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StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-.

Cystic Fibrosis Related Diabetes (CFRD)

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Last Update: November 10, 2019.

Introduction

Cystic fibrosis-related diabetes (CFRD) is an extrapulmonary complication of cystic fibrosis (CF) and is associated with increased morbidity and mortality in affected individuals. Cystic fibrosis-related diabetes is the result of abnormal glucose metabolism primarily characterized by insulin deficiency, intermittently exacerbated by insulin resistance. It is crucial to recognize the early signs of abnormal glucose metabolism in individuals with CF to make the diagnosis of CFRD. Early diagnosis and treatment correlate with slower rates of pulmonary decline and improved growth. This activity will provide an overview of CFRD.

Etiology

The etiology of cystic fibrosis-related diabetes is not completely understood. The current view of CFRD is that it is a multifactorial condition resulting from a combination of beta-cell dysfunction and a decrease in islet cell mass.

Epidemiology

Cystic fibrosis-related diabetes has a high prevalence in the CF population. The incidence increases with age. It is present in 2% of children, 19% of adolescents, 40% of individuals in their 20s, and up to 50% of individuals 30 years of age and older with cystic fibrosis. The prevalence rate may appear to be lower at centers that do not perform universal oral glucose tolerance screening testing.[1][2]

Pathophysiology

The pathophysiology of cystic fibrosis-related diabetes is complex and not completely understood. It is believed to be multifactorial with both a functional and structural component.

Functional abnormalities seen in CFRD stem from a defect in the cystic fibrosis transmembrane regulator (CFTR) gene. CFTR gets expressed in pancreatic beta-cells where its exact role remains unknown. Animal models suggest that CFTR has an intrinsic role in insulin secretion, and mutations in the CFTR gene result in abnormal beta-cell function with decreased insulin secretion in response to a glucose load.

In addition to functional impairment of the beta cell, structural damage to pancreatic islet cells also occurs as a consequence of the defective CFTR protein. CFTR protein is present in the ductal epithelial cells of the pancreas. A mutation in this protein interferes with normal chloride channel function, resulting in pancreatic secretions with lower water content and higher viscosity; this results in pooling of pancreatic enzymes leading to autodigestion, cyst formation and progressive fibrosis of the pancreas. This progressive fibrosis ultimately causes decreased islet cell mass by the destruction of endocrine beta, alpha, and pancreatic polypeptide secreting cells. Both insulin and

glucagon insufficiencies occur as a result of total islet destruction. Premature loss of exocrine function is an increased risk factor for the development of CFRD.[1][3][4][5]

History and Physical

The majority of individuals with CFRD present with no obvious clinical symptoms at the time of diagnosis. Polyuria and polydipsia as presenting symptoms are less common in CFRD than in other forms of new-onset diabetes. A chronic decline in pulmonary function may be the first sign of CFRD. Failure to maintain or gain weight irrespective of adequate nutrition may also present as the first indication of CFRD. Growth deceleration and weight loss generally precede the manifestation of CFRD by several years in the pediatric patient population with CF. A reduction in BMI before the diagnosis of CFRD may not necessarily appear in the pediatric population due to parallel decreases in weight and height. [6] Monitoring growth and weight trends are crucial in pediatric patients with cystic fibrosis.

Evaluation

The majority of individuals with cystic fibrosis-related diabetes do not present with classic symptoms of diabetes at the time of diagnosis. Therefore routine screening for CFRD is vital in individuals with cystic fibrosis. Guidelines published by the Cystic Fibrosis Foundation and American Diabetes Association recommend the 2-hour 75-gram oral glucose tolerance test (or 1.75 gm glucose/kg for individuals under 42 kg body weight) as the only acceptable screening test for CFRD. Annual screening for CFRD should begin by ten years of age in all individuals with cystic fibrosis.[2]

Additional screening methods such as urine glucose testing, random plasma glucose measurements, fructosamine testing, and monitoring of hemoglobin A1c levels are not recommended due to their low sensitivity.[7]

At baseline health the standard American Diabetes Association criteria are used to make the diagnosis of CFRD: 2-hour plasma glucose level greater than or equal to 200 mg/dL on oral glucose tolerance testing, fasting plasma glucose greater than or equal to 126mg/dL, HgA1c greater than or equal to 6.5%, and/or random glucose greater than or equal to 200mg/dL with clinical symptoms. In a state of acute illness, a 2-hour postprandial plasma glucose level greater than or equal to 200 mg/dL or a fasting plasma glucose greater than or equal to 126mg/dL that persists for 48 hours or more is diagnostic.[1][2]

Treatment / Management

Insulin is the preferred treatment for individuals with cystic fibrosis-related diabetes. Insulin therapy has been associated with better glycemic control, improved weight gain, and improved pulmonary function in CFRD. Individuals with CFRD are advised to maintain the same level of caloric intake recommended before their diagnosis in addition to starting insulin therapy to optimize their glycemic control. Management of CFRD without fasting hyperglycemia is possible with rapid-acting insulin alone for meals. Premeal doses are calculated using insulin to carbohydrate ratios. Individuals with CFRD who experience fasting hyperglycemia should start an insulin regimen consisting of long-acting basal insulin in combination with rapid-acting insulin for meals. CFRD patients receiving overnight continuous gastrostomy tube feeding may benefit from an insulin regimen consisting of combined intermediate-acting insulin such as regular insulin and NPH insulin to handle the prolonged carbohydrate load delivered throughout the overnight hours.

Individuals with CFRD may develop insulin resistance, and experience increased insulin requirements during times of acute illness as a result of inflammatory cytokines. Insulin requirements may decrease rapidly as the acute illness resolves. Blood sugars in CFRD require close monitoring during times of acute illness. Based on current guidelines,

the recommended fasting glucose target in patients with CFRD is between 70 to 130 mg/dL, and a 3-hour postprandial glucose target is below 180 mg/dL.

There is currently insufficient data to recommend non-insulin injectables or oral hypoglycemic agents in CFRD. Prescribing these medications should not take place in this population outside of clinical trials.[1][2]

Differential Diagnosis

CFRD shares several similarities with diabetes mellitus type 1 and type 2, however, it has fundamentally different pathophysiology, and it is important to recognize the differences for proper diagnosis and management.

CFRD differentiates itself from type 1 diabetes by its gradual onset over the years, rather than weeks to months. Individuals with CFRD will maintain some degree of insulin function compared to individuals with type 1 diabetes. Ketoacidosis, a common finding in type I diabetes, is uncommon in CFRD due to the residual insulin production present. The destruction of beta cells seen in CFRD is not related to autoimmune disease, and individuals with CFRD generally test negative for diabetes autoantibodies.

Insulin resistance seen in CFRD is generally transient as a result of acute illness or steroid therapies compared to the insulin resistance seen in type 2 diabetes, which is longstanding and is present even in the baseline state of health.

Prognosis

Cystic fibrosis-related diabetes is a lifelong disorder with no definitive cure, but it is a treatable condition that responds well to insulin therapy. Individuals with cystic fibrosis with the additional diagnosis of CFRD have a higher risk of early death compared to those without CFRD. The mortality associated with CF and CFRD has significantly reduced with the addition of annual diabetes screening and early initiation of insulin therapy. The most common cause of death associated with CFRD is pulmonary failure. While all of the links between CFRD and accelerated pulmonary decline have not been elucidated, chronic hyperglycemia is known to exert negative effects on lung function by impeding bacterial clearance and increasing oxidative stress in the lungs resulting in decreased pulmonary function and ultimately pulmonary failure.[8][9][10][11][10]

Complications

Microvascular complications are the most common finding in individuals with CFRD. A study by Schwarzenberg et al. looked at 285 individuals with CFRD with fasting hyperglycemia. They reported neuropathy in 55% of subjects, gastropathy in 50% of subjects, retinopathy in 16% of subjects, and microalbuminuria in 14% of subjects. Complications rarely occur in patients who have had CFRD with fasting hyperglycemia for less than ten years. There are no reports of microvascular complications in individuals with CFRD without fasting hyperglycemia. Unlike type 1 and type 2 diabetes, macrovascular complications rarely present in CFRD.[1][2][12]

Deterrence and Patient Education

To date, no identified intervention successfully prevents progression to CFRD in individuals with cystic fibrosis. With routine annual screening, however, many patients are diagnosed with impaired glucose tolerance before the development of frank diabetes. This screening approach allows an opportunity for patient and family education about diabetes before the time that insulin therapy is necessary. After the diagnosis of cystic fibrosis-related diabetes has been established, a referral to an endocrinologist should be made to initiate insulin therapy. Routine self-monitoring of blood glucose, generally a minimum of three times a day, is required by the patient and/or patient's family. Insulin injections may be necessary as infrequently as once daily or as frequently as four to six times daily, depending on the patient's pattern of blood glucose. CFRD is a condition that cannot receive optimal therapy without

extensive education and effective engagement of the patient and/or parents.

Pearls and Other Issues

Hemoglobin A1c levels may appear falsely low in individuals with cystic fibrosis. Chronic inflammation may result in a shorter red blood cell life cycle resulting in a falsely normal hemoglobin A1c level. Relying on a hemoglobin A1c level will also miss individuals with impaired glucose tolerance that present with only abnormal postprandial glucose levels but normal fasting glucose levels. Hemoglobin A1c levels are not sensitive enough to screen for CFRD; however, it can be a useful tool to measure the response to treatment in CFRD.

A high suspicion should be maintained for type 1 diabetes occurring in combination with CF in any individual with CF who is experiencing hyperglycemia, ketoacidosis, and positive diabetes autoantibodies. These individuals should be treated as type 1 diabetes patients until proven otherwise.

Enhancing Healthcare Team Outcomes

CFRD management is best with an interprofessional team consisting of an endocrinologist, pulmonologist, nutritionist, and a primary care provider, along with specialty care nursing staff and pharmacists. Routine self-monitoring of blood glucose at least three times a day is recommended in CFRD. CFRD requires strong communication between providers and patients to achieve optimal glycemic control. Nurses and pharmacists both can be invaluable in training for proper glucose meter use, how to inject insulin, and answering questions the patient and/or their family may have. Pharmacists need to perform medication reconciliation and verify dosing to prevent adverse reactions. Nursing can monitor treatment progress as well as be alert for adverse medication reactions as well. Only with a full collaborative interprofessional team approach can CFRD patients achieve optimal results. [Level 5]

Questions

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Bookshelf ID: NBK545192 PMID: 31424776