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Original Article

Disposition index identifies defective beta-cell function in cystic fibrosis subjects with normal glucose tolerance☆

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Abstract

Background: In non-cystic fibrosis (CF) subjects, the disposition index (DI) is a strong predictor of the development of type 2 diabetes. CF subjects are at high risk of diabetes. We hypothesized that DI would be reduced in CF patients with normal glucose tolerance (NGT), indicating β-cell dysfunction, and DI would worsen with progression from CF with NGT to CF-related diabetes (CFRD).
Methods: This was a cross-sectional study in 39 CF patients and 21 healthy controls (Con) who underwent oral glucose tolerance test (OGTT). Insulin sensitivity was estimated as (1/fasting insulin) and insulin secretion as (Δinsulin 0–30 min/Δglucose 0–30 min). DI was calculated as (insulin sensitivity) × (insulin secretion).
Results: Among CF subjects, 14 had NGT, 20 had prediabetes and 5 had CFRD. Among the controls, 14 had NGT and 7 had prediabetes. DI was significantly lower in CF-NGT compared to Con-NGT ($p = 0.0035$). DI was also lower in CFRD compared to CF-NGT ($p = 0.025$). There were no significant relationships in the CF groups between DI and age, BMI, percent body fat or FEV1.
Conclusion: β-Cell function as measured by DI is reduced in CF patients compared to non-CF controls—even in CF-NGT—and is decreased further in CF patients with diabetes. If DI proves to be a predictor of the development of CFRD in larger studies, then it could be used to identify CF patients who are at particularly high risk, allowing early interventions aimed to delay or prevent CFRD.

Keywords: Cystic fibrosis; Diabetes; OGTT; Beta-cell function

1. Introduction

Cystic fibrosis-related diabetes (CFRD) is one of the most common comorbidities in patients with cystic fibrosis (CF). It occurs in 2% of young children, 19% of adolescents and 40–50% of adults with CF [1]. CFRD is associated with increased morbidity and mortality, worse nutritional status and higher rates of respiratory exacerbations requiring hospitalization—which contribute to the accelerated decline in lung function in these patients [2–5]. The overall mortality rate per 100 person-years is 3.5 ± 0.6 in patients with CFRD, compared to 1.0 ± 0.2 per 100 person-years for CF patients without CFRD [1]. Lang *et al.* have shown that in patients with CF, prediabetes starts 4 to 6 years before overt CFRD presents. CF patients with prediabetes exhibit a lower BMI and more rapid decline in lung function compared to CF patients with normal glucose tolerance (NGT) [6]. CFRD is

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usually treated with insulin, and early treatment with insulin is thought to decrease morbidity and mortality [7].

It is recommended that screening for CFRD should begin by the age of 10 years, using oral glucose tolerance tests (OGTTs) [8]. However, some CF patients with normal fasting and 2-h glucose levels have elevated serum glucose levels and higher glucose readings on continuous glucose monitoring in the middle of the OGTT [9], and those patients with elevation in 1-h glucose levels are thought to be at high risk of worse pulmonary disease [10]. Such observations highlight the need for a measurement that can predict the development of prediabetes and diabetes in CF subjects when their OGTTs are still normal since early treatment might help to delay or prevent the development of morbidities.

We sought to examine the disposition index (DI), a measure of β-cell function adjusted for insulin sensitivity, in a cohort of CF patients and healthy controls. In non-CF subjects, there is a hyperbolic relationship between early insulin secretion and insulin action [11]. On the basis of this hyperbolic relationship, the product of these two variables can be calculated to yield the DI, which can be understood as the ability of β-cells to compensate for alterations in insulin sensitivity. Utzschneider *et al.* [12] have shown that the baseline DI in non-CF subjects who later developed type 2 diabetes was significantly lower than that in subjects who remained without diabetes.

Based on this information, we first determined if the relationship between insulin sensitivity and insulin secretion followed a hyperbolic pattern, and then we estimated the DI in our CF subjects and healthy controls. We then tested two hypotheses: (i) the DI will be reduced in CF patients with NGT, indicating β-cell dysfunction despite normal glucose values, and (ii) the DI will be lower in CFRD and CF prediabetes patients compared to CF patients with NGT, indicating worsening of DI with progression to diabetes. We also examined the utility of the 30-min OGTT glucose level—as a potential proxy for DI—to identify the development of β-cell dysfunction in patients with CF.

2. Patients and methods

Thirty-nine CF subjects, 16 years and older, who were clinically stable with no pulmonary exacerbations within 6 weeks of study and who had no current or recent oral corticosteroid use, were recruited from the Emory CF Clinic after providing informed consent. Healthy controls consisted of 21 subjects, 16 years and older, with no chronic illness requiring prescription medications, no acute illness within 3 weeks of study and no known history of diabetes or an abnormal glucose tolerance test. The study was approved by the Emory University Institutional Review Board.

All subjects fasted starting the evening before the test at 10:00 p.m. with nothing to eat or drink except for water. Subjects were admitted to the Atlanta Clinical and Translational Science Institute (ACTSI) research unit in the morning. Height and weight were measured, and percent body fat was assessed with air displacement plethysmography (BOD POD® Body Composition System, COSMED USA, Inc.). Spirometry was performed in CF subjects using the American Thoracic Society standards and percent predicted forced expired volume in 1 second (FEV1) was calculated in order to determine if there was any correlation between DI and lung function. Then an OGTT was performed with administration of glucose 1.75 mg/kg body weight, to a maximum of 75 grams. Blood was drawn at 0, 30 min and 2 h for measurement of glucose and insulin.

Using the 2003 American Diabetes Association criteria [13], subjects were categorized as having normal glucose tolerance (fasting plasma glucose [FPG] < 5.56 mmol/l and 2-h plasma glucose < 7.78 mmol/l), prediabetes (impaired fasting glucose [IFG] with FPG 5.56–6.99 mmol/l, and/or impaired glucose tolerance [IGT] with 2-h plasma glucose 7.78–11.10 mmol/l) or diabetes (FPG >7.0 mmol/l and/or 2-h plasma glucose > 11.11 mmol/l).

Glucose and insulin assays were performed by Cardiovascular Specialty Laboratories in Atlanta, Georgia. Insulin was measured using Sekisui Diagnostics immunoturbidimetric assay.

Insulin sensitivity was calculated as 1/fasting insulin. Insulin secretion was calculated as the ratio of the change in insulin to the change in glucose from 0 to 30 min ($\Delta I0–30/\Delta G0–30$). Disposition index was calculated as 1/fasting insulin multiplied by ($\Delta I\ 0–30/\Delta G\ 0–30$).

To determine whether there was a hyperbolic relationship between insulin sensitivity and insulin secretion (insulin sensitivity × insulin secretion = constant) within each group, we used linear regression analysis to estimate ln(insulin sensitivity) as a linear function of ln(insulin secretion). A hyperbolic relationship was presumed if the 95% CI of the slope included −1.

The Kruskal–Wallis test was used to compare continuous variables and the Fisher's exact test was performed to compare categorical variables among the CF and control groups, namely, Con-NGT, Con-prediabetes, CF-NGT, CF-prediabetes and CFRD. Spearman correlation coefficients were calculated between DI and other continuous variables. The Wilcoxon rank sum test was used to determine whether DI was different between males and females and between pairs of patient groups. Discrimination of glucose tolerance status by the OGTT 30 min glucose level compared with DI was evaluated by receiver operating characteristic (ROC) analyses, using identification of diabetes and normal glucose tolerance as the end points in separate analyses. Linear regression was also used to investigate the relationship between DI and other variables after adjusting for potential confounders. A p-value of <0.05 was considered statistically significant. Statistical analysis was performed using R software, version 2.15.2 (R foundation for statistical computing, Vienna, Austria).

3. Results

The subjects were categorized based on their OGTT results on the day of the study (Table 1). Among the CF subjects, 14 had NGT, 20 had prediabetes and 5 had CFRD. Among the controls, 14 subjects had NGT and 7 subjects had previously unrecognized prediabetes. There was no statistical difference between the 5 groups in regard to gender, BMI or % fat. There was a difference in age, with CF-prediabetes and CFRD subjects being significantly younger than Con-NGT. There was also a difference in the 30-min glucose values, with all of the CF groups having significantly higher values than Con-NGT.