CYSTIC FIBROSIS-RELATED DIABETES

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ABSTRACT

Introduction: Cystic Fibrosis-Related Diabetes (CFRD) is classified as a specific type of diabetes due to disease of the exocrine pancreas. It is estimated that 15-30% of adults with Cystic Fibrosis (CF) develop CFRD, and the risk of Diabetes Mellitus (DM) in CF is 20 times higher than in the general population. Although it is not as highly prevalent as type 1 DM and type 2 DM, early diagnosis and treatment of CFRD are also essential to prevent complications and reduce morbidity and mortality in patients with this disease. Objective: To conduct a literature review on DM as a comorbidity of Cystic Fibrosis. Methods: Literature review by searching the terms "Cystic fibrosis", "Diabetes" from PubMed and Scielo of the most relevant articles of the last 15 years. Results and Discussion: CFRD is the most common extrapulmonary comorbidity in people with CF. The main risk factors are female gender and advancing age. CFRD is associated with increased frequency of pulmonary exacerbations, greater reduction in lung function, and poorer nutritional status. Genetic variants in the CFTR gene cause depolarization of β cells, interfering with insulin release and causing postprandial hyperglycemia; reduction in the volume of islets; increased protein concentrations in the pancreatic duct, leading to its obstruction; oxidative stress, among other effects. Therefore, postprandial hyperglycemia alone, ESRD without fasting hyperglycemia, and ESRD with fasting hyperglycemia may develop, and these categories may be switched between. CFRD screening is recommended annually from 10 years of age in patients with CF. The most used test for screening and diagnosis is the Oral Glucose Tolerance Test (OGTT). The treatment is multidisciplinary, based on insulin therapy and, in addition, a high-calorie diet is recommended. Conclusion: In patients with CFRD, complications, especially pulmonary exacerbations, are more frequent. The diagnosis is challenging due to the dynamic profile of blood glucose in these patients and, to date, there are no specific cut-off points for CFRD, and diagnostic parameters based on data from adults with type 2 DM are used.

Keywords: Diabetes Mellitus; Cystic fibrosis; Transmembrane Conductance Regulator in Cystic Fibrosis; Oral Glucose Tolerance Test.

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INTRODUCTION

Diabetes Mellitus (DM) is a chronic disease characterized by the inability of the pancreas to produce insulin or defects in insulin action, resulting in persistent hyperglycemia1. In a literature review between 1990 and 2016, the prevalence of diabetes was estimated at 451 million diabetics; however, half of the population diagnosed with DM, approximately 224 million adults, has not been diagnosed2.

More than 90% of Diabetes Mellitus cases are Type 23. Type 2 Diabetes Mellitus (DM2) occurs when there is resistance to the action of insulin, which leads to greater glucose production in the liver, decreased glucose uptake from muscle and adipose tissue, and dysfunction of pancreatic beta cells4. Type 1 Diabetes Mellitus (DM1) corresponds to 5 to 10% of cases. DM1 is characterized by absolute deficiency of insulin production by an autoimmune destruction of pancreatic cells of the β5 type. Gestational Diabetes Mellitus (GDM), in turn, occurs due to an increase in hyperglycemic hormones during pregnancy, which are placental lactogen, cortisol, estrogen and progesterone6.

DM also has other specific types resulting from genetic variations such as Type MODY Diabetes and Lipoatrophic Diabetes. Endocrinopathies; pharmaceuticals or chemicals; genetic syndromes can trigger metabolic alterations and, consequently, DM. Finally, diseases of the exocrine pancreas such as neoplasms, pancreatitis and cystic fibrosis can also cause DM7. Thus, Cystic Fibrosis-Related Diabetes (CFRD) is classified as a specific type of diabetes due to exocrine pancreatic disease and usually manifests between 15 and 21 years of age. It is estimated that 15-30% of adults with cystic fibrosis (CF) develop CFRD, and the risk of DM in CF is 20 times higher than in the general population8, 9.

In this study, we conducted a review of CFRD which, although not as highly prevalent as DM1 and DM2, its early diagnosis and treatment are also essential to prevent complications and reduce morbidity and mortality in patients with this disease.

OBJECTIVES

To conduct a literature review on Diabetes Mellitus as a comorbidity of Cystic Fibrosis with a focus on its pathophysiology, diagnosis and treatment.

METHODS

A systematic review of the literature was carried out using articles from the PubMed® and Scielo® databases. The descriptors "cystic fibrosis" and "diabetes" were used.

After applying the publication period filter from January 1, 2005 to April 7, 2020, 1,367 and 20 results were obtained in the PubMed® and Scielo® databases, respectively. The articles were selected according to their title, abstract, and relevance. Only studies related to the pathophysiology, diagnosis, and treatment of Cystic Fibrosis-Related Diabetes that were relevant and provided updated information on the subject were included. Finally, 47 articles were selected.

RESULTS AND DISCUSSION

CYSTIC FIBROSIS

Cystic Fibrosis (CF) is an autosomal recessive multisystem disease caused by mutations in the *Cystic Fibrosis Transmembrane Conductance Regulator* (*CFTR)* gene10. In Brazil, it is estimated that the incidence of CF is, on average, 1:7,576 live births, but higher values were found in the South region, as shown by a study by a private laboratory in Rio Grande do Sul, which found an incidence of 1:1,587 live births11.

The *CFTR* gene encodes a Transmembrane Chlorine Conductive Protein, a chloride and bicarbonate channel essential for proper anion secretion and mucociliary clearance of airway epithelial cells, so mutations in this gene result in mucus retention, chronic respiratory tract infections, and deterioration of lung function12.

The complications of CF, in addition to lung diseases, involve other organs where the Chlorine Conductive Protein is expressed. In the pancreas, obstruction of the pancreatic canaliculi and ducts occurs, which leads to autolysis, tissue fibrosis, and pancreatic insufficiency; obstructed hepatic ducts can lead to cirrhosis; in the testes, agenesis of the vas deferens and, consequently, sterility; electrolyte disturbances may lead to hyponatremic dehydration; among other complications13. However, approximately 95% of the morbidity and mortality rate of CF corresponds to pulmonary diseases, and lung transplantation is the definitive cure14.

Improvements in the management of complications have been responsible for increasing the life expectancy of patients with this disease15. As survival improves, other complications are becoming more prevalent16. Among them, CFRD, the most common extrapulmonary comorbidity in people with CF17.

CYSTIC FIBROSIS-RELATED DIABETES

The prevalence of CFRD increases with age: it affects approximately 2% of children, 19% of adolescents, and 40 to 50% of adults. About 80% of people with severe mutations develop CFRD after 40 years of age, with a higher prevalence in women18. However, there

is no difference in mortality between the two sexes19, [20]. Risk factors associated with the development of CFRD are: more severe CFTR genotypes, family history of DM2, risk states for developing diabetes such as altered fasting glucose or glucose intolerance, CF-related exocrine pancreatic insufficiency, hepatobiliary disease, solid organ transplantation, and systemic use of corticosteroids18, [21, 22].

Patients with CFRD have been shown to have up to twice as many pulmonary exacerbations compared to CF patients without diabetes17. In addition to the impact on lung function, CFRD is related to the catabolic effect of insulin insufficiency on nutritional status and muscle mass23. Impaired glucose tolerance has also been associated with a great clinical deterioration21.

This progressive pathogenesis is responsible for a six-fold higher mortality rate in CFRD patients compared to CF patients with normal glucose tolerance17. Less than a quarter of patients with CFRD survive beyond the age of 30, compared with 60% of CF individuals without diabetes24.

However, recently in the last two decades, broad screening followed by early diagnosis and treatment of diabetes has resulted in lower mortality rates for patients with CFRD due to a reduction in the frequency of pulmonary exacerbations and improvements in lung function and nutritional status18.

PATHOGENESIS

CFRD is recognized as a unique form of diabetes18. However, it is evidenced in the literature that a family history of DM2 increases the risk of CFRD. This correlation is explained by genes associated with T2DM as possible CFRD modifiers. A variant in the *TCF7L2* gene associates with T2DM and CFRD, revealing the modifying effects and reiterating the concept that diabetes develops in patients with underlying susceptibility to β25 cell dysfunction. In addition, a genome-wide association study of 3,059 individuals with CF identified single nucleotide polymorphisms (SNPs) in the *SLC26A9* gene whose variants are associated with CFRD susceptibility, and which are present in three other susceptibility loci for T2DM in the general population26. In addition to genetic characteristics, the pathogenesis of CFRD is largely based on *CFTR25 mutations*.

In α cells, *CFTR* has a role in suppressing glucagon, as they have a KCl cotransporter that maintains a low level of chloride in the cell. The opening of the Transmembrane Chlorine Conductive Protein, therefore, induces chloride entry, causing hyperpolarization of the membrane, inhibiting the secretion of glucagon. On the other hand, β cells retain a high electrochemical chloride potential. The opening of the Chlorine

Conductive Transmembrane Protein in the β cell, allows the efflux of chloride, playing an important role in the depolarization of β cells and the release of insulin. Thus, *CFTR* dysfunction impairs vesicle displacement, reducing insulin release after depolarization. CFRD is associated with decreased first-phase insulin release (depolarization-dependent), while second-phase insulin (depolarization-independent) remains intact. The fact that insulin release in the second phase is independent of depolarization and spared in CFRD is consistent with the hypothesis that *CFTR* is involved in β cell depolarization and insulin release in the first phase, which may explain why hyperglycemia is seen mainly in the postprandial period in CFRD19.

Thus, CFTR dysfunctions decrease the secretory volume of the islets, increasing the concentrations of proteins in the pancreatic duct, leading to its obstruction and interstitial edema19. This process corroborates progressive fibrosis, which in CF patients is already expressive due to the natural history of the disease16. Progressive fibrosis, in turn, is accentuated due to duct obstruction, infiltration of amyloid content and fat19. Pancreatic fibrosis accentuates the loss and dysfunction of β cells, aggravating the exocrine function of the pancreas and feeds back into this process16.

In addition, *CFTR* plays a protective role in cells β against oxidative stress26. Studies have shown high levels of peroxidized fats and oxysterols in the plasma of CF patients, indicating greater susceptibility to lipid oxidation19. In addition, pancreatic insufficiency and decreased bile acid cause malabsorption of fat-soluble antioxidants, such as carotenoids, tocopherols, and coenzyme Q-1027. CFTR silencing is associated with impaired insulin secretion, this disorder is amplified by oxidative stress, evidenced by abnormal ATP production, fatty acid β-oxidation, apoptosis, and inflammation. Thus, it is likely that the effects of oxidative stress develop over time and reflect in the gradual increase in glucose intolerance in CF, increasing the chances of developing CFRD28.

Evidence indicates that some types of *CFTR* mutation are related to greater chances of developing CFRD. Genetic variations associated with *CFTR* dysfunctionality in the cell membrane promote more severe phenotypes, while mutations with residual *CFTR* activity result in less severe disease16. In addition, pancreatic insufficiency, present in 85% of adults with CF, alters the incretin axis due to fat malabsorption19. Fat digestion regulates gastric emptying and postprandial blood glucose through the enteroinsular axis. Patients with CFRD generally have faster gastric emptying and lower secretion of gastric inhibitor polypeptide (GIP) and glucagon-like peptide type 1 (GLP-1), which stimulate insulin release after meals29. This condition underlies the postprandial glycemic variations, consistent with CFRD, and is associated with impaired primary insulin release19. Malabsorption of fats

corroborates inflammation, which worsens insulin resistance and contributes to the pathogenesis of CFRD18.

Another factor involved is lymphocyte dysfunction, probably due to glucose fluctuations. These variations promote an exaggerated lymphocyte response, which generates an increase in pro-inflammatory cytokines, corroborating the damage in β30 cells. In addition, non-optimal levels of vitamin D are known to aggravate exposed immune imbalance15. Hypovitaminosis D is frequent in CF patients, mainly due to intestinal malabsorption of its precursors, which contributes to the development of CFRD31.

CFRD is considered a distinct classification of diabetes, although it shares clinical features of T1D and T232. As with T1D, patients with CFRD are insulin deficient, thin, and adolescent or young adults at the time of diagnosis, however, CFRD is not an autoimmune condition and has an insidious onset over years to decades17, [21]. Insulin secretion is never totally absent in CFRD because beta cell destruction is incomplete32. Consequently, ketoacidosis is uncommon21.

Although CFRD has a modest insulin resistance compatible with a DM2 phenotype, it is not the defining characteristic of the disorder in CFRD17, [21]. In addition, unlike DM2, obesity in CFRD is uncommon33. In DM2, dietary restriction usually stops or delays the progression of the disease, while in CF patients, increased energy expenditure requires a high caloric intake to maintain weight and nutritional status, requiring a high-calorie diet34. However, this high-energy diet is typically high in fat and sugar, resulting in inadequate glycemic control in patients with CFRD24. A systematic review conducted in 2012 to evaluate the effects of a low-glycemic dietary intervention on young people with CF concluded that there is a lack of evidence in this area24, [35].

Similar to DM1 and DM2, CFRD is associated with microvascular complications, such as retinopathy and nephropathy, and the risk depends on the duration of the disease and glycemic control21. Compared to T1DM and T2DM, this risk is reduced, probably due to the persistence of endogenous insulin secretion in HR18.

However, unlike DM1 and DM2, in which cardiovascular disease is the main cause of death, CFRD has Chronic Obstructive Pulmonary Disease as the main cause of death18, [23]. Therefore, while the treatment of T1DM and T2DM is adapted to the prevention of vascular complications, the management of CFRD aims to stabilize and improve pulmonary function and nutritional status36.

DIAGNOSIS

The importance of early screening for glucose abnormalities in CF should be highlighted to ensure an immediate diagnosis with minimization of the effects of hyperglycemia on the overall outcome of the disease15. The ideal diagnostic method should provide indications about glucose tolerance and the risk of accelerated loss of lung function and weight, which already begins in states of increased risk for DM37.

Because the initial presentation of CFRD may be clinically silent, annual screening is recommended from 10 years of age18 and is critical in CF patients who have received solid organ transplantation, as post-transplant DM is common and is associated with increased infections and mortality. Unexplained decline in lung function, weight loss, or increased rate of pulmonary exacerbations are also indicative for investigation of CFRD36.

The diagnosis of CFRD can be biochemically and clinically challenging36. It is common for patients to have a dynamic and changeable level of glucose tolerance16. Initially, clinical hyperglycemia may manifest only during periods of acute lung infections or corticosteroid therapy. With disease progression, postprandial hyperglycemia may develop, followed by CFRD without fasting hyperglycemia and, subsequently, CFRD with fasting hyperglycemia21. Patients may switch between these categories depending on their increasing or decreasing infectious status18. In addition, the classic symptoms of polyuria, polydipsia, and low weight gain observed in conventional diabetes are present in only one third of patients with CFRD36.

Currently, the recommended screening test for CFRD is the 2-hour Oral Glucose Tolerance Test (OGTT)17. Based on the guidelines developed by a consensus of the *Cystic Fibrosis Foundation*, *American Diabetes Association,* and *Pediatric Endocrine Society* in 2009, patients with plasma glucose collected 2h after 75g overload in OGTT greater than 200 mg/dL meet the criteria for the diagnosis of CFRD18, [38].

However, the OGTT cut-off points that define CFRD were established based on microvascular complications and risk of retinopathy in patients with DM2, so they are questioned in CF. Thresholds associated with the risk of accelerated weight loss and lung function in patients with CFRD would be more relevant, however, to date, there are no large systematic studies that determine specific cutoffs for the risk of adverse clinical outcomes in CFRD19, [34, 39]. In addition, the test is time-consuming and requires patients to fast beforehand; consequently, there is low adherence to annual screenings19, [38]. Therefore, although screening rates for CFRD have increased since the publication of the OGTT guidelines, they are still quite low38.

CF patients are known to have a specific OGTT pattern characterized by early glucose excursion with rapid normalization. Therefore, instead of fasting glucose (G0) and 2h (G2) values, intermediate OGTT time points may provide more pertinent information to identify risks associated with hyperglycemia in these patients39. Against this backdrop, the *American Diabetes Association* and the *Cystic Fibrosis Foundation* have proposed a new CF-specific glucose tolerance subgroup, called indeterminate (INDET). This group has normal G2, but high glucose TOTG values of 1h (G1), above 200 mg/dL37. In fact, one study revealed that a pediatric population with CF had a worsening of pulmonary function associated with OGTT with elevated G1 and normal G239.

CFRD can also be defined as a fasting plasma glucose level ≥ 126 mg/dL34. However, patients with CFRD have transient postprandial hyperglycemia, while fasting hyperglycemia may never develop or appear only years after the initial diagnosis19. Therefore, fasting glucose is not recommended as a screening method for CFRD, as it has low sensitivity and, consequently, false-negative results in 20% of patients with CF19, [34].

Another option for diagnosing CFRD would be hemoglobin A1c (HbA1c), which measures mean glycemic status from 90 to 120 days. CFRD can be diagnosed when HbA1c is greater than 6.5%[18]. However, there are still many controversies about the sensitivity and specificity of HbA1c for screening for CFRD16, [19, 37]. It is considered that this test underestimates the degree of hyperglycemia in CF, since it was found that 2/3 of patients with CFRD have normal HbA1c values. It is thought that patients with CFRD have transient postprandial hyperglycemia does not significantly affect the glycation status of red blood cells, so HbA1c may be low in CF patients. In addition, there is possibly an influence of the increase in red blood cell turnover as a result of inflammation. However, recent evidence suggests that, once the diagnosis of CFRD is established, HbA1c is the most commonly used method to monitor diabetes control18.

In view of the controversies regarding the use of methods commonly used for the diagnosis of DM1 and DM2 in the diagnosis of CFRD, alternative methods are being proposed for the diagnosis of CFRD. Among them is Continuous Glucose Monitoring (GCM), which can be used to assess plasma glucose profile over several days and has been validated in CF. It detects earlier blood glucose abnormalities through a technology that allows frequent measurements (every 5 minutes) that monitor glucose trends in real time18, [19].

The device produces individual plasma glucose profiles and can identify non-evident hyperglycemic episodes in OGTT40. There is growing evidence that, prior to the

diagnosis of diabetes by 2-hour OGTT, early insulin deficiency in CF has a significant impact on clinical status. Increasing the frequency of monitoring glucose changes for 3 to 5 days increases the chance of detecting a greater number of glycemic abnormalities during baseline and postprandial conditions compared to other short-term methods19. However, there is a lack of consensus on screening thresholds. Further research is needed to determine which GCM results and which cut-off points correlate with clinical outcomes in HR18.

Finally, other methods proposed for the diagnosis of CFRD are the Disposition Index (DI) and circulating immunoreactive trypsinogen. DI, which can be understood as the ability of β cells to compensate for changes in insulin sensitivity, is greatly reduced in individuals with CFRD. Circulating immunoreactive trypsinogen, a biomarker of exocrine pancreatic activity, decreases rapidly in the first years of life of infants with severe *CFTR* genotypes, reflecting a more severe pancreatic disease with an increased risk of developing CFRD. However, further investigations of the efficacy of both methods are needed for their introduction into clinical practice15, [41].

TREATMENT

The multidisciplinary approach in patients with CFRD is recommended by current guidelines, after all, the consequences of the disease include the domains of several health specialists, with greater attention to the teams of endocrinologists and pulmonologists. The therapy chosen is the use of insulin due to its positive effects in terms of glycemic control, weight gain, improvement in lung function, reduction in pulmonary exacerbations, and increase in patient survival42.

Current guidelines recommend the use of insulin therapy as the only one in the pharmacological treatment of CFRD, due to the limitation of randomized clinical trials and evidence regarding other drugs43. Patients with CFRD without fasting hyperglycemia can be treated with pre-meal ultrarapid insulins or with basal insulin given once daily, depending on the daily feeding pattern. For CFRD patients with fasting hyperglycemia, the combination of basal and ultrarapid insulin is used44.

In an attempt to gain more patient adherence to treatment, the use of oral medications for glycemic control was proposed, and some studies even indicated that oral medications demonstrated only a clinical advantage in this subgroup of people with CF in the first 6 months of therapy. However, it is not possible to affirm the inefficiency of oral hypoglycemic agents, after all, there are not enough studies to prove the superiority of

insulin treatment compared to the use of oral medications to control the blood glucose of patients with CFRD45.

The use of continuous subcutaneous insulin infusion in patients with DM (ICS) was considered an effective alternative compared to the insulin injection proposed by conventional treatment and, in addition, it was effective in terms of improving glycemic control, body weight control, and increasing lean body mass46. Even with this demonstration of benefits, little use of the pump is observed in patients with CFRD, most likely due to the lack of scientific evidence of effectiveness in the treatment of these patients with CFRD47. Another alternative to insulin injections is the use of inhaled insulin, which is available for prandial use, but is contraindicated in cases in which patients have pulmonary diseases, something that should be evaluated more closely in patients with cystic fibrosis, since they have a high rate of pulmonary involvement42.

In association with insulin therapy, it is important to adjust the diet of the patient with CFRD. Patients with CFRD have a height below the expected mean for age, as well as weight and BMI when compared to patients without diabetes, so it is important to pay attention to the nutrition of these patients so that they are not in a state of malnutrition44. The guidelines for nutritional goals for CF patients are the same as those used for CFRD patients, i.e., in order to maintain body weight, it is recommended that the patient ingest 110 to 200% of the expected daily caloric intake adjusted for a given age group and sex. However, in CFRD, one should always seek to maintain a good nutritional status associated with good serum glucose, always avoiding restrictive diets, which lead to marked weight loss that is not beneficial for patients with CFRD22.

The dietary recommendations for calories ingested for these patients are 1.2 to 1.5 times the expected daily intake for their age, in addition to individualized and based on weight gain and growth. With regard to carbohydrate intake, they should be monitored to achieve the expected glycemic control, prioritizing the use of artificial sweeteners due to the lower caloric content. As for protein intake, approximately 1.2 to 1.5 times the expected daily consumption for age should be consumed, with no reduction in nephropathy. There is no restriction on the type of fat. High fat intake is important for weight maintenance, so you should always try to reach the goal of 35 to 40% of total calories ingested. In warm conditions and when there is physical exercise, the diet should be hypersodium22.

CONCLUSION

Although it is not as highly prevalent as T1DM and T2DM, CFRD is associated with increased frequency of pulmonary exacerbations, greater reduction in lung function, and poorer nutritional status. The mortality rate is 6 times higher compared to CF patients with normal glucose tolerance. Thus, diagnosis and treatment are essential to reduce the morbidity and mortality of patients with this disease.

However, the diagnostic parameters currently used are based on data from adults with T2DM and there are no specific cut-off points for CFR to determine the risk of CFRD. In addition, diagnosis is challenging due to the dynamic level of plasma glucose, varying according to acute lung infections, corticosteroid therapy, and disease progression. Regarding treatment, insulin therapy and a high-calorie diet are indicated, in addition to multidisciplinary follow-up. The efficacy of oral hypoglycemic agents has not been defined, since there is insufficient evidence to prove the superiority of this treatment over insulin.

Gaps still exist in the literature with regard to diagnostic methods, the best therapy, and the prognosis of CFRD, including more frequent pulmonary exacerbations and an increased number of long-term complications. Thus, it is extremely important to deepen the scientific investigation of the subject in order to always aim to improve the quality of life of these patients.

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