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Original Article

Insulin secretion abnormalities in exocrine pancreatic sufficient cystic fibrosis patients☆

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Abstract

Background: The aim of this study is to assess insulin secretion in pediatric cystic fibrosis (CF) patients with exocrine pancreatic sufficiency.
Methods: Glucose and insulin responses during an oral glucose tolerance test (OGTT) were measured in 146 CF patients. Patients were divided into exocrine sufficient (CF-PS) and insufficient (CF-PI) groups based on pancreatic enzyme usage and fecal elastase. A reference group included healthy, non-diabetic subjects.
Results: All CF groups showed reduced insulin secretion as measured by insulinogenic index. The CF-PS patients had normal glucose tolerance. There was a direct correlation between BMI *z*-score and insulin area under the curve.
Conclusion: Patients with CF have reduced insulin secretion during an OGTT regardless of exocrine pancreatic status. The abnormal insulin secretion in all CF patients may predispose them for glucose intolerance, particularly when challenged by inflammation, infection, or nutritional deficiency. In addition, the diminished insulin secretion may contribute to increased catabolism. Lastly, the CF-related diabetes (CFRD) screening guidelines should be followed by all CF patients regardless of pancreatic status.

Keywords: Insulin deficiency; Pancreatic cystic fibrosis; Hyperglycemia; Anabolism; Insulin-secreting cells

1. Introduction

Pulmonary disease is the major cause of morbidity and mortality in patients with CF. However, pancreatic disease also significantly contributes to poor outcomes in patients with CF. The CF transmembrane regulator (CFTR) protein is expressed in the intralobular and intercalated duct epithelia of the exocrine pancreas [1]. In the normal pancreas, chloride/bicarbonate exchangers and the CFTR protein create a bicarbonate-rich pancreatic secretion. This secretion aids in the digestion of protein and fat

Abbreviations: AGM, Abnormal glucose metabolism; ANOVA, Analysis of variance; ANCOVA, Analysis of covariance; AUC, Area under the curve; BMI, Body mass index; CCHMC, Cincinnati Children's Medical Hospital Center; CF, Cystic fibrosis; CFRD, Cystic fibrosis-related diabetes; CFTR, Cystic fibrosis transmembrane conductance regulator; DM, Diabetes mellitus; FEV1, Forced expiratory volume in 1 s; GLU, Glucose; HgbA1C, Hemoglobin A1C; IAPP, Islet amyloid polypeptide; IFG, Impaired fasting glucose; IGT, Impaired glucose tolerance with normal fasting glucose; INS, Insulin; LSM, Least-square means; NGT, Normal glucose tolerance; OGTT, Oral glucose tolerance test; PI, Exocrine pancreatic insufficient; PS, Exocrine pancreatic sufficient; REF, Reference group

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in the small intestine. In patients with CF, the impairment of epithelial chloride secretion caused by a disruption in CFTR results in the precipitation of proenzymes and the obstruction of pancreaticobiliary ducts [1]. Pancreaticobiliary duct obstruction leads to inflammation, necrosis, and fibrosis of the exocrine pancreas resulting in exocrine pancreatic insufficiency. This process begins *in utero* and approximately 85% of CF patients have exocrine pancreatic insufficiency (CF-PI) with associated malabsorption within the first year of life [2].

The process of pancreaticobiliary duct obstruction places patients with CF at risk for developing endocrine pancreatic dysfunction and eventually CF-related diabetes (CFRD). The most common view of the etiology of CFRD is that inflammation, necrosis, and fibrosis associated with pancreatic duct obstruction cause fibrosis and fatty infiltration of the islets of Langerhans [3–5] leading to secondary β-cell dysfunction, reduced islet mass, and insulin deficiency. However, several groups have implicated decreased insulin sensitivity related to pulmonary disease and systemic inflammation in the pathogenesis of CFRD [6,7]. At present there is a general agreement that insulin deficiency and insulin resistance contribute to hyperglycemia, and ultimately CFRD, in the CF-PI population, but this model is not well defined [8].

Previous reports suggest that 15% of patients with CF who are exocrine pancreatic sufficient (CF-PS) are not at risk for secondary β-cell dysfunction and CFRD [9]. These reports are based on the concept that if pancreatic ductal plugging and fibrosis have not progressed sufficiently to cause exocrine insufficiency, then β-cells will remain functional. Recent reports, however, challenge this concept, suggesting a primary mechanism of β-cell injury and insulin deficiency [10–12]. Furthermore, in our own clinical experience, oral glucose tolerance testing (OGTT) in patients with CF-PS suggests abnormalities in insulin secretion. In view of our clinical observations and recent reports of primary β-cell dysfunction, we hypothesized that all CF patients regardless of exocrine pancreatic status would have insulin deficiency secondary to dysfunctional β-cell mass, even if they did not have prediabetes or CFRD. To test this hypothesis, we compared OGTT results from pediatric CF patients subgrouped by exocrine pancreatic status to OGTT results from lean, healthy patients.

2. Methods

2.1. Patient population

The study population included all CF patients followed at Cincinnati Children's Medical Hospital Center (CCHMC) who were 5 years of age and older and who underwent at least one OGTT between January 1, 2004 and June 30, 2009. These patients had undergone OGTT as part of the annual screening assessment and were considered baseline in health. We identified these patients using a clinical database established in 1998 that contains clinical and biochemical data on patients with CF who were followed by the pulmonary division at CCHMC. Nine percent of the patients included in this study population were also included in work previously published by the authors [13].

We analyzed the weight, height, and spirometry values of these patients, as recorded during clinic appointments closest to the time of the OGTT testing. The mean number of days between recording height, weight, and spirometry data and the OGTT data was 17. Additionally, all study subjects had measures of hemoglobin A1C at the time of the OGTT. In patients who had undergone OGTT testing more than once, the data from the most recent OGTT were used for this study.

A reference group included 12 lean subjects enrolled in a previous study of glucose metabolism [14]. These subjects were non-diabetic, free of chronic medical conditions, not taking medication, and healthy at the time of evaluation. These patients were similar to other previously published control groups used for measures of beta-cell function [15].

2.2. Nutritional status

Weight and height measurements were performed as part of a standard clinic visit. Body mass index (BMI) was calculated as weight (kg) / height (m) ^{2}. *Z*-scores for BMI were derived based on sex- and age-specific BMI charts developed by the Centers for Disease Control and Prevention [16].

2.3. Spirometry

We performed spirometry in the pulmonary function laboratory according to the American Thoracic Guidelines [17] and recorded the forced expiratory volume in 1 s (FEV1). We then calculated percent predicted FEV1 (FEV1%) using Wang *et al.* [18] for study subjects ages 5–16 years and Hankinson *et al.* [19] for subjects older than age 16.

2.4. Fecal elastase analysis

Patients not demonstrating symptoms of malabsorption underwent fecal elastase testing. Quest Diagnostics® laboratories (San Juan Capistrano, CA) performed the fecal elastase measurements using a quantitative enzyme linked immunosorbent assay for measuring concentrations of elastase-1 in feces. We defined CF-PS patients as those not taking pancreatic enzyme supplements and having a fecal elastase value of ≥ 246. Patients who did not meet these criteria were considered CF-PI.

2.5. Oral glucose tolerance testing

Following an overnight fast, patients ingested an oral glucose solution containing 1.75 mg/kg of glucose (maximum of 75 g). Venous blood samples were obtained through an intravenous catheter before glucose ingestion and 30, 60, and 120 min after glucose ingestion. Samples were placed on ice and centrifuged within 1 h. Plasma was then collected and stored for measurement of glucose and insulin.

We categorized patients as having normal or abnormal glucose metabolism using criteria recommended by the American Diabetes Association (ADA) [20], and divided our patients into normal glucose tolerance (CF-NGT) and abnormal glucose metabolism (CF-AGM) as we have done previously