0

* < 70 mg/dL, ** < 55 mg/dL.
CGMS: continuous glucose monitoring systems

in patients with CF (7). This hypothesis is consistent with the fact that the first step in the progression to CFRD is impaired first-phase insulin secretion (6). Compatible with this mechanism, in the presented case there was a rapid increase in serum glucose level in the postprandial first hour due to fast gastric emptying, followed by delayed and exaggerated hyperinsulinemia and reactive hypoglycemia.

The diagnosis of CFRD may be more challenging than the classical diagnosis of diabetes, and HbA1c in the diagnosis is questioned. In the ISPAD CFRD guideline, diagnosis of CFRD is made according to American Diabetes Association criteria during a period of stable baseline health:

a. 2-hour blood glucose on OGTT ≥11.1 mmol/L (≥200 mg/dL),

b. Fasting blood glucose ≥7.0 mmol/L (≥126 mg/dL),

i. Fasting blood glucose ≤7.0 mmol/L (≤126 mg/dL) does not rule out diabetes in CF,

c. HbA1c ≥ 48 mmol/mol (≥6.5%),

ii. HbA1c < 48 mmol/mol (< 6.5%) does not rule out diabetes in CF,

d. Random blood glucose ≥11.1 mmol/L (≥200 mg/dL) with classic symptoms of diabetes (2).

Although it has been demonstrated that the sensitivity of HbA1c in the diagnosis of CFRD is low, ISPAD 2022 CFRD guideline recommends classical diabetes criteria for diagnosis of CFRD. However, the guideline also states that a normal or low HbA1c value does not exclude CFRD. Consequently, it cannot be asserted that HbA1c is no longer commonly utilized in the monitoring of patients with CF.

Glucose abnormalities demonstrated by CGM are common in CF, including in very young children, however there are as yet no established criteria using CGM for either screening or diagnosing diabetes. Retrospective and cross-sectional single-center studies have associated glucose abnormalities on CGM with ß-cell dysfunction on OGTT, weight decline, lower lung function, and elevated inflammatory markers. However, evidence from larger multi-center studies are lacking to support the benefits of treating intermittent elevations in blood glucose concentrations prior to a diagnosis of diabetes (2).

Many studies have questioned the adequacy of the OGTT for the early detection of impaired glucose regulation, emphasizing that the decline in the patient's weight and pulmonary function would have started much earlier if the diagnosis was based solely on OGTT (8). Mainguy et al. (9) reported that the capacity of an OGTT to diagnose CFRD was weak and pathological glucose fluctuations were frequent, even in the early stages of life. Hameed et al. (10) showed that peak glucose occurred earlier than the routinely measured 120-minute sample, occurring within 30 minutes in 18% of patients, 60 minutes in 45%, 90 minutes in 33%, and 120 minutes in only 3%.

Many studies have shown that CGM is a useful clinical tool in CF, and many studies continue to be conducted on the interpretation and predictiveness of CGMS (11). It should be kept in mind that weight loss and poor weight gain may also be predisposing to CFRD, as in our case. Thus it should not be overlooked that close CGMS monitoring should be performed in patients with CF who need continuous enteral nutrition. As recommended in the ISPAD 2022 CFRD guideline, these patients should have their blood glucose checked in the middle and at the end of feeding. Furthermore, these patients are suggested to be suitable candidates for follow-up with CGMS.

Another important problem in CF patients with abnormal glucose tolerance is reactive hypoglycemia. It has been reported that the prevalence of reactive hypoglycemia may be as high as 29% during OGTT, especially if the test is performed > 2 hours (6).

In the presented case, CFRD was diagnosed with both OGTT and CGMS. However, it should be noted that we did not perform the standard OGTT, which is currently recommended in the CFRD guidelines. Since we used OGTT with frequent sampling, hyperglycemia was detected reaching 400 mg/dL in the first hour and hypoglycemia after 120 minutes. Had the standard OGTT been employed, a hyperglycemic level of 181 mg/dL would have been identified at the 120-minute mark; however, hypoglycemia occurring after 120 minutes would not have been recognized. Consequently, the patient would receive a diagnosis of impaired glucose tolerance exclusively. Therefore, we suggest that the standard OGTT is not applicable for safe diagnosis when CFRD is suspected. We recommend that all patients with CF be screened with CGMS before the age of 10 years, if possible. More studies are needed for the initiation of the age of screening but it has been suggested that screening should start after the age of 6 years (12).

Acarbose is an alpha-glucosidase inhibitor and a competitive inhibitor of pancreatic α-amylase and intestinal brush border α-glucosidases and delays the hydrolysis of polysaccharides, oligosaccharides, and disaccharides to monosaccharides, blunting and prolonging the postprandial increase in plasma glucose, which reduces insulin secretion. In addition, acarbose has been shown to increase postprandial GLP-1 levels and regulate insulin secretion in both normal and diabetic patients. This increase

in GLP-1 has been attributed to the decrease in carbohydrate absorption in the proximal part of the small intestine and the corresponding increase in nutrient load in the distal intestine, where GLP-1 secretion is higher.

In the multicenter study of Sels et al. (13) a significant decrease in postprandial hyperglycemia and HbA1c by 0.4% was reported after adding acarbose to the treatment in patients with type 1 diabetes. Riccardi et al. (14) in a study with 121 patients with type 1 diabetes showed that adding acarbose to the treatment provided a significant decrease in the 120 minute glucose level without any serious side effects. In a placebo-controlled study conducted by Kentrup et al. (5) in CF patients with impaired glucose tolerance, use of acarbose had a positive effect on glucose tolerance by providing a significant attenuation in postprandial glucose increase and a decrease in insulin secretion. However, these authors reported that the gastro-intestinal system side effects, seen in 67% of the patients using acarbose, may negatively affect the long-term continuation of the treatment. Acarbose is generally used in adults with dumping syndrome at 50-100 mg three times a day with meals. However, in children, treatment is usually started with lower doses, such as 12.5-25 mg.

Some studies have shown that acarbose can be safely taken up to 100 mg before each feeding in children without significant side effects (15). The most common side effect is gastrointestinal symptoms, such as bloating due to carbohydrate malabsorption. There is evidence that these gastrointestinal side effects are not as common as some have reported and are generally mild and it has been suggested that acarbose can be used safely (15).

We started with a low dose (3x12.5 mg) in this case and managed to gradually increase up to 6x25 mg/daily without any serious side effects related to acarbose treatment. We were able to achieve significant improvement in glucose regulation with only acarbose.

Conclusion

In the early diagnosis of CFRD, screening with OGTT after 10 years of age causes a delay in the diagnosis of CFRD and so we suggest periodic screening of patients with CF with CGMS may be a good alternative. In CFRD with severe hypoglycemia, acarbose is an important alternative in the treatment of glycemic dysregulation. We recommend keeping high dose acarbose among the treatment options, especially in patients with CF who have frequent hypoglycemia, as patients may not suffer severe side-effects, as was the case with our patient and in whom we were able to achieve improved glucose regulation.

Ethics

Informed Consent: Written informed consent was obtained from all patients.

Acknowledgements

The authors would like to thank the patient's parents for agreeing to the publication of this report. The authors would also like to thank Tanja Janjic, MD PhD, for cMRI interpretation (professional relationship), and Andrea Katharina Lindner, MD, for her writing assistance and critical input (professional relationship).

Footnotes

Authorship Contributions

Surgical and Medical Practices: Emrullah Arslan, Deniz Özalp Kızılay, Yasemin Atik Altınok, Bahar Girgin Dündar, Arzu Jalilova, Günay Demir, Samim Özen, Şükran Darcan, Ruhsar Damla Gökşen, Concept: Emrullah Arslan, Samim Özen, Şükran Darcan, Ruhsar Damla Gökşen, Data Collection or Processing: Emrullah Arslan, Deniz Özalp Kızılay, Analysis or Interpretation: Emrullah Arslan, Samim Özen, Literature Search: Emrullah Arslan, Yasemin Atik Altınok, Samim Özen, Şükran Darcan, Ruhsar Damla Gökşen, Writing: Emrullah Arslan, Deniz Özalp Kızılay, Bahar Girgin Dündar, Günay Demir, Samim Özen, Şükran Darcan, Ruhsar Damla Gökşen.

Conflict of Interest: Two authors of this article, Samim Özen and Ruhsar Damla Gökşen, are members of the Editorial Board of the Journal of Clinical Research in Pediatric Endocrinology. However, they did not involved in any stage of the editorial decision of the manuscript. The other authors declared no conflict of interest.

Financial Disclosure: The authors declared that this study received no financial support.

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