

Case report

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

Arslan E et al. Glucose Monitoring with Continuous Glucose Monitoring and the Efficacy of Acarbose Treatment in Cystic Fibrosis-related Dysglycemia

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Abstract

Early detection of glycemic dysregulation and optimization of glycemic control at cystic fibrosis 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 cystic fibrosis (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 20th day of treatment, glycemic dysregulation was resolved. In the early detection of CFRD, screening with OGTT after the age of 10 is insufficient; therefore, routine use of continuous or intermittent glucose monitoring systems should be considered. In addition, in CFRDs with severe hypoglycemia, acarbose is an important alternative in the high and increased dose range.

Keywords: CFRD, acarbose, CGMS, cystic fibrosis

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Introduction

The incidence of CFRD increased while the life expectancy of patients with CF extended. The prevalence of CFRD increases markedly with age; it affects approximately 2% of children, 19% of adolescents, and 40% to 50% of adults (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 an important discussion topic. The standard 2-hour OGTT is currently the routine screening test for CFRD and is recommended annually after 10 years of age; however, hyperglycemia (>200 mg/dl) (2) can be detected by continuous glucose monitoring systems (CGMS) in patients with normal OGTT evaluation. Therefore, CGMS should be used 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 (3–5).

Case

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

Since age 4, routine annual HbA1c has remained below 6.5% (N: 5.4% to 6.4%). OGTT was performed with frequent sampling and symptomatic severe fasting hypoglycemia (29 mg/dL), severe hyperglycemia at the 1st hr (400 mg/dL), impaired glucose tolerance at the 2nd hour (180 mg/dL) and severe hypoglycemia at the 3rd hour (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, had insufficient weight gain, and underwent a gastrostomy at the age of four. His weight was 20 kg (-1.18 SDS), height: 124 cm (-0.21 SDS), and BMI: 13.1 (-2.39 SDS). He was on a high energy diet by oral and gastrostomy route; continuous infusion overnight and pump assisted infusion during day.

Further testing for pancreatic autoantibodies was 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). Due to frequent acute exacerbations, history of hospitalization, and insufficient weight gain, the need for gastrostomy was accepted as a symptom

of CFRD for our patient. The patient was diagnosed as CFRD according to the ISPAD 2022 CFRD guideline with hyperglycemia exceeding 200 mg/dl, which was detected in 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 gradually increased. Although glucose fluctuations decreased, hyperglycemia persisted during the meals without acarbose treatment, therefore, treatment was increased to 6x12.5 mg and then gradually to 6x25 mg without any side effects (Figure 2). On the 20th 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, the patient's weight was 22.5 kg (-0.62 SDS), height: 127 cm (-0.14 SDS), and BMI: 13.95 (-1.56).

Discussion

CFRD is a unique entity that shares some characteristics with both type 1 and type 2 diabetes, yet also has unique pathophysiologic considerations. CFRD is not an autoimmune disease; 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 applied to achieve weight gain, and disruptions in the incretin system.

The incretin axis is involved in the etiology of the development of CFRD. Incretins, such as glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1), are intestinal hormones that are secreted after meals, primarily 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 is accompanied by profound disruptions in the GLP-1 secretion and suggested that this is one of the causes of postprandial glycemic variability in patients with CF (7). It 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; our patient had 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 includes difficulties compared to the classical diagnosis of diabetes, and HbA1c in the diagnosis is questioned. In the ISPAD CFRD guideline, diagnosis of CFRD is done according to American Diabetes Association (ADA) criteria during a period of stable baseline health:

- a. 2-h BGL on OGTT ≥ 11.1 mmol/L (200 mg/dl)
- b. Fasting BGL ≥ 7.0 mmol/L (126 mg/dl)
- i. Fasting BGL ≤ 7.0 mmol/L (126 mg/dl) does not rule out diabetes in CF
- c. HbA1C ≥ 48 mmol/mol (6.5%)
- i. HbA1C < 48 mmol/mol (6.5%) does not rule out diabetes in CF
- d. Random BGL ≥ 11.1 mmol/L (200 mg/dl) with classic symptoms of diabetes (2)

Although it is known 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, it was also emphasized in the guideline that a normal or low HbA1C value does not exclude CFRD. Therefore, HbA1C is not completely excluded from the follow-up of patients with CF.

Glucose abnormalities captured by CGM are common in CF, including very young children; however, there are as yet neither established criteria using CGM for screening nor diagnosing diabetes. Retrospective and cross-sectional single-center studies have associated glucose abnormalities on CGM with β -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 question 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 years ago if the diagnosis was awaited according to the OGTT (8). Mainguy et al. revealed that the OGTT's capacity to diagnose CFRD is weak and pathological glucose fluctuations are frequent even in the early stages of life (9). Hameed et al. showed that peak glucose occurred earlier than the routinely measured 120-minute sample, occurring within 30 minutes in 18%, 60 minutes in 45%, 90 minutes in 33%, and 120 minutes in only 3% (10).

Many studies have proven that CGM is a useful clinical tool in cystic fibrosis, 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 gaining inadequate weight are also stimulants for CFRD as in our case, and it should not be overlooked that close blood glucose monitoring should be performed in patients with CF who need continuous enteral nutrition. As recommended in the ISPAD 2022 CFRD guideline, it should not be forgotten that these patients should have their blood glucose checked in the middle and at the end of the feeding. Especially these patients are 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 is up to 29% during the OGTT, especially if the test is performed >2 hours (6). In our 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, we detected hyperglycemia reaching 400mg/dl in the first hour and hypoglycemia after 120 minutes. If we had used the standard OGTT, we would have detected a hyperglycemia of 181 mg/dl at 120 minutes and diagnosed impaired glucose tolerance. Therefore, we think that the standard OGTT is not sufficient for the diagnosis of CFRD. We recommend that all cystic

fibrosis patients be screened with CGMS before the age of 10, if possible. More studies are needed for the initiation of the age of screening; but at least we think that screening should start after the age of 6, as shown in other studies (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., they found a significant decrease in postprandial hyperglycemia and HbA1c by 0.4% after adding acarbose to the treatment in patients with Type 1 diabetes (13). Riccardi et al. with 121 patients with type 1 diabetes, it was shown that adding acarbose to the treatment provided a significant decrease in the 2nd-hour glucose level without any serious side effects (14). In a placebo-controlled study conducted by Kentrup et al. 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, in this study, it was emphasized that the GIS side effects seen in 67% of the patients using acarbose may negatively affect the long-term continuation of the treatment (5). 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 showed 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. With many studies, these gastrointestinal side effects are not as common as expected and are generally mild; and it has been shown that they can be used safely (15).

We started with a low dose (3x12.5mg) in our patient and managed to increase up to 6x25mg daily gradually without any serious side effects related to acarbose treatment. We were able to achieve significant improvement in glucose regulation only with acarbose.

We recommend keeping acarbose in high doses among the treatment options, especially in patients with CF who have frequent hypoglycemia.

Learning Points:

- In the early diagnosis of CFRD, screening with OGTT after 10 years of age causes a delay in the diagnosis of CFRD; therefore, periodic screening of patients with CF with CGMS may be a good alternative
- In CFRDs with severe hypoglycemia, acarbose is an important alternative in the treatment of glycemic dysregulation.

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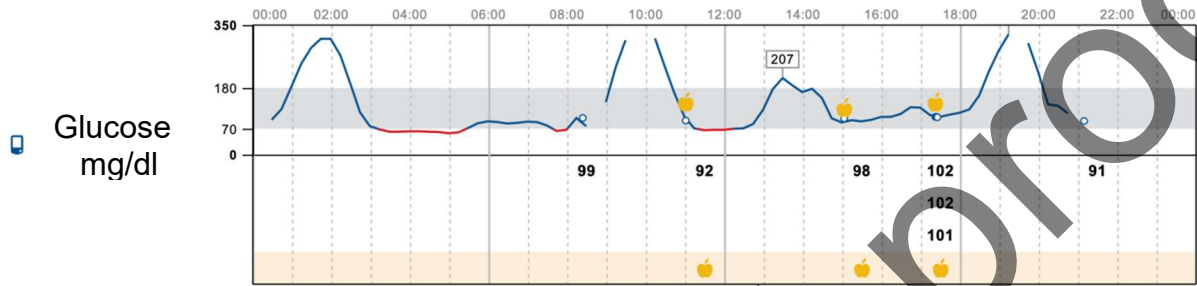
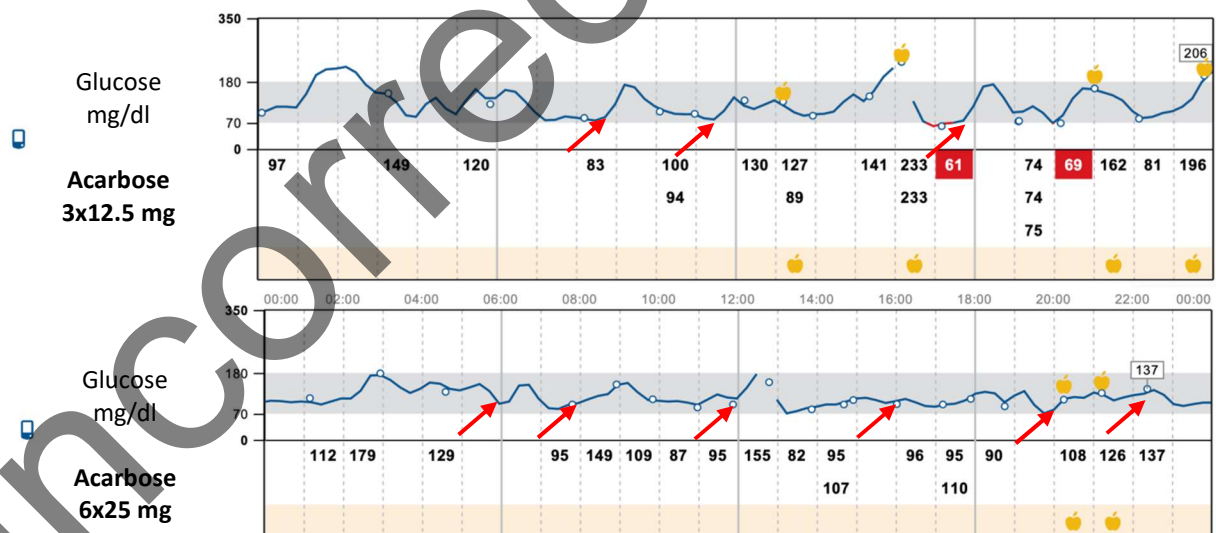


Figure 1: Pre-treatment continuous glucose monitoring systems



*Red arrows indicated with meals added acarbose

Figure 2: After Adding Acarbose to meals

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
Insülin (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

Table 2: CGMS data before and after treatment changes

	Before treatment	withThickener	Akarbose 3x12.5 mg	Akorbose 6x25 mg
GMI, %	7,2	6,8	6,8	6,0
Average glucose, mg/dl	164	145	144	114
CV, %	40,7	38,7	36,2	22,9
TIR, %	60	74	80	96
Low glucose*, %	6	4	2	1
Very low glucose**, %	2	1	1	0