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SYMPOSIUM

Cystic Fibrosis-Related Diabetes in Adults: Inpatient Management of 121 Patients during 410 Admissions

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Abstract

Background:

With improved longevity, cystic fibrosis (CF)-related diabetes (CFRD) has emerged as the most common nonpulmonary complication of CF. Patients with CFRD are frequently admitted to the hospital with infections and deterioration of pulmonary function, during which time glycemic control might have an impact on pulmonary function, recovery from infection, and survival.

Methods and Results:

In an attempt to share our insight into inpatient management of CFRD, this article summarizes the experience of our inpatient glucose management team with hospital management of 121 adult CFRD patients who were hospitalized on 410 occasions at the University of Colorado Hospital between January 2009 and September 2011. This is a retrospective chart review descriptive study of inpatient management of CFRD in our center. Our cohort includes CFRD patients treated with basal and mealtime insulin through multiple daily injections or continuous subcutaneous insulin infusion (CSII), as well as patients receiving steroids or enteral nutrition, which adds complexity to the management of CFRD during hospitalization.

Conclusions:

Multiple hospitalizations and intensive inpatient management of CF are integral elements of treatment. Inpatient therapy for CFRD requires a customized approach that is uniquely different from that of type 1 or type 2 diabetes. Our experience highlights clinical circumstances such as irregular food intake, high dose steroid therapy, and supplemental tube feeding. For many patients, it is possible to continue CSII therapy during hospitalization through a combination of mutual trust between the patient and hospital staff and oversight provided by the glucose management team.

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Abbreviations: : (C) carbohydrate, (CF) cystic fibrosis, (CFRD) cystic fibrosis-related diabetes, (CSII) continuous subcutaneous insulin infusion, (GMT) glucose management team, (I) insulin, (NPH) neutral protamine Hagedorn, (SD) standard deviation, (UCH) University of Colorado Hospital

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Introduction

Cystic fibrosis (CF) is one of the most common life-threatening autosomal recessive diseases that causes significant morbidity and shortens life expectancy.[1] Approximately 1 in 30 Caucasian Americans is a carrier, and 1 in 3500–4000 children in the United States is born with CF.[2] Advances in medical and nutritional treatment of CF have dramatically improved the life expectancy of affected individuals.[3–5] Survival into their 5th and 6th decades of life is no longer a medical miracle but a realistic expectation for many individuals with CF.

With improved longevity, CF-related diabetes (CFRD) has emerged as the most common nonpulmonary complication of CF, adding more complexity to therapy and negatively affecting overall outcome.[6] The prevalence of CFRD is only 5–8% in children between 5 and 10 years of age but rises sharply after puberty.[6,7] It is estimated that approximately half of CF adult patients develop CFRD.[3–5]

The pathogenesis of CFRD is incompletely understood.[3,8] Clearly, insulin insufficiency, particularly in the postprandial state, plays a principal role in the pathogenesis of CFRD.[9–13] In many patients, insulin secretory response to oral glucose (and meals) declines progressively over the span of years. Even though the prevalence of fasting hyperglycemia rises with age,[6] patients with CFRD do not develop complete absence of insulin secretion. Additionally, patients with CFRD demonstrate varying degrees of insulin resistance, especially during episodes of infection and steroid therapy.[14–16]

The clinical course of diabetes in CFRD patients is generally mild. In many patients, it may remain undetected for years. It is recommended that screening for CFRD be performed annually starting at the age of 10.[4,17,18] Clinical care guidelines for CFRD have been developed by the joint effort of the American Diabetes Association with the Cystic Fibrosis Foundation and endorsed by the Lawson Wilkins Pediatric Endocrine Society.[17] Recent publication of the consensus statement on diagnosis, pathophysiology, and treatment of CFRD is a contemporary milestone in our approach to this dreaded disease.[17] A few simultaneously published reviews on various aspects of CFRD have strengthened the importance of good glycemic control in patients with CFRD.[3,19]

Even though most CF and CFRD care occurs on an outpatient basis, patients are frequently admitted to the hospital, primarily with infections and deterioration of pulmonary function. In fact, one of the critical components of improved therapy is efficacious inpatient treatment of CF exacerbations. These hospitalizations are not only crucial for the effective treatment of hyperglycemia associated with acute illness, use of steroids, or clinical nutrition, but they also provide a unique opportunity for patient education and selection of appropriate therapy for the outpatient setting. Knowing that CFRD has a negative impact on pulmonary function, recovery from infection, and survival,[3,7,20–25] it is imperative to achieve the best possible glycemic control in hospitalized patients with CF. In this article, we summarize the experience of our inpatient glucose management team consisting of endocrinologists, trained nurse practitioners, physician assistants, and diabetes educators with hospital management of 121 CFRD patients who were hospitalized at the University of Colorado Hospital (UCH) between January 2009 and September 2011.

Methods

This is a retrospective chart review descriptive study of inpatient management of CFRD in our center. The institutional review board approved the study. Medical charts of 209 CF patients who were admitted to UCH for exacerbation of their disease from January 1, 2009, until September 2, 2011, were reviewed. The results are expressed as means ± standard deviation (SD). Differences between groups were compared using Student's *t*-test. A p value of .05 was considered to be significant.

Results

During the period of observation, 209 CF patients were admitted to UCH for exacerbation of their disease. They accounted for 581 admissions. Among them, there were 121 patients with CFRD (57.9%) who accounted for 410 admissions (70.6% of all admissions; $p < .0001$ vs non-CFRD patients), and 88 CF patients without CFRD who accounted for 171 admissions (**Table 1**). During the 32-month observation period, CFRD patients were hospitalized an average of 3.4 times per patient, which was significantly greater than non-CFRD patients who were hospitalized on average 1.9 times per patient ($p < .01$ for admission rate of CFRD vs non-CFRD patients).

There were almost twice as many women than men in the CFRD group (75 females and 46 males), whereas

in the non-CFRD group, there were 47 women and 41 men. It was reported that women are diagnosed with CFRD significantly earlier than men,[22,26] but the reason for this clinical observation remains unclear.[4,7] The average age was 34.8 ± 13 in the non-CFRD group (range 15–69 years old) and 31.9 ± 11 in the CFRD group (range 18–63 years old).

Seven patients with CFRD (5.8%, 4 men and 3 women) and 3 without CFRD (3.4%, all 4 men) died in the hospital during this period of time. Higher mortality among women with CFRD has been reported,[22] but with only 7 patients in this group, our mortality data do not confirm this suggestion.

There were 410 admissions among 121 patients with CFRD during this period. During 359 admissions, CFRD patients were treated with insulin (87.6% of all admissions). Of these 359 admissions, 140 patients were treated with basal/bolus regimen (39%), 142 were treated with rapid-acting prandial insulin only (39.6%), 4 patients were treated with long-acting insulin alone (1.1%), 59 patients were on insulin pump (16.4%), and 14 patients (3.8%) were on neutral protamine Hagedorn (NPH) insulin.

During 238 admissions (58% of all admissions), patients with CFRD were treated with steroids—either injectable (methylprednisolone) or oral (prednisone). We have a great deal of experience with the use of NPH insulin to treat steroid-induced hyperglycemia.[27] On 79 admissions (33.2%), we added NPH insulin to patients' existing insulin regimen. Neutral protamine Hagedorn insulin was given concomitantly with steroid administration (**Table 2** and text herein) in addition to either insulin pump (9 admissions, or 11.4%) or basal/bolus regimen (70 admissions, or 24.5%).

Adequate caloric intake is critical for the health and survival of patients with CF with and without diabetes. Cystic fibrosis patients frequently require a high calorie diet to compensate for increased resting energy expenditure and inadequate absorption of calories related to pancreatic insufficiency. The catabolic state in patients with CFRD is frequently more severe than in a CF patient without diabetes.[28] Not infrequently, hospitalized patients with CFRD receive enteral or parenteral nutritional support, which is a very important element of therapy for patients with CFRD who display greater nutritional needs. Among our CFRD patients, 7 received total parenteral nutrition, (1.7%) and 9 (2.2%) received either continuous or nighttime bolus tube feeding.

Table 1.
Characteristics of Cystic Fibrosis and Cystic Fibrosis-Related Diabetes Patients Admitted to the University of Colorado Hospital between January 1, 2009 and September 2, 2011

	CF without diabetes (n = 88)	CFRD (n = 121)	p value <
Women (%)	47 (53%)	75 (62%)	
Age (mean ± SD)	34.8 ± 13	31.9 ± 11	NS
Number of admissions	171	410	.0001
Admissions/ patient	1.9	3.4	.01

Table 2.
Number of Patients with Cystic Fibrosis-Related Diabetes Treated at the University of Colorado Hospital[a]

	# of patients	% of total	% of patients on insulin
Total number	410	100%	—
Patients on insulin	359	87.6%	100%
Basal/bolus	140	34.1%	39.0%
Rapid-acting only (mealtime)	142	34.6%	39.2%
Long-acting only	4	1.0%	1.1%
CSII	59	14.4%	16.4%
NPH with rapid-acting (no steroids)	7	1.7%	1.9%
NPH alone (no steroids)	7	1.7%	1.9%
NPH with steroids	79	19.3	22.0% (or 33.2% of all patients on steroids)
Steroids	238	58.0%	66.3%
Total parental nutrition	7	1.7%	1.9%
Tube feeding	9	2.2%	2.5%

[a] Some patients were treated on more than one admission.

Discussion

In this section, we summarize our experience and suggestions for management of adult CFRD patients during hospitalization.

Basal and Mealtime Insulin

Patients with CFRD with fasting hyperglycemia are likely to benefit from basal insulin. At least initially, a small dose of long-acting insulin administered at bedtime is sufficient to control fasting hyperglycemia. Patients without fasting

hyperglycemia may do well for many years on prandial insulin only.

Our preferred way of dosing rapid-acting insulin for CFRD patients is to use a carbohydrate (C) to insulin (I) ratio for meals and snacks with an adequate correction factor. While a C:I ratio is designed to provide adequate doses of insulin depending on the amount of C consumed, a correction factor allows the patient to correct for preprandial hyperglycemia using an estimated ratio of how much 1 unit of rapid-acting insulin will lower glucose values. In most patients, their home C:I ratio and correction factor are a good place to start. For those not on insulin therapy at home or who have not previously used a C:I ratio, we suggest a starting ratio of 20:1 with a correction factor of 60:1 (i.e., an estimate that 1 unit of rapid-acting insulin will lower blood glucose level by 60 mg/dl) when the patient's glycemia is above 150 mg/dl. These conservative starting doses account for the retained insulin sensitivity of CFRD patients. Adjustments are then made daily as needed.

Erratic meal patterns represent one of the most prevalent difficulties in the management of hospitalized patients with CFRD. Many hospitals encourage patients to order meals at the time of their own choosing, thus creating unpredictable intervals between meals. Depending on the level of hunger or gastrointestinal symptoms, patients with CFRD either skip meals or double up on meals. Many younger adults with CFRD stay awake late into the morning hours and sleep until either late morning or afternoon hours. In addition to scheduled meals, many CFRD patients consume high sugar snacks and beverages throughout the day to increase their caloric intake. Some patients forgo regular meals and continuously graze on snacks and beverages throughout the day.

On the other hand, there is at least one care-related reason for the mismatch between the timing of insulin administration and meal consumption. Many hospitals, UCH included, require that prandial insulin be given immediately after the meal and not before or at the beginning of the meal as most patients do at home. This policy is designed to increase patient safety and to prevent hypoglycemia if a patient, for whatever reason, does not eat after receiving insulin. This approach works well if the prandial insulin is given immediately following the meal, but unfortunately, if the prandial insulin is administered too long after the meal is completed, then the delayed injection of rapid-acting insulin does not match the patient's glycemic excursion and may result in either hyper- or hypoglycemia. Furthermore, communication between patients and the nursing staff may not be optimal, with patients neglecting to inform their nurses when the tray arrives or when they finish their meal.

To minimize the potential delay in administration of insulin, our patients are taught to call the nurse as soon as they finish their meals. These variables are very difficult and not always possible to control. For all of these reasons, education of patients and of the nursing staff is critical for proper management of hospitalized patients with CFRD.

Steroids in Patients with Cystic Fibrosis-Related Diabetes

Most of the CFRD patients received 40–60 mg of intravenous methylprednisolone between 1 and 4 times a day with a subsequent taper. Acute or short-term administration of methylprednisolone causes predominantly postprandial hyperglycemia that lasts 6 to 12 h. Because NPH insulin has duration of action of approximately 6 to 12 h, we routinely use NPH insulin administered at the time of methylprednisolone administration to counteract the hyperglycemic effect of this steroid.[27] We typically use lower doses of NPH insulin in CFRD patients for steroid-induced hyperglycemia compared with the dose we recommend for patients with other types of diabetes, because patients with CFRD are generally much more insulin-sensitive than patients with type 1 and type 2 diabetes. Neutral protamine Hagedorn insulin is administered in addition to the basal/bolus insulin these patients receive. Our experience indicates that adding NPH insulin to a standard basal/bolus regimen results in better glycemic control than increasing long- and/or rapid-acting insulins.[28] Because the NPH insulin is stopped as soon as methylprednisolone is discontinued, this provides a safer option than having residual effects from high doses of long-acting insulin onboard. The following are our recommendations for initial NPH doses that are adjusted daily as needed:

a) For CFRD patients receiving methylprednisolone once daily, we recommend using NPH insulin 0.25 units per 1 mg of methylprednisolone administered concomitantly with methylprednisolone once daily. For example, we use 10 units of NPH for 40 mg of methylprednisolone and 15 units of NPH for 60 mg of methylprednisolone. The dose of insulin is then adjusted daily as needed.

b) For patients on methylprednisolone two, three, or four times a day, we order NPH insulin 0.25 units

per 1 mg of methylprednisolone with morning and evening methylprednisolone administration. For example, we suggest 10 units of NPH insulin with 6 a.m. and 6 p.m. steroid administration for a CFRD patient receiving 40 mg methylprednisolone four times a day.

c) For CF patients without CFRD but with steroid-induced hyperglycemia, we recommend smaller initial doses of NPH. We use 0.1–0.15 units per 1 mg of methylprednisolone. For example, a patient receiving 40 mg methylprednisolone would be given 4–6 units of NPH.

Even though most patients with CFRD are insulin-sensitive, a few display significant insulin resistance. This group includes patients with longer duration of diabetes and with frequent infections. For these patients, we use 1 unit of NPH per 1 mg of methylprednisolone for the first 20 mg of steroid, 0.5 units for 1 mg of methylprednisolone for the next 20 mg of steroid, and 0.25 unit of NPH for 1 mg of methylprednisolone for each subsequent milligram of steroid.[27]

Tube Feeding

Adequate nutrition is a cornerstone of successful therapy for CF.[8,29] Provision of appropriate caloric content may be challenging at times, and patients are placed on supplemental tube feeds, frequently overnight, to meet nutritional needs. In the hospital, CF and CFRD patients may be placed on either bolus tube feeding or continuous tube feeding. Insulin therapy during the periods of tube feeding is not only helpful in controlling hyperglycemia but is also essential for better utilization of administered carbohydrates.

We have previously shown that administration of premixed 70/30 insulin divided in three daily doses is the safest and most effective method for controlling hyperglycemia in diabetes patients on continuous tube feeding.[30] Patients with CFRD are not an exception. Patients with CFRD on continuous tube feeding receive 70/30 insulin three times daily with initial total daily insulin of 1 unit of insulin for every 15 g of C in the bag when administered at 30–40 ml/h.

If the patient is placed on overnight tube feeding, we administer 70/30 insulin (initially 1 unit for 15 g of C) at the beginning of the tube feeding. In these patients, both long-acting and rapid-acting insulins are administered to control daytime glycemia as needed. For multiple daily gravity-driven tube feeding sessions lasting 1 or 2 h, one should use rapid-acting insulin 1 unit per 15–20 g of C administered with each bolus. Daily adjustments in insulin dose must be made as needed.

It is important to realize that continuous tube feeding as well as periods of time during or immediately after bolus tube feeding corresponds to a postprandial state. For this reason, glycemic goals while patients are on tube feeding must be in the range of 140–180 mg/dl. Lower glycemic goals incorrectly assume a fasting state and increase the risk of hypoglycemia if and when the tube feeding is discontinued.

Continuous Subcutaneous Insulin Infusion.

As long as the patient is alert, oriented, and cognitively stable, we recommend allowing continuation of continuous subcutaneous insulin infusion (CSII) (insulin pump therapy) in the hospital under the supervision of the glucose management team (GMT). Patients on CSII must keep a log of their blood glucose values and insulin rates at the bedside for review by the primary team and by the GMT. All adjustments in CSII settings are done only in consultation with the GMT. The GMT rounds on these patients daily and is available by pager or cell phone to patients, nursing staff, and house staff 24 h a day, 7 days per week, every day of the year.

Patients with CFRD on CSII and treated with steroids must increase their pump settings by approximately 30–40% to control glycemia.[31] Alternatively, previous settings can be continued and NPH insulin added concomitantly with steroid administration as described above. We recommend adjustments not only in the basal rates, but also of the C:I ratio as postprandial hyperglycemia is the hallmark of steroid-induced derangements in glycemic control.

Conclusion

Multiple hospitalizations and intensive inpatient management of CF are integral elements of treatment. With greatly improved therapy and longevity of patients with CF, CFRD has emerged as the most common nonpulmonary complication of this disease. Patients with CFRD are hospitalized much more frequently than non-CFRD patients (3.4 vs 1.9 admissions per patient). It has been well-recognized that patients with CFRD have lower lung function and more frequent hospitalizations than CF patients without diabetes.[3,6,8,23,26] Increased frequency of hospitalization among CFRD patients most likely reflects the presence of more severe disease.[6,26] It has been

suggested that both insulin deficiency and hyperglycemia negatively affect pulmonary disease in CF.[3,20,28,32,33]

In concert with other reported mortality data,[5,7,22,24,25,34] mortality among our CFRD patients was almost twice as high as among CF patients without diabetes, but we did not observe a gender difference. We believe that every hospital admission presents an opportunity to educate patients and optimize the treatment of diabetes. As patients with CF continue to have frequent admissions and prolonged hospital stays, it is clear that the inpatient management of CFRD is just as important as outpatient care.

Cystic fibrosis-related diabetes is unique in pathophysiology and clinical course. While sensitive to insulin at baseline, patients with CFRD experience significant postprandial hyperglycemia, frequently due to high dose steroids or acute-on-chronic illness. Carbohydrate intake must not be limited due to their high metabolic requirements,[35] but limit of simple sugars can be recommended[36] if deemed appropriate for the ongoing circumstances. Although exocrine pancreatic function typically fails early in CF, endocrine function may wax and wane for years. Inpatient therapy for CFRD requires a customized approach uniquely different from that of type 1 or type 2 diabetes. We have described our experience treating 121 CFRD patients in the inpatient setting during 410 admissions at the UCH, highlighting clinical circumstances such as irregular food intake, high dose steroid therapy, and supplemental tube feeding. We have also been successful in continuing CSII therapy during hospitalization, through a combination of mutual trust between the patient and hospital staff, and oversight provided by the glucose management team.

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