

Evaluation of Diagnosis and Management Plan of Diabetes Mellitus Related Cystic Fibrosis in Children

Eyman Abdulmajeed Alfaraj¹, Fatimah Mohammed AlOmran¹, Hassan Abdullah Alashwan¹, Abdullah Jameel Almajed¹, Redha Ali Alsaleh¹, Hassan Abdulmohsen Alhumrran¹, Rawan Abdulqawi Bobakr², Seham Matar Alotaibi², Nouf ghazi S. Abuhekmah³, Nasser Subeeh Alshammri⁴

1- Imam Abdulrahman bin Faisal University, 2- Umm Al-Qura University, 3- King Khaled university, 4- Jordan University of Sciences and Technology

Abstract

Background: Cystic fibrosis (CF) is a disease that occurs as a result of genetic mutations in cystic fibrosis transmembrane conductance regulator gene (CFTR). CFTR can be found in airways epithelial cells, intestine and cells with exocrine and exocrine function. CF is associated with variant complications, Cystic Fibrosis-Related Diabetes (CFRD) is considered as one of the most common complications of CF. **Objective:** In this review, we discussed the recent updates about Cystic Fibrosis-Related Diabetes (CFRD) diagnosis and management plan. **Methods:** PubMed database were used for articles selection. All relevant articles related to our review were chosen to cover the following topics: Cystic Fibrosis, Cystic Fibrosis Related Diabetes management, Cystic Fibrosis Related Diabetes diagnosis. We excluded other articles, which are not related to our objectives. **Conclusion:** CFRD can significantly worse the health condition of CF patients. However, with the recent advancement of management plans of CFRD, previous sex differences in mortality have disappeared and that the gap in mortality between CF patients with diabetes and CF patients without diabetes has considerably narrowed. Early diagnosis and early intervention also helped in improving the quality of CFRD patients and preventing the complications. This can be obtained by annual screening for DM among CF patients since 10 years of age using OGTT as recommended by ADA. The primary pathologic feature of CFRD is insulin insufficiency. It leads to increased breakdown of protein and fat. So, insulin replacement is the only recommended medical treatment and it has been shown to improve clinical outcomes. Oral diabetes agents are usually not recommended in CFRD.

Keywords: evaluation, management plan, diabetes mellitus, cystic fibrosis, children.

INTRODUCTION:

Cystic fibrosis (CF) is an inflammatory disease occurs as a result of mutations in the CF transmembrane conductance regulator (CFTR) gene ⁽¹⁾. CFTR is a chloride bicarbonate channel responsible for correction of epithelial cell secretions. In case of CFTR dysfunction, there will be ionic imbalance in the secretions which will lead to accumulation of mucus in exocrine-associated organs ^(2, 3, 4). The main symptoms include a persistent cough that produces mucus, recurrent lung infection, intestinal obstruction, malabsorption, nasal polyps, rectal prolapse, pancreatitis, increase of blood sugar level, and growth hormones disorders ^(2, 5). Therefore, the main affected organs in CF diseases are respiratory, digestive, and reproductive tracts. Lungs in CF diseases lose their ability to maintain a sterile surface. That is, these organs will be damaged by bacterial infections gradually ⁽⁶⁾. The

amount of intestinal fluid is lower than normal; hence, after a dehydration of the stool, patient will suffer from bowel obstruction ⁽⁷⁾. The pancreatic duct also secretes less fluid than normal, causing ductal blockage and eventually pancreatic degeneration. As a result, loss of pancreatic enzymes causes steatorrhea that may offset the tendency for intestinal block.

CF has been generally well defined throughout the world although its prevalence is very difficult to ascertain for a number of reasons, including the fact that the medical/scientific literature and patient registries vary in quality in different countries. According to the recent literatures, the higher frequency of registered CF patients was in the European Union. This could be due to strong clinical awareness and greater health facilities. In contrast, we found a very irregular report from

Asian and African countries. In these countries, the national CF registration system is mostly lacking or it is individualized-based research. In the Middle East the incidence is almost 1 in 2000 to 1 in 5800 live births, and the median survival was estimated to be from 10 to 20 years of age ⁽⁸⁾. Chronic complications arising from CF become increasingly prevalent with age, and cystic fibrosis related diabetes mellitus (CFRD) is currently diagnosed at a median age of 21 years. CFRD can significantly worsen the health condition of CF patients ⁽⁹⁾. It can affect their health by poor weight gain, decreased lung function and increased mortality observed amongst affected patients ⁽¹⁰⁾. Also, the new literatures found that CFRD is associated with a lot of microvascular complications. They reported a high prevalence of microalbuminuria (14%), retinopathy (16%) and autonomic neuropathy (52%) in patients who have had CFRD for 10 years or more ⁽¹¹⁾. Currently diabetes-related macrovascular disease is not observed in patients with CFRD, although many patients have abnormalities in serum lipid profiles (e.g. elevated triglyceride levels) and cardiovascular complications may emerge as a problem should the age of survival with CFRD continue to increase beyond current limits ⁽¹²⁾.

As a result of the significant effect of CFRD on the patients' health, early detection, diagnosis and treatment of this complication have been recommended. However, the currently used approaches for the management and diagnosis for type 1 and Type 2 DM are not suitable for CFRD because of the different underlying pathophysiology of this condition. Therefore, we reviewed the recent literatures done in this field to assess the various diagnostic and management measures that can be done, and provided a review paper that summarized the recent progression done.

METHODOLOGY:

Sample

PubMed database was used for articles selection, and the following keys used in the mesh ("Cystic Fibrosis/epidemiology"[Mesh] OR "Cystic Fibrosis Related Diabetes Mellitus/etiology"[Mesh] OR " Cystic Fibrosis Related Diabetes Mellitus /management"[Mesh]). A total of 420 articles were found, with further restriction by PubMed filters, and reviewing the articles titles and abstracts the final results were 7 articles.

Inclusion criteria included the articles were selected based on the relevance to the project which should include one of the following topics, {Cystic Fibrosis, Diabetes Mellitus, Diagnosis, Management, Insulin}. **Exclusion criteria** excluded all other articles which did not have one of these topics as their primary end point, or repeated studies.

Analysis

No software was used to analyze the data. The data were extracted based on specific form that contains (Title of the study, name of the author, Objective, Summary, Results, and Outcomes), these data were reviewed by the group members. Double revision of each member's outcomes was applied to ensure the validity of the results.

RESULTS:

We enrolled a total of 7 studies according to our inclusion, and exclusion criteria described above. All the studies aimed at evaluating different management plans for CFRD. The studies characteristics are shown in Table 1.

Table 1: The included studies:

Study	Study Design	Country	Participants (n)	Objective	Duration	Outcome and Conclusion
Moran <i>et al.</i> ⁽¹³⁾	Retrospective	USA	872	To determine the current trends in CFRD prevalence, incidence, and mortality	16 years	Previously noted sex differences in mortality have disappeared, and the gap in mortality between CF patients with and without diabetes has considerably narrowed. We believe that early diagnosis and aggressive treatment have played a major role in improving survival in these patients.
Kern A and Prestridge ⁽¹⁴⁾		USA	68	To implement an outpatient system to provide effective, evidence-based screening for CFRD	1 year	A systematic, quality improvement approach effectively increased the rate of outpatient screening for CFRD at a pediatric CF program.
Pincikova <i>et al.</i> ⁽¹⁵⁾	cross-sectional	Scandinavian countries	898	To assess the relationship between vitamin D and cystic fibrosis-related glucose intolerance	3 years	Degree of vitamin D insufficiency and were significant risk factors for cystic fibrosis-related diabetes.
Noronha <i>et al.</i> ⁽¹⁶⁾	cross-sectional	Brazil	60	To evaluate (a) the prevalence of cystic fibrosis-related diabetes mellitus (CFRD) in a non-Caucasian population with oral glucose tolerance test (OGTT)	13 years	The prevalence of CFRD in our patients is high, similar to the data from Caucasian populations, and significantly higher than previously reported in Brazil. Screening with OGTT resulted in earlier diagnosis of CFRD by 8 yr.
Mohan <i>et al.</i> ⁽¹⁷⁾	Cross-sectional	UK	5,378	To assess clinical practice and determine adherence to the recent recommendations among recognized CF centers in UK	3 months	The survey highlights the disparities in the management of CFRD with regards to screening and diagnostic practice, and poor adherence to national guidelines.
Ballmann <i>et al.</i> ⁽¹⁸⁾	RCT	Austria, France, Germany, and Italy	75	To compare the efficacy of repaglinide, an oral antidiabetic drug, with insulin therapy cystic-fibrosis-related diabetes	2 years	They found that repaglinide for glycaemic control in patients with cystic-fibrosis-related diabetes is as efficacious and safe as insulin
Dashiff <i>et al.</i> ⁽¹⁹⁾	Cross-sectional	USA	10	To describe the experience of cystic fibrosis-related diabetes (CFRD), parental support of adolescent self-management, and the relationship of parental autonomy support with disease self-management.		Parents and adolescents lacked confidence to manage CFRD. Mothers' autonomy support was associated with adolescents' CFRD competence and cystic fibrosis self-care. Fathers' autonomy support was associated with mothers' reports of adolescent cystic fibrosis self-care.

DISCUSSION:

Cystic fibrosis (CF) is an autosomal recessive disease. It is the most common hereditary disease in Caucasian populations, with an incidence in the US of 1 in 4100 live births and an estimated gene frequency of 3% ⁽²⁰⁾. The incidence of CF in Saudi Arabia has been estimated to be 1:4243 live births ⁽²¹⁾. Reported prevalence of diabetes in children with CF < 10 years of age is low. However, the prevalence increases significantly with age, with 50% of patients developing CFRD

by the age of 30 years. Diabetes is an expected complication as individuals with CF grow Older ⁽²²⁾.

Maron *et al.* ⁽¹³⁾ reviewed data of 872 CF patients from 1992 to 2008 and compared between the earlier and the new management to determine whether modern diabetes screening and management have influenced prevalence, incidence, and mortality figures. They noted that previous sex differences in mortality have

disappeared and that the gap in mortality between CF patients with diabetes and CF

patients without diabetes has considerably narrowed. Although many factors have changed in the management of individuals with CF over the last decade, they believed that early diagnosis and aggressive treatment of CFRD have played a major role in improving survival in these patients⁽¹³⁾. Speaking of which, (Kern ET Prestridge)

found that targeting education about CFRD and Few studies have demonstrated a plausible relationship between CFRD and poor nutritional and respiratory status. In patients with severely impaired insulin secretion, a more rapid deterioration in the respiratory status is observed. Similar to rectal prolapse, the worsening in respiratory status may also predate the diagnosis of CFRD⁽²²⁾. Pincikova *et al.*⁽¹⁵⁾ also found a relationship between vitamin D deficiency and CFRD⁽¹⁵⁾. Their paper demonstrated that vitamin D insufficiency plays a role in the pathogenesis of impaired glucose tolerance and CFRD in cystic fibrosis patients. Degree of vitamin D insufficiency, s25OHD<30 nmol/l and s25OHD<50 nmol/l were shown to be associated with higher HbA1c values, and degree of vitamin D insufficiency as well as s25OHD<30 nmol/l were shown to be significant independent risk factors for CFRD diagnosis. Moreover, Konrad *et al.*⁽²³⁾ group found a relationship between b-cell autoimmunity and CFRD. Presence of b-cell autoantibodies in their paper was associated with female sex, earlier onset of diabetes, and higher insulin requirement. Insulin pump therapy was used significantly more often in patients with b-cell antibodies. Severe hypoglycemia and ketoacidosis were significantly more frequent in CFRD with b-cell autoimmunity compared to b-cell antibody-negative patients with CFRD⁽²³⁾.

CFRD can be with fasting hyperglycemia (CFRD FH+) or can be without fasting hyperglycemia (CFRD FH-). Approximately 15% have diabetes with fasting hyperglycemia (CFRD FH+) and require insulin therapy to prevent classic diabetes symptoms and microvascular complications. The 25% of adult patients with cystic fibrosis who have diabetes without fasting hyperglycemia (CFRD FH-) pose a greater clinical dilemma. During a standard oral glucose tolerance test (OGTT), they have normal fasting glucose levels, but their 2-h glucose is >200 mg/dl. However,

the OGTT, communication with families, and scheduling processes, is effective in improving the rate of screening for diabetes at their pediatric CF program. This led to early diagnosis and early control of CFRD⁽¹⁴⁾. Also, Noronha *et al.*⁽¹⁶⁾ emphasized on the need for implementing routine screening with OGTT for patients with CF⁽¹⁶⁾.

they do not appear to be at risk for microvascular or macrovascular complications unlike the general diabetic population. Diabetes microvascular complications occur in CFRD, but they tend to be relatively mild in nature. Schwarzenberg *et al.*⁽²⁴⁾ group showed that diabetes complications were rare before 10 year duration of diabetes. After that period, in subjects with fasting hyperglycemia, microalbuminuria, retinopathy, neuropathy, and gastropathy were found. No microvascular complications were remarked in CFRD patients who had never experienced fasting hyperglycemia as mentioned earlier⁽²⁴⁾.

The pathophysiology of cystic fibrosis-related diabetes is complex and includes the loss of pancreatic islet cells leading to combines both impaired insulin secretion and insulin resistance. Data on the pathophysiology of cystic fibrosis related diabetes, which involves the cystic fibrosis transmembrane conductance regulator, have revealed an early insulin secretion deficiency that increases with disease progression. Insulin deficiency can increase malnutrition, having serious clinical consequences in patients with cystic fibrosis because protein and lipid catabolism is accelerated in chronic infections⁽²⁵⁻²⁶⁾.

OGTT is the diagnostic test for CFRD. Recently, the American Diabetes Association (ADA) and the Cystic Fibrosis Foundation, and the Pediatric Endocrine Society updated the diagnostic criteria for CFRD and added HbA1c to OGTT as a part of the criteria. However, it should be noted that low or normal HbA1c levels do not exclude the diagnosis of CFRD because HbA1c is often spuriously low in CF. So, HbA1c should not be the only parameter in prognosis and follow up measures. In addition, even when the fasting and 2-h OGTT glucose levels normal, variable, and intermittent postprandial hyperglycemia can

often be detected at home by continuous glucose monitoring (CGM). So, CFRD must be always suspected in order to

detect it early especially in stressful conditions which cause hyperglycemia such as during pregnancy in women with CF because of their underlying insulin insufficiency. Moreover, the presence of symptoms can raise the suspicion index of CFRD. Symptoms like unexplained polyuria or polydipsia, failure to gain or maintain weight despite nutritional Intervention, poor growth velocity, delayed progression of puberty, or unexplained chronic decline in pulmonary function. Anyhow, it is important to note that CFRD develops insidiously and the majority of patients have no obvious symptoms. Therefore, ADA recommends annual screening for CFRD with OGTT and it should begin by age 10 years in all patients with cystic fibrosis not previously diagnosed with CFRD ⁽²⁷⁾.

Given its complexity, CFRD should be managed by a multidisciplinary team of health professionals with expertise in the care of persons with CF and CFRD. The team should consist of an endocrinologist, a diabetes educator, a CF nutritionist and a mental health professional. The goals of hyperglycemia management in the CF population are to reverse protein catabolism, maintain a healthy weight, and reduce acute and chronic diabetes complications ⁽²⁸⁾.

CF patients require a very high-calorie diet that is usually 120–150% of the daily recommended intake for age because they have both increased resting energy expenditure and increased loss of calories through malabsorption. Thus, calories should almost never be restricted. The need for high caloric intake, however, does not replace well-established principles of good nutrition and a healthy, well-balanced diet. Insulin replacement is the only recommended medical treatment because insulin insufficiency is the primary pathologic feature of CFRD. Insulin is a potent anabolic hormone, and insulin deficiency leads to increased breakdown of protein and fat. So, treatment with insulin has been shown to improve clinical outcomes, both in the short and long term. Oral diabetes agents are usually not recommended in CFRD. On the other hand, insulin therapy is not easy. Though effective, the use of insulin is associated with some disadvantages such as the inconvenience of repeated injections, high cost, and storage problems. Treatment with an oral antidiabetic drug is less invasive than multiple daily

injections, which might be particularly important for patients who already have a complex and demanding pharmaceutical therapy schedule that includes antibiotics, pancreatic enzymes, bronchodilators, and mucolytic agents, and additional supportive care ⁽²⁴⁾. **Ballmann *et al.*** ⁽¹⁸⁾ conducted an RCT to compare the efficacy of repaglinide, an oral antidiabetic drug, with insulin therapy among CFRD patients. They found that treatment with oral repaglinide achieved similar glycaemic control, clinical effects, and safety to insulin. They recommended that treatment guidelines include repaglinide as an option for early-stage CFRD because treatment with an oral antidiabetic drug might reduce the treatment burden for patients and the care burden for their caregivers ⁽¹⁸⁾. Nevertheless, **Ballmann *et al.*** ⁽¹⁸⁾ paper can be criticized because they used regular insulin given at meal times. The kinetics of regular insulin, with a peak 3 h after injection and duration of action of 6 h, does not allow for optimum postprandial hyperglycemia control and the treatment has a risk of delayed hypoglycemia. Other insulin regimens might potentially provide better results in patients with CFRD such as faster-acting insulin as part, insulin pumps, or other approaches ⁽²⁶⁾.

There was a hypothesis that insulin insufficiency compromises health and survival in cystic fibrosis by producing a catabolic state because of the associated weight loss and reduced lean body mass. Previous reports have suggested that weight and/or pulmonary function may improve after institution of insulin therapy but this statement was not supported by strong evidence ⁽²⁹⁾. In 2009, **Moran *et al.*** ⁽²⁴⁾ conducted an RCT study that compared three regimens regarding changes of BMI throughout one year of therapy. The three regimens were premeal insulin as part, repaglinide, and oral placebo ⁽²⁴⁾. They found that insulin replacement therapy significantly reversed the trajectory of chronic weight loss in CFRD FH- patients. In **Moran *et al.*** ⁽²⁴⁾ paper, insulin-treated patients stopped losing weight and gained both fat and lean body mass. This result seemed to be mediated primarily via the anabolic rather than the glucose homeostatic effect of insulin because it was accomplished without a significant change in HbA1c or blood glucose levels ⁽²⁴⁾.

As mentioned earlier, CF management is complex. Adherence to many chronic disease regimens are known to be poor. Parental involvement is known to improve self-management of chronic disease and facilitate the transition to adulthood. Further, the management of CF can be complicated by the diagnosis of CFRD, which adds another layer to the management regimen such as multiple daily administration of insulin, matching the dose of insulin to carbohydrate intake, regular blood glucose monitoring, and minimization of hypoglycemia and hyperglycemia. This can challenge parents' abilities to support adolescent autonomy and maintain appropriate involvement in disease management. Parent's support of autonomy leads to autonomously motivated behavior and contributes to the adolescents' feelings of competence and confidence in their ability to self-manage. In **Dashiff et al.** ⁽¹⁹⁾ paper, parents and adolescents lacked confidence to manage CFRD. Mothers' autonomy support was associated with adolescents' CFRD competence and cystic fibrosis self-care. Fathers' autonomy support was associated with mothers' reports of adolescent cystic fibrosis self-care ⁽¹⁹⁾. In addition, one of the challenges that face a CF patient is the transition from pediatric and adult CF care. **Middleton et al.** ⁽³⁰⁾ emphasized on the need to comprehensive education of the young adult with CF, together with their parents prior to transition lessens and the need for lengthy discussions during the "settling in" period in the adult CF clinic. A unified approach to CF pulmonary disease, CFRD and any other health issues is essential. Optimal transition of the young person with CF requires good communication and coordination of both CF pulmonary and CF endocrine teams with common management goals ⁽³⁰⁾.

CONCLUSION:

CFRD can significantly worsen the health condition of CF patients. However, with the recent advancement of management plans of CFRD, previous sex differences in mortality have disappeared and that the gap in mortality between CF patients with diabetes and CF patients without diabetes has considerably narrowed. Early diagnosis and early intervention also helped in improving the quality of CFRD patients and

preventing the complications. This can be obtained by annual screening for DM among CF patients since 10 years of age using OGTT as recommended by ADA. The primary pathologic feature of CFRD is insulin insufficiency. It leads to increased breakdown of protein and fat. So, insulin replacement is the only recommended medical treatment and it has been shown to improve clinical outcomes. Oral diabetes agents are usually not recommended in CFRD.

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