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Original Article

Variation of glucose tolerance in adult patients with cystic fibrosis: What is the potential contribution of insulin sensitivity?

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Abstract

Background: Reduced insulin secretion is a key factor to explain high prevalence of glucose intolerance in patients with cystic fibrosis (CF). However, the role of insulin sensitivity remains unclear. The aim of this study is to investigate the association of insulin secretion and sensitivity with the evolution of glucose tolerance.
Methods: A total of 152 patients without known diabetes from the Montreal CF cohort underwent two 2-h oral glucose tolerance tests (OGTT) at baseline and again after 21.2 ± 5.5 months. Pulmonary function and anthropometric measurements were also collected at each visit. At both visits, based on their OGTT results, patients were categorized in glucose tolerance groups (normal glucose tolerance, impaired glucose tolerance or CF-related diabetes) and stratified in 3 groups according to the variation of their glucose tolerance: stable, improved or deteriorated.
Results: At baseline, patients in the deteriorated group had a better sensitivity to insulin than those in the improved group ($P = 0.029$). At follow-up glucose tolerance remained stable in 55.3%, improved in 14.5% and deteriorated in 30.3% of patients. During follow-up, insulin secretion remained stable in all 3 groups. While insulin sensitivity remained stable in patients without changes in glucose tolerance it worsened in patients who deteriorated glucose tolerance ($P < 0.001$) and improved in patients who improved their glucose tolerance ($P = 0.003$).
Conclusion: In a context of significantly reduced insulin secretion, variations of insulin sensitivity are associated with variations of glucose tolerance in adult patients with CF.

Keywords: Cystic fibrosis; Adult; CFRD; Insulin sensitivity; Oral glucose tolerance test

1. Introduction

Cystic fibrosis (CF) is the most common autosomal genetic disease in Caucasians. The disease leads to an accumulation of thick secretions in the lungs, pancreas and other organs [1]. Life expectancy of CF patients has increased in the past decades due to improved clinical management of the disease. Consequently, other long-term complications have emerged including CF-related diabetes (CFRD) [2]. CFRD prevalence increases with age [2] and is diagnosed in approximately 40% of CF adult patients, while another 35% have impaired glucose tolerance

Abbreviations: ANOVA, analyses of variance; AUC, area under the curve; CF, cystic fibrosis; CFRD, cystic fibrosis-related diabetes; FEV_1, forced expiratory volume in 1 s; HbA1c, glycated hemoglobin; IGT, impaired glucose tolerance; BMI, body mass index; MCFC, Montreal Cystic Fibrosis Cohort; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test

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(IGT) [3,4]. CFRD is preceded by a long phase of glucose intolerance. During this period, patients that develop CFRD have a more pronounced decline in nutritional and pulmonary status compared to patients that do not develop CFRD [3,5,6]. The occurrence of CFRD is associated with a significantly worse prognosis including an increased risk of mortality [2,7].

CFRD is characterized by a severe but not complete insulin secretion deficiency [8]. Reduced insulin secretion is in large part secondary to pancreatic fibrosis [5]. The role of additional factors contributing to glucose intolerance is suggested by the fact that despite low insulin secretion in almost all adult patients with CF, some patients do not develop dysglycemia [4]. In addition, unexplained high variability in oral glucose tolerance has been reported in CF patients [9]. The contribution of insulin sensitivity to CFRD physiopathology is controversial [10–14]. In CF populations, insulin sensitivity has been reported to be preserved [10,11], improved [12] or reduced [13,14]. Multiple factors including pulmonary exacerbation, variation of nutritional intake and physical activity, some treatments and chronic low-grade inflammation could impact insulin sensitivity in patients with CF [15]. In a context of significantly reduced insulin secretion, such variation in insulin sensitivity could have a significant impact on glucose tolerance [16].

The aim of this observational study was thus to investigate the association of insulin secretion and sensitivity with the evolution of glucose tolerance in adults with CF with different glucose tolerances. We hypothesized that in the context of CF-associated reduced insulin secretion, changes in insulin sensitivity will be associated with varying glucose tolerance over time.

2. Methods

2.1. Subjects

The Montreal Cystic Fibrosis Cohort (MCFC) was established in 2004 as part of an ongoing systematic screening program for glucose abnormalities, including CFRD. The main objective of this prospective observational cohort is to study mechanisms leading to glucose intolerance as well as the association of prediabetic states with CF outcomes.

Inclusion and exclusion criteria of the MCFC were previously described [17]. In brief, the exclusion criteria were previous diagnosis of diabetes, pregnancy, CF exacerbations in the past month or conditions that could interfere with glucose metabolism such as intravenous antibiotic, steroids (oral or intravenous) or growth hormone treatment.

Patients (≥18 years) for which an OGTT was available at baseline and again after 18 to 24 months were included in the analysis (n = 152; 74 women and 78 men). Glucose tolerance status (NGT: normal glucose tolerant; IGT: impaired glucose tolerance and newly diagnosed CFRD) was examined at baseline and at follow-up. All patients included at baseline had either a NGT or IGT status. Patients diagnosed with CFRD at baseline were excluded from the follow-up and referred to an endocrinologist after confirmation of CFRD diagnosis by a second OGTT.

2.2. Anthropometric and pulmonary data

On the day of the OGTT, pulmonary function was measured by spirometry using predicted forced expiratory volume in 1 s (%FEV_1: Medgraphic) as the main variable. Exocrine pancreatic insufficiency was defined by current enzyme supplementation. Genotype status was extracted from the medical files. Body weight and standing height were measured using an electronic scale (Tanita Corporation Arlington heights, IL, USA) and a wall stadiometer, respectively. Body mass index (BMI) was calculated using weight in kilograms divided by height in meter (kg/m^2).

2.3. Genotype classification

Genotype was categorized into five established classes reflecting CFTR expression and function [18]. Patients with two mutations of the same class were assigned that class. Heterozygotes for F508del were assigned the class of the non-F508del allele. Mutations of the "other" category are those who have not yet been clearly established for the patient or which include two different mutation classes for the same patient (e.g. I–IV). Patients with mutant alleles of classes I, II and III were categorized as having severe genotype, while patients with mutations of classes IV, V or other were categorized as having mild genotype [19,20].

2.4. Oral glucose tolerance test and biochemical dosages

At each visit, all subjects underwent a 2-h OGTT. After an overnight fast, they ingested in less than 5 min a glucose solution of 1.75 g/kg of body weight to a maximum of 75 g according to the Canadian Diabetes Association guidelines [21]. Blood samples were taken at 0, 30, 60, 90 and 120 min to measure plasma glucose and insulin levels. Plasma glucose level was measured immediately in duplicate with a Glucose Analyzer (YSI 2300 STAT plus, glucose and lactate analyzing; YSI Inc.). Insulin samples were frozen at −80 °C and then measured in duplicate using human insulin RIA (Linco Research, Inc.). Glycated hemoglobin (HbA1c) was measured by routine chemistry (Immunotubidimeter, ADVIAI650; Bayer Health Care diagnosis).

2.5. Patient categorization

Based on their 2-hour glucose value during the OGTT, subjects were categorized as having normal glucose tolerance (NGT; <7.8 mmol/L), impaired glucose tolerance (IGT; ≥7.8 mmol/L and <11.1 mmol/L) or de novo CFRD (≥11.1 mmol/L).

Using these classical glucose categories patients were then stratified in 3 groups according to the variation of their glucose tolerance between baseline and follow-up:

- *Stable glucose tolerance* for patients who maintained a similar glucose tolerance (NGT or IGT) at both tests.
- *Improved glucose tolerance* for patients who reverted from IGT at baseline to NGT at follow-up.