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Diagnosis of cystic fibrosis-related diabetes: too early or too late?

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Cystic fibrosis-related diabetes (CFRD) is the most common comorbidity associated with cystic fibrosis (CF). In its typical form, CFRD develops insidiously as the terminal event of glucose metabolism abnormalities, which begins with early insulinopenia causing glucose intolerance and finally results in clinical symptoms such as malnutrition, steep decline in lung function, changes in lung microbiota, and decreased quality of life and life expectancy.[1] The presence of glucose in bronchial secretion raises the risk for bacterial respiratory infections with methicillin-resistant *Staphylococcus aureus* and *Pseudomonas aeruginosa*, as well as more frequent pulmonary exacerbations. Metabolic stabilization after insulin treatment initiation leads to weight gain and improvement of lung function.

The etiology of CFRD is complex and primarily related to insulin deficiency, but some other processes contribute to it, mostly chronic inflammation and peripheral insulin resistance.[2] The prevalence of CFRD, according to the latest annual reports from Brazilian and European CF Society Registries,[3,4] is 4.3% in Brazil and 22.2% in Europe, and it has been increasing as the age of CF patients increases. This prevalence varies due to different time points when screening is performed and diverse diagnostic criteria in use.

The common methods for diagnosing diabetes mellitus, such as the determination of random or fasting plasma glucose (FPG) or glycated hemoglobin (HbA_1C) levels, are not sufficiently sensitive. FPG levels are normal in half of the patients with CFRD, and HbA_1C levels have demonstrated low predictive values.[2] Nevertheless, FPG levels ≥ 126 mg/dL (≥ 7.0 mmol/L) or random plasma glucose levels ≥ 200 mg/dL (≥ 11.1 mmol/L), as well as HbA_1C ≥ 6.5% are diagnostic criteria for CFRD.[5] The widely used 2-h 75-g oral glucose tolerance test (OGTT) has been recognized by the American Diabetes Association as a standard of care procedure and is recommended to be performed annually in CF patients ≥ 10 years of age.[2,5] The results allow to distinguish among normal glucose tolerance (< 7.8 mmol/L), impaired glucose tolerance (7.8-11.1 mmol/L), and CFRD (> 11.1 mmol/L).[6] In the last decade, it has become evident that OGTT underestimates early glucose tolerance abnormalities and practically shows a weak capacity to diagnose CFRD when compared with other diagnostic methods available.[7] In addition, the test itself is inconvenient for patients, leading to low annual screening adherence. Interestingly, the current data available have failed to confirm the beneficial effects of cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapy (lumacaftor/ivacaftor) on glucose metabolism and insulin secretion over 1 year of follow-up.[8] Thus, it is of great importance to identify an alternative screening method that is practical, sensitive, and specific for diagnosing subtle glucose abnormalities that characterize the early stage of CFRD. It should independently correlate with improvements in lung function after insulin therapy initiation, regardless of eventual use of CFTR modulator therapy.

Continuous glucose monitoring (CGM) is a method that is primarily used in order to control the efficiency of insulin pump therapy in patients with diabetes mellitus type 1. It is validated for use in children, adolescents, and adults with CF as a valuable tool for early detection of glucose tolerance abnormalities. Placed subcutaneously, it measures glucose concentrations in the interstitial fluid every three to five minutes over time, mostly from three to seven days. CGM allows precise measurements of peaks and valleys of glucose concentrations, as well as the proportion of time that glucose levels are above pre-defined cutoff points.[9] Maximum CGM levels are directly correlated with the decline in lung function over time.[10,11]

In the current issue of the *Jornal Brasileiro de Pneumonogia*, Zorron et al.[12] reported the results of a longitudinal prospective study that evaluated the effectiveness of CGM to predict the onset of CFRD in 43 children and adolescents. At baseline, the CGM classification of the study participants was based on OGTT cutoff values, by analyzing the data collected from 36 h up to three days. After an average of 3 years of follow-up, OGTT was repeated, and 3 of the participants had developed CFRD over time. Interestingly, lower BMI z-scores at baseline and at follow-up were noted in the study participants who had glucose levels > 140 mg/dL on CGM. This major finding affirms the usefulness of CGM in the identification of glucose metabolism abnormalities not detected by OGTT. Finally, Zorron et al.[12] showed that none of the major variables obtained from CGM, such as peak/valley pattern, AUC, and percentage of time above cutoff values, were conclusive for CFRD diagnosis, showing no associations with the development of CFRD.

In conclusion, a better understanding of the etiology and the deleterious effects of insidious development of CFRD should lead to a more frequent use of reliable, practical, and simple tools, such as CGM, that are able to detect metabolic abnormalities that precede symptoms of CFRD. Beneficial effects of timely insulin replacement therapy initiation on the overall outcome should lead to prompt modifications of official recommendations of diagnostic criteria for CFRD.

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