Evidence-Based Management of Cystic Fibrosis-Related Diabetes

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Introduction

Cystic fibrosis (CF) is the most common fatal genetic disease in Caucasians, affecting approximately 1 in every 2,500 births worldwide (1). CF is an autosomal recessive disease that is caused by a mutation in the cystic fibrosis transmembrane conductance regulator gene which leads to the production of a mutated cell membrane protein and defective chloride channel function throughout the body (2). This defect prohibits water and ions from properly entering and exiting cells throughout the body leading to the buildup of thick, sticky mucus in organs. This defect disturbs a variety of body systems including the respiratory, digestive, endocrine, and reproductive systems.

The digestive and endocrine functions that are disturbed refer particularly to the effect that CF has on the pancreas. The accumulation of mucus on pancreatic cells prevents digestive enzymes from being delivered to the digestive tract where food is broken down. As CF progresses with age, the endocrine functions of the pancreas are also disturbed, namely the production and secretion of insulin for the regulation of blood glucose levels. This particular manifestation of CF leads to hyperglycemia and the development of cystic fibrosis-related diabetes or CFRD.

CFRD is the most common co-morbidity of cystic fibrosis, and its incidence is expected to increase as the median survival age for CF patients continues to rise (3). Currently at 37.4 years, the median survival age has consistently increased throughout the past several decades as a result of extensive research and innovative treatments that aim to maintain and improve disease status. The unique nutritional requirements of this disease, namely a high-calorie, high-fat diet, pose an interesting dilemma in the management of this co-morbidity as it requires much different treatment than the more common types of diabetes, type 1 and type 2 (1, 2, 4). The unique needs

of CF patients combined with the importance of glycemic control in the maintenance of clinical and nutritional status has led many CF healthcare teams to stray from dietary management of CFRD and rely more heavily upon insulin therapy and oral hypoglycemic agents. This paper discusses the underlying issues in CFRD as well as the efficacy of dietary intervention, insulin therapy, and the use of oral hypoglycemic agents in the management of CFRD.

Pathophysiology

Hyperglycemia in CF patients results from multiple factors including insulin deficiency, insulin resistance, and a genetic predisposition (5, 6). The primary physiological cause is insulin deficiency (7) resulting from progressive damage to pancreatic islet cells. This is a result of the faulty chloride channel function characteristic of CF, which over time, leads to blockage of pancreatic ducts and fatty infiltration and fibrosis of the pancreas (1). This damage prevents adequate production and secretion of insulin, leading to hyperglycemia. Though insulin resistance plays a much smaller role in the physiology of CFRD, its role must not be overlooked, especially during infection, inflammation, and corticosteroid use which are all common in CF (6). These processes increase the production of cytokines and counter-regulatory hormones, making glycemic control in these stressful times even more challenging (6). Lastly, some CF mutations, particularly ΔF508 (the most common defect in CF), increase a patient's likelihood of developing hyperglycemia and CFRD as they age (5, 6).

Development of CFRD takes place in stages (8) beginning with normal glucose tolerance. The second stage is impaired glucose tolerance which affects 75% of the CF population (8). With time, these patients may develop diabetes without fasting hyperglycemia and then diabetes with fasting hyperglycemia.

Diagnosis

The presence of CFRD is associated with a slow but steady clinical decline including decreased lung function, nutritional status, and overall survival (9). Consequently, it is imperative that the dietitian and CF care team be proactive in identifying hyperglycemia before the onset of symptoms. Numerous diagnostic methods have been tested in the CFRD population including HbA1c, fasting glucose, oral glucose tolerance testing (OGTT), and continuous glucose monitoring (1). After rigorous review, the International Society for Pediatric and Adolescent Diabetes (ISPAD) developed a set of clinical practice guidelines in 2008 which included the most recent evidence-based recommendations for diagnosis of CFRD (1). These guidelines identified OGTT as the gold standard for diagnosing CFRD (1). This is due to the fact that Hemoglobin A1c (HbA1c) in CFRD patients is often normal despite postprandial and fasting hyperglycemia (7). Thus, HbA1c is an unreliable tool for the diagnosis of CFRD (7). Additionally, since CFRD manifests as postprandial hyperglycemia before fasting levels are affected (1), screening with fasting glucose levels is ineffective for those patients still in the early stages of CFRD. The OGTT is able to identify the primary issue in CFRD, that is, postprandial hyperglycemia; once a diagnosis of CFRD is established using the OGTT, a fasting glucose level may be appropriate to assess the patient's management needs.

Complications of Untreated CFRD

As aforementioned, CFRD is associated with decreased pulmonary and nutritional status which significantly impacts mortality in patients with CF (9). Clinical decline can also occur before the diagnosis of CFRD (2), emphasizing the need for regular screening to minimize the complications associated with untreated hyperglycemia. The nutritional impact of CFRD is likely due to the anabolic role of insulin (1, 2). As serum levels of insulin decrease, its protective

effect on body protein diminishes, leading to increased body protein breakdown and other catabolic processes.

As with type 1 and type 2 diabetes mellitus, microvascular complications may develop over time in CF patients with diabetes. One large prospective cohort study that followed 775 individuals with hyperglycemia reported the following distribution of microvascular complications after 10 or more years with CFRD: microalbuminuria in 14%, retinopathy in 16%, and neuropathy in 55% (10). Diabetic nephropathy has also been reported as a microvascular complication of CFRD (2). Since these complications may present as early as five years after the development of CFRD, it is recommended that these patients receive annual screening to assess vision, kidney function, and neurological function (6). This recommendation will become increasingly important as average life expectancy continuously rises and more individuals are affected by the long term complications of CFRD. Presently, there have been no reports of the macrovascular complications often seen in type 1 and type 2 diabetes (2), possibly due to malabsorption of fat and cholesterol; however, this may change as average life expectancy enters and surpasses the fifth decade of life.

In a population with already-compromised life expectancy, early identification of hyperglycemia is critical to minimize the detrimental effects of uncontrolled hyperglycemia. This has led the Cystic Fibrosis Foundation (CFF) to recommend annual testing for CFRD using OGTT for all patients 10 years of age and older (3). Unfortunately, only 12.8 and 14.6 percent of patients with CF enrolled in the CFF Patient Registry were screened with an OGTT in 2008 and 2009, respectively (3).

Management of CFRD

The management of CFRD requires careful teamwork among healthcare professionals and open communication with patients and their families to determine the best treatment plan for each individual. Blood glucose goals for patients with CFRD are outlined below in Table 1 (6). These are comparable to the goal values suggested by the American Diabetes Association for glycemic control with the exception of the postprandial reading that is measured two to three hours following a meal rather than one to two due to delayed gastric emptying in cystic fibrosis patients. The overarching goal of CFRD management is good glycemic control to achieve healthy weight maintenance, reversal of protein catabolism, prevention of microvascular complications, and adequate growth in pediatric patients (6). Following is a discussion of nutritional management, insulin therapy, and the use of oral hypoglycemic agents in the management of CFRD.

Table 1. Blood Glucose Goals for CFRD Patients

	Fasting and Pre-Meal mg/dl	2-3 h Postprandial mg/dl	Bedtime mg/dl
Adults	70-130	<180	90-150
Adolescents	90-130	<180	90-150

Nutritional Management

Nutritional management of cystic fibrosis is unique and essential. Malnutrition is a very plausible risk for CF patients due to malabsorption of nutrients and increased energy expenditure (6). Therefore, a high-calorie, high-fat diet is recommended to reach BMI goals outlined by the Cystic Fibrosis Foundation: $\geq$ 22 kg/m^2 for adult females, $\geq$ 23 kg/m^2 for adult males, and $\geq$ 50th percentile of BMI-for-age for children ages 2-20 years (3). To achieve these goals, energy requirements for CFRD are $\geq$ 120-150% of that typically recommended for an individual of the same weight and height, and protein requirements are double the recommended intake to

minimize protein catabolism (1). Fat intake is recommended to provide approximately 40% of calories with no set recommendations for distribution of saturated and unsaturated fats due to the current absence of macrovascular complications in CFRD (6). It is recommended that carbohydrates provide 45-50% of total energy with no restriction on refined carbohydrates due to the concern that restriction may cause a deficit in energy intake. Sodium intake is also unrestricted in patients with CFRD with a recommended intake of > 4000 mg/day. This is unique from the dietary recommendations for type 1 and type 2 diabetes in which sodium intake is restricted to reduce the risk of developing macrovascular complications (2, 11). These guidelines contradict typical treatment recommendations for other types of diabetes like type 1 and type 2 as outlined in Table 2 below (1).

Table 2. A comparison of dietary management of CFRD, Type 1, and Type 2 DM

Dietary Component	Cystic Fibrosis-Related Diabetes (CFRD)	Type 1 and Type 2 Diabetes Mellitus
Calories	≥120-150% of caloric needs for age and gender to promote weight gain or maintenance	Calorie restriction for weight loss or weight maintenance
Carbohydrate	45-50% of total energy	50-55% of total energy
Protein	200% of reference intake	10-15% of total energy
Fat	40% of total energy	30-35% of total energy
Fiber	Limit in malnourished patients (may compromise intake); encouraged in well-nourished patients	Encouraged in all patients (Recommendation: age + 5 grams per day)
Refined Carbohydrates	No restriction	Up to 10% of total energy
Sodium	No restriction; > 4000 mg/day	Restricted to 1500 mg/day

The primary goals of nutrition therapy for CFRD are proper dosing of insulin to cover carbohydrate consumption at meals and prevention of malnutrition (2, 6). The registered dietitian's role in this process is to teach patients how to count carbohydrates to match their insulin dose with the varying number of carbohydrates consumed at each meal. This allows for unrestricted energy intake and good glycemic control simultaneously. In conclusion, though

nutrition therapy is an essential component of CF care, insufficient evidence exists for controlling hyperglycemia in CFRD with diet alone.

Insulin Therapy

Currently, insulin therapy is the only recommended therapy for the treatment of CFRD (8). This has been linked to the fact that insulin is an anabolic hormone which prevents catabolic processes throughout the body (1). One study highlighted the ability of insulin to improve several clinical outcomes in patients with CFRD including body mass index (BMI), forced expiratory volume in one second (FEV_1), and Shwachman score (SS), which is calculated from several parameters including physical activity, nutritional status, and findings from the physical examination (12). This five year prospective study followed 30 CF patients among which six developed CFRD and required insulin therapy. Prior to diagnosis of CFRD, there was a marked decrease in first-phase insulin response (12). At diagnosis, BMI, FEV_1, and SS had decreased significantly, but these parameters were significantly improved after six months of insulin therapy (12). Another interesting finding from this study was a positive correlation between BMI and first-phase insulin response in all 30 participants (12).

There is debate over when insulin therapy should be initiated in patients with CFRD. Since postprandial hyperglycemia without fasting hyperglycemia is not associated with an increased risk of developing microvascular and macrovascular complications, necessity of insulin therapy during this phase of CFRD is questioned. This question was addressed in a recent multicenter, randomized trial that assessed the effect of fast-acting aspart insulin on patients with CFRD without fasting hyperglycemia (13). Eighty one participants without fasting hyperglycemia were randomly assigned to one of three groups. The first group was prescribed fast-acting aspart insulin, the second received oral repaglinide, and the third was given an oral

placebo. One year prior to initiation of the study, mean BMI declined in all groups (13). After one year of therapy, only the group receiving the aspart insulin demonstrated a sustained improvement in BMI (+0.39±21 BMI units) (13). Though the group that received oral repaglinide experienced rapid initial weight gain, this was not sustained throughout the entire year following initiation of therapy; in fact, after six months, participants in this group began to lose weight, balancing the initial weight gain and resulting in no significant difference at the one-year mark (13). The authors of this study concluded that insulin therapy provides beneficial effects, namely reversed chronic weight loss, even in patients with diagnosed CFRD without fasting hyperglycemia.

Several types of insulin therapy are currently available, and it is essential to identify which type of insulin therapy is indicated for maximum benefit. In CFRD, postprandial blood glucose levels are the first measures to be affected due to improper insulin secretion from the pancreas. Consequently, these patients need little or no basal insulin but have a great need for fast-acting insulin prior to each meal and snack to prevent postprandial hyperglycemia (2, 14). The CFF has backed this hypothesis by recommending pre-meal injections of fast-acting insulin accompanied by a small dose of long-acting insulin at night (8).

In addition to the postprandial glycemic control achieved through the use of fast-acting insulin at each meal and snack, Grover et al hypothesized that long-acting bedtime insulin glargine would provide additional glycemic control without causing hypoglycemia (14). In this randomized cross-over study, participants were randomized to one of two initial groups: 12-week therapy with bedtime NPH or 12-week therapy with bedtime glargine. After the first 12-week period, there was a one-month washout period, and then patients were switched to the alternative intervention. Mean duration of diabetes of all participants was 9±5 years, and all

participants had diabetes that was well-controlled (14). During the interventions, individuals in both groups continued their established fast-acting insulin therapy. This study confirmed the authors' hypothesis that glargine insulin is effective in improving glycemic control as evidenced by a significant reduction in fasting plasma glucose (14). Participants also experienced a non-significant increase in weight which may have been limited by the short study period (14). No serious hypoglycemia occurred, again confirming the authors' hypothesis (14). This study confirmed the indication of long-acting insulin in addition to fast-acting insulin in the management of CFRD.

In combination with the intense therapies required to manage other complications of CF, patient compliance with intense insulin therapy may render concern. Thus, some researchers have assessed the effectiveness of continuous subcutaneous insulin infusion (CSII) using an insulin pump in the management of CFRD (5, 15, 16). One study led by Hardin et al aimed to assess the effect of CSII using an insulin pump on glycemic control, weight, lean body mass, whole body protein turnover, and hepatic glucose production (16). Nine patients being treated with subcutaneous insulin injections at least three times per day prior to the initiation of the study were enrolled, and the following measurements were taken prior to pump placement: whole body protein turnover using the stable isotope leucine, lean body mass using a DEXA scan, anthropometric measurements, and HbA1c. The patients then received basal and bolus insulin therapy from the insulin pumps for six months, monitoring blood glucose in a daily log. At the end of six months, the aforementioned measurements were repeated and analyzed for statistical differences. Statistical analysis revealed significant improvements in fasting and postprandial blood glucose measurements, body weight, HbA1c, and lean body mass (16). Decreases in protein catabolism and hepatic glucose production were also statistically significant (16). These

results may indicate that better glycemic control and improvements in other metabolic measures can be achieved by using an insulin pump possibly as a result of simpler dosing for periodic snacks and increased corrective dosing in response to postprandial hyperglycemia (16). Another small study comprised of three case studies demonstrated that the use of CSII in patients previously receiving at least four insulin injections per day improves glycemic control (decreased HbA1c) and nutritional status (increased BMI) (15).

Often during illness, patients may experience short-term insulin resistance, signifying a need for increasing or initiating insulin therapy (2). As the patient's clinical status improves, insulin dosing should be decreased to levels required to maintain adequate glycemic control. Insulin therapy may also need to be increased in patients who receive overnight tube feedings to increase energy intake. In such cases, blood glucose should be monitored carefully, even once during the night, to assess the need for increasing the insulin dose (1, 5).

Oral Hypoglycemic Agent Use

Due to concerns with decreased quality of life associated with frequent insulin injections (17), many researchers have aimed to evaluate the efficacy of oral hypoglycemic agents in the management of CFRD. A large portion of the research conducted has evaluated the effect of sulfonylureas due to their mode of action on the pancreas to increase insulin secretion and their association with weight gain (17, 18). Culler et al conducted a study to assess the effect of glipizide, a sulfonylurea, on glucose tolerance and weight in CF patients with impaired glucose tolerance. After three months of treatment with glipizide, there were significant improvements in insulin secretion and glucose tolerance (18). Glycosuria was significantly decreased, and HbA1c was also decreased significantly, indicating improved glycemic control (18). Weight and body mass index were not significantly altered (18).

Another study compared the effect of insulin versus sulfonylurea treatment on glycemic control in CFRD (17). This multicenter, retrospective study assessed the mean time in months that a group of patients with CFRD were able to be maintained on oral hypoglycemic agents before needing to be started on insulin therapy as a result of elevated HbA1c levels. The results indicated that patients with CFRD could be maintained on oral hypoglycemic agent therapy for a mean interval of 18.2±14.5 months with 50% of males and 50% of females being able to remain on oral agent therapy for a mean interval of 24 months (17). Treatment with oral agents did not result in significant changes in FEV_1 or forced vital capacity (FVC), indicating that temporary treatment of CFRD with oral hypoglycemic agents is safe and effective until HbA1c levels indicate the necessity of switching to insulin therapy (17).

Both of these studies assessed the effect of sulfonylureas on patients with impaired glucose tolerance or CFRD without fasting hyperglycemia, and both yielded promising results. However, as CFRD progressed, these oral medications proved to be less effective on glycemic control indicating only short-term treatment options for these oral medications. One concern with this class of oral hypoglycemic agents is hypoglycemia (5) which can be detrimental if severe. Therefore, if patients are prescribed this drug for short-term glycemic control in CFRD, the CF care team must educate the patient on symptoms and treatment of hypoglycemia in the case that it does occur.

Onady et al conducted a prospective case based comparison study to compare the effectiveness of several oral hypoglycemic agents (sulfonylurea, metformin, or thiazolidinediones) versus insulin on glycemic control (19). This study showed no statistical differences among treatments (19), but this result could be limited by the fact that only 20

patients were enrolled and four different medications were used, possibly leading to insufficient power to determine statistical significance between groups.

Lastly, Moran et al compared insulin lispro and oral repaglinide on their ability to decrease peak glucose level and two- and five-hour postprandial blood glucose levels in patients with CFRD without fasting hyperglycemia (20). In this study, insulin lispro was more effective in significantly decreasing the peak glucose level, two-hour, and five-hour postprandial plasma glucose levels while the oral agent, repaglinide, was only effective in significantly decreasing the five-hour postprandial plasma glucose level (20). These results indicate that postprandial glycemic control may be more achievable with the use of fast-acting insulin versus oral agents.

Conclusion

Evidence for glycemic control in CFRD heavily favors insulin therapy, and this remains the only recommended therapy for treatment of CFRD (8). Insulin therapy results in multiple favorable outcomes for the CFRD patient including glycemic control (12, 13), reversal of chronic weight loss (13), decreased protein catabolism (1), and improved FEV_1 and BMI (12). However, if the patient desires, short-term glycemic control may be achievable through the use of oral hypoglycemic agents, particularly sulfonylureas. Nutrition therapy, alone, is not recommended for the treatment of CFRD as this may compromise caloric intake and nutritional status. To determine the best treatment option for CFRD, multiple patient factors must be evaluated including current CFRD stage, clinical status, nutritional status, expected compliance, eating patterns, needed flexibility, education, and quality of life.

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