

Original Article



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

L. Merjaneh <sup>a,\*</sup>, Q. He <sup>b</sup>, Q. Long <sup>b</sup>, L.S. Phillips <sup>c,d</sup>, A.A. Stecenko <sup>e</sup>

<sup>a</sup> Division of Endocrinology and Diabetes, Department of Pediatrics, Emory University School of Medicine, Atlanta, GA, USA

<sup>b</sup> Department of Biostatistics and Bioinformatics, Rollins School of Public Health, Emory University, Atlanta, GA, USA

<sup>c</sup> Atlanta VA Medical Center, Decatur, GA, USA

<sup>d</sup> Division of Endocrinology and Diabetes, Department of Medicine, Emory University School of Medicine, Atlanta, GA, USA

<sup>e</sup> Division of Pulmonary, Allergy/Immunology, Cystic Fibrosis, and Sleep, Department of Pediatrics, Emory University School of Medicine, Atlanta, GA, USA

Received 19 March 2014; received in revised form 7 June 2014; accepted 11 June 2014

Available online 4 July 2014

## 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  $\beta$ -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  $(1/\text{fasting insulin})$  and insulin secretion as  $(\Delta\text{insulin } 0\text{--}30 \text{ min}/\Delta\text{glucose } 0\text{--}30 \text{ min})$ . DI was calculated as  $(\text{insulin sensitivity}) \times (\text{insulin secretion})$ .

**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:**  $\beta$ -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.

© 2014 European Cystic Fibrosis Society. Published by Elsevier B.V. All rights reserved.

**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  $3.5 \pm 0.6$  in patients with CFRD, compared to  $1.0 \pm 0.2$  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

☆ Part of this work was presented in the 27th annual North American Cystic Fibrosis conference in Salt Lake city, UT, in October 2013.

\* Corresponding author at: Emory University, Division of Pediatric Endocrinology, 2015 Upper Gate Dr NE, Atlanta, GA 30322, USA. Tel.: +1 404 785 2000; fax: +1 404 785 9022.

E-mail addresses: [linamerjane@msn.com](mailto:linamerjane@msn.com) (L. Merjaneh), [Qing.he@emory.edu](mailto:Qing.he@emory.edu) (Q. He), [qlong@emory.edu](mailto:qlong@emory.edu) (Q. Long), [medlsp@emory.edu](mailto:medlsp@emory.edu) (L.S. Phillips), [astecen@emory.edu](mailto:astecen@emory.edu) (A.A. Stecenko).

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  $\beta$ -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  $\beta$ -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  $\beta$ -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  $\beta$ -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  $1/\text{fasting insulin}$ . Insulin secretion was calculated as the ratio of the change in insulin to the change in glucose from 0 to 30 min ( $\Delta I_{0-30}/\Delta G_{0-30}$ ). Disposition index was calculated as  $1/\text{fasting insulin}$  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  $\times$  insulin secretion = constant) within each group, we used linear regression analysis to estimate  $\ln(\text{insulin sensitivity})$  as a linear function of  $\ln(\text{insulin secretion})$ . 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.

Table 1  
Characteristics of CF subjects and controls by glucose tolerance category.

Subjects	Con-NGT <i>n</i> = 14	Con-prediabetes <i>n</i> = 7	CF-NGT <i>n</i> = 14	CF-prediabetes <i>n</i> = 20	CFRD <i>n</i> = 5	<i>p</i> -value <sup>b</sup>
Age (years)	31.2 ± 7.9	30 ± 10	26.8 ± 7.88	22.8 ± 6.6	22.6 ± 6.61	0.018 <sup>c</sup>
Gender (women/men)	5/9	4/3	8/6	7/13	3/2	0.56 <sup>d</sup>
BMI (kg/m <sup>2</sup> )	24 ± 2.9	24.9 ± 5.3	22.8 ± 3.18	22.4 ± 3.3	22.1 ± 3.1	0.39
Fat %	22.6 ± 7.2	28.3 ± 7.3	26.7 ± 4.85	28.1 ± 5.7	26.7 ± 12.1	0.49
FEV1%			82.9 ± 22	85.6 ± 20.3	86.6 ± 15	0.39
Fasting PG (mmol/l) <sup>a</sup>	4.9 (0.8)	5.5 (0.14)	4.87 (0.82)	5.4 (1.07)	5.3 (1)	
30 min PG (mmol/l) <sup>a</sup>	7.36 (1.48)	8.25 (0.64)	8.36 (2.46)	8.6 (1.88)	9.5 (1.42)	0.03 <sup>c</sup>
2-h PG (mmol/l) <sup>a</sup>	5.66 (1.2)	7.78 (0.19)	5.76 (1.46)	8.4 (1.74)	13.2 (1.85)	
Fasting insulin (pmol/l) <sup>a</sup>	27.78 (3.1)	65.28 (29.8)	27.78(17.28)	38.2 (14.4)	27.78(0.69)	

PG: plasma glucose. Values are presented as mean ± SD unless otherwise specified.

<sup>a</sup> Values in median (interquartile range).

<sup>b</sup> Kruskal–Wallis test.

<sup>c</sup> Con-NGT vs. CF-prediabetes (*p* = 0.003). Con-NGT vs. CFRD (*p* = 0.025).

<sup>d</sup> Fisher exact test.

<sup>e</sup> Con-NGT vs. CF-NGT (*p* = 0.03), Con-NGT vs. CF-prediabetes (*p* = 0.004), Con-NGT vs. CFRD (*p* = 0.02).

The 95% CI for the regression slopes included  $-1$  for the relationship between  $\ln(1/\text{fasting insulin})$  and  $\ln(\Delta I0-30/\Delta G0-30)$  in all groups except the CFRD group (Fig. 1), suggesting a hyperbolic relationship between insulin sensitivity and insulin secretion in Con-NGT, Con-prediabetes, CF-NGT, and CF-prediabetes.

Based on this hyperbolic relationship, the composite measure of insulin sensitivity and insulin secretion was calculated to yield the DI. The insulin sensitivity, insulin secretion and DI results are shown in Table 2. Based on the Kruskal–Wallis test, there were significant differences among the 5 groups in insulin secretion (*p* < 0.0001) and in DI (*p* < 0.0001) but no significant differences

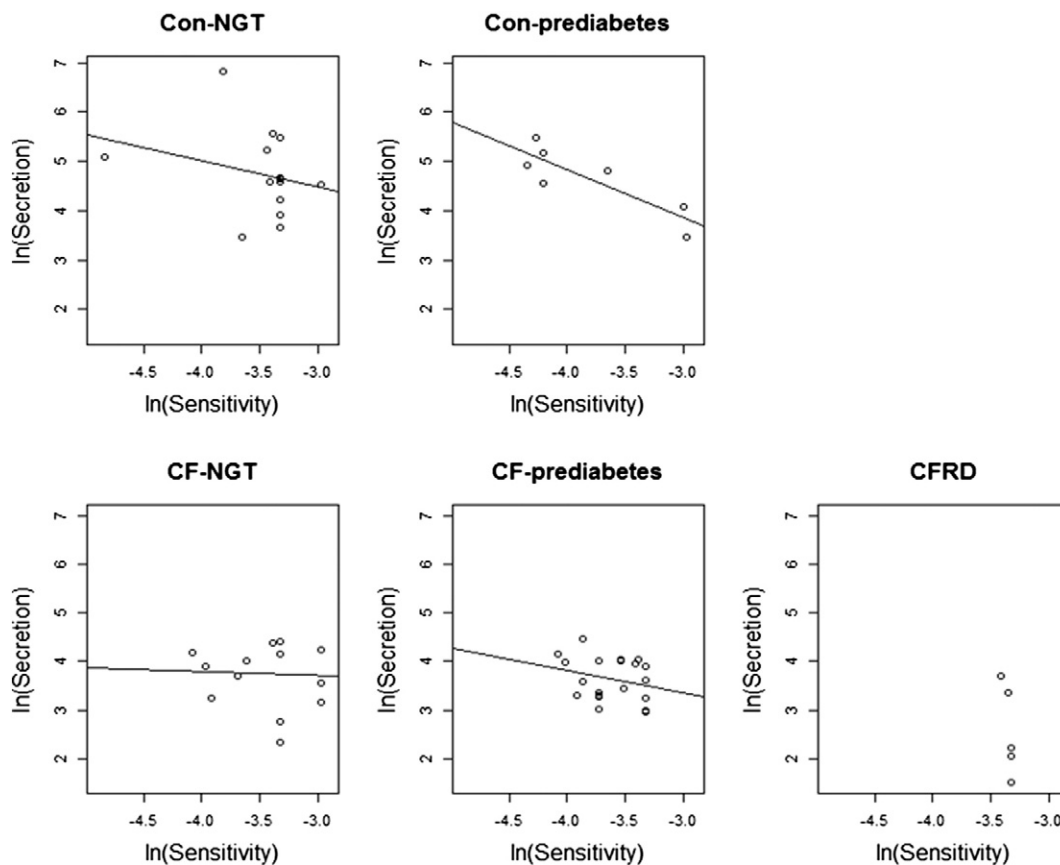


Fig. 1. The computed slopes for  $\ln(\text{Insulin secretion})$  versus  $\ln(\text{Insulin sensitivity})$  in the five groups showing that the slope includes  $-1$  for all groups except CFRD. The slope and confidence interval (CI) for each of the groups is as follows. Con-NGT: slope  $-0.5364$  with CI  $[-1.6383, 0.5655]$ ; Con-prediabetes: slope  $-0.9698$  with CI  $[-1.4689, -0.4707]$ ; CF-NGT: slope  $-0.0824$  with CI  $[-1.0339, 0.8690]$ ; CF-prediabetes: slope  $-0.4622$  with CI  $[-1.2518, 0.3273]$ ; CFRD: slope  $-21.2791$  with CI  $[-35.0945, -7.4637]$ .

Table 2  
Insulin sensitivity, insulin secretion and disposition index in all groups.

	Con-NGT <i>n</i> = 14	Con-prediabetes <i>n</i> = 7	CF-NGT <i>n</i> = 14	CF-prediabetes <i>n</i> = 20	CFRD <i>n</i> = 5	<i>p</i> -value for all groups <sup>a</sup>	<i>p</i> -value for CF only <sup>a</sup>
Insulin sensitivity ( $\text{pM}^{-1}$ )	0.0327 (0.0095)	0.0263 (0.0171)	0.0350 (0.0124)	0.0276 (0.0067)	0.0352 (0.0013)	0.0817	0.064
Insulin secretion ( $\text{pmol}/\text{mmol}$ )	174.60 (222.29)	122.74 (69.36)	49.22 (24.11)	41.43 (18.16)	18.17 (15.79)	<0.0001	0.038
Disposition index ( $\text{mM}^{-1}$ )	5.00 (4.94)	2.41 (0.79)	1.72 (1.10)	1.11 (0.49)	0.63 (0.53)	<0.0001	0.053

Values are presented as mean (SD).

<sup>a</sup> Kruskal–Wallis test.

in insulin sensitivity. Fig. 2 shows the disposition index in all 5 groups. Based on the Wilcoxon rank sum test, there were significant differences in DI between Con-NGT and each of the CF groups, between Con-prediabetes and each of CF-prediabetes and CFRD, and between CF-NGT and CFRD (Table 3a). In regard to the 30-min glucose levels, there were only significant differences between the Con-NGT and each of the CF groups (Table 3b).

There were no significant relationships in the CF groups between DI and age, BMI, percent body fat or FEV1. There was a significant negative correlation between DI and the 30-min glucose levels in each of Con-NGT, CF-NGT and CFRD separately and in the 3 CF groups and in all five groups combined (Supplementary table 1). Metabolic discrimination by DI vs. the 30-min glucose level was compared by ROC analysis. To identify NGT, the area under the ROC curve (AUC) for DI was 0.729, slightly but not significantly greater than the AUC for the 30-min glucose, 0.681 ( $p = 0.44$ ). To identify diabetes, the ROC AUC for DI was 0.858, again slightly but not significantly greater than the ROC AUC for 30-min glucose, 0.652 ( $p = 0.06$ ) (Fig. 3).

#### 4. Discussion

The development of improved measures of glucoregulatory metabolism is important for the care of patients with CF because prediabetes and diabetes have a major impact on the course of the disease, and conventional assessments (HbA1c, fasting and OGTT 2-h glucose levels) are insensitive to early dysfunction. Our study shows that compared to non-CF controls with normal

glucose tolerance, DI is reduced in patients with CF even when their glucose tolerance is normal, and it is further decreased in those with diabetes. Our findings indicate that measurement of DI may be clinically useful in patients with CF to detect subtle defects in  $\beta$ -cell function, and identify progression of the disease.

A hyperbolic relationship between insulin sensitivity and secretion—critical to the rigorous use of DI—has not been demonstrated previously in patients with CF. After initial studies with intravenous approaches established the potential utility of DI assessments in non-CF subjects [14], Kahn *et al.* showed that the nature of the relationship between insulin sensitivity and secretion is consistent with a feedback loop control system [11]. More recently, Utzschneider *et al.* have shown that the relationship also applies to more physiologic, oral glucose administration and is present not only in subjects with NGT but also in subjects with prediabetes and diabetes [12], and that DI measured using an OGTT is predictive of the future development of diabetes. Our demonstration of the hyperbolic relationship in our non-CF subjects is consistent with their results, and we have established that this relationship holds in CF patients as well.

Furthermore, we found that CF subjects demonstrated early hyperglycemia during the OGTT, as shown by their 30-min glucose levels that were significantly higher than values in non-CF controls; 30-min glucose levels were even elevated in CF patients with NGT. Previous studies found that OGTTs and HbA1c measurements may fail to detect early glucose abnormalities in CF subjects. Dobson *et al.* reported that glycemic status measured by both the combined response at 30, 60 and 90 min and continuous glucose monitoring (CGM) during an OGTT is higher in CF subjects than in controls who have similar HbA1c, fasting and 2-h glucose values [9]. Moreau *et al.* reported that in CF subjects,

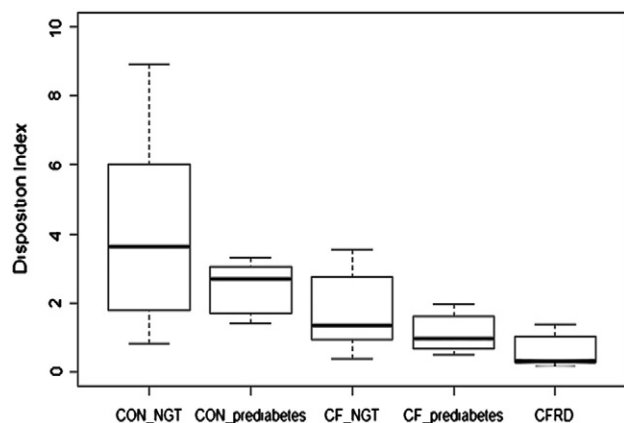


Fig. 2. The disposition index in controls and CF subjects according to their glucose tolerance category.

Table 3  
The *p*-values using the Wilcoxon rank sum test for testing differences in DI (a) and the 30-min glucose levels (b) between pairs of groups.

	Con-prediabetes	CF-NGT	CF-prediabetes	CFRD
(a)				
Con-NGT	0.1718	0.0035*	0.0001*	0.0012*
Con-prediabetes		0.1490	0.0021*	0.0025*
CF-NGT			0.1894	0.0258*
CF-prediabetes				0.0960
(b)				
Con-NGT	0.0931	0.0029*	0.0048*	0.0233*
Con-prediabetes		0.971	0.455	0.53
CF-NGT			0.391	0.443
CF-prediabetes				0.8384

\* *p*-value <0.05.



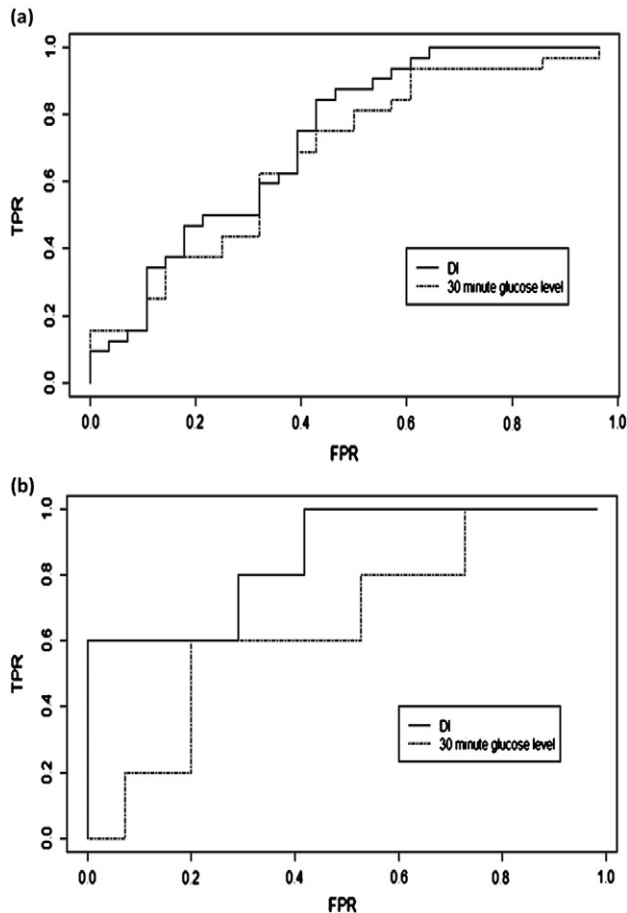


Fig. 3. ROC curves for DI and 30-min glucose levels on determination of normal glucose tolerance (a) and determination of diabetes (b). TPR: true-positive rate; FPR: false-positive rate.

CGM revealed peaks of glucose values above 11.11 mmol/l at least once after a meal in 36% of CF patients with NGT, 52% of patients with IGT and in all patients with CFRD [15]. In addition, higher 1-h OGTT glucose levels in CF patients were found to be associated with an increased risk for future CFRD [16] and correlated with worse pulmonary function [10]. Similarly, in non-CF subjects, the 1-h glucose level during the OGTT was shown to be a strong predictor of future risk for type 2 diabetes [17]. Although 30-min glucose levels have not previously been studied systematically in patients with CF, such early postprandial/postchallenge hyperglycemia might reflect underlying defects in pancreatic beta-cell function, and the findings reviewed above constitute evidence that it might be a risk factor for the development of CFRD and deterioration in lung function.

The DI was significantly lower in all the CF groups—even in CF patients with NGT—compared to non-CF controls. There was no significant difference in insulin sensitivity between these groups, which indicates that the defect is mainly in the inability of  $\beta$ -cells in CF patients to secrete insulin. Although there have been no previous studies of DI in CF patients, our findings are consistent with earlier work showing that insulin secretion is impaired in CF patients even when they have NGT, while their insulin sensitivity is not affected [18–20]. We found no correlation between DI and BMI, % fat or lung function in

CF subjects. Our CF subjects were also not different from controls in regard to gender, BMI or % fat, and their mean lung function was within the normal range. Our sample accordingly represents stable, well-nourished CF patients in good clinical condition. The low DI in these patients indicates that the insulin secretory defect is likely primary in the pathogenesis of CFRD, and that it declines well before deterioration in clinical status. It also implies that the defect might be unmasked if insulin resistance increases, possibly limiting glycemic compensation in times of illness, infection or during puberty, and resulting in hyperglycemia.

DI, or possibly 30-min OGTT glucose levels, could potentially be used to identify the subset of CF subjects who are at particularly high risk for developing diabetes and perhaps allow such patients to be targeted for more frequent monitoring or early intervention. DI was not superior to the 30-min glucose levels in identifying diabetes or NGT in our ROC analyses, but DI was superior to 30-min glucose levels in metabolic discrimination of individual patient groups. Both DI and 30-min glucose discriminated between con-NGT and all CF groups, but only DI discriminated CF-NGT from CFRD (Table 3). It is possible that DI measurement could be used to help predict the subsequent development of CFRD in CF-NGT patients who are in stable clinical condition. We found an overlap in the DI values between controls with NGT and CF with NGT and therefore not all CF patients may be at increased risk of developing diabetes. However, there may well be a subset of these CF patients with NGT and with a lower DI value that is at increased risk. The cutoff value for DI below which the risk for developing prediabetes and diabetes is higher could be determined after conducting a large prospective trial and following CF patients with NGT over time.

The strengths of our study include the following: (1) the first study to assess DI in CF patients and compare it to non-CF controls; (2) the use of a broad range of patient groups that were physiologically comparable except for CF and glycemic status; (3) the rigorous assessments of discrimination according to DI and 30-min glucose levels; and (4) in 2010, the CF Foundation recommended that an OGTT be done annually as a screen for CFRD in all CF patients 10 years of age and older. Adding the insulin assay at two time points during this standard clinically recommended screening test will be practical and easy to implement if DI proves to be effective in larger studies. The limitations to our study include the following: (1) the relatively small sample size. Our findings including the hyperbolic relationship between insulin secretion and sensitivity in CF patients need to be validated in future larger studies. (2) The regression analysis that we used to demonstrate the hyperbolic relationship may not account for measurement error in predictors, noting that it is difficult to correct for such measurement error in the absence of replicate or validation data. (3) It is a cross-sectional study. We do not know how DI may change in individuals as they develop CFRD, and we cannot confirm that it will predict progression to CFRD. (4) The OGTT measures can be variable compared with intravenous testing [21] and the insulin secretion measure that we used ( $\Delta I 0-30/\Delta G 0-30$ ) is not thorough as it includes only two insulin measurements. However, this measure has been validated in CF patients and found to have

a good correlation with measures obtained from IV glucose tolerance testing [22]. The insulin sensitivity measure we used (1/fasting insulin) has also been validated in non-CF patients and found to correlate well with insulin sensitivity measured via glucose clamps [23]. (5) We did not obtain 1 hr glucose values during the OGTT and thus we are unable to assess if it has a superior prediction value compared to DI.

In summary, we have found that  $\beta$ -cell function as measured by the DI is reduced in CF patients compared to non-CF controls—even in CF patients with normal glucose tolerance—and is further decreased in CF patients with diabetes. The low DI in this sample of CF patients was due primarily to an insulin secretory defect that was present despite stable pulmonary disease and adequate nutritional status. Our findings indicate that in CF patients with normal glucose tolerance, the underlying insulin secretion defect might be unmasked during times of acute stress when insulin resistance increases, possibly resulting in hyperglycemia. If DI proves to be a predictor of the development of prediabetes and CFRD in larger studies, it is possible that it could be used to identify the subset of CF patients who are at particularly high risk. This would allow early intervention aimed to preserve their  $\beta$ -cells and help prevent or delay the development of CFRD and its associated morbidity and mortality.

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.jcf.2014.06.004>.

### Conflicts of interest

Within the past several years, Dr. Phillips served on a Scientific Advisory Board for Boehringer Ingelheim and has or had research support from Merck, Amylin, Eli Lilly, Novo Nordisk, Sanofi, PhaseBio, Roche, and the Cystic Fibrosis Foundation. In the past, he was a speaker for Novartis and Merck, but not for the last several years. These activities involve diabetes but have nothing to do with this manuscript. Dr. Stecenko receives support from NIH and the Cystic Fibrosis Foundation and is part of the Cystic Foundation clinical research network that conducts industry-sponsored research. She does not serve as consultant or board member for any pharmaceutical company. Dr. Long receives support from NIH and the Cystic Fibrosis Foundation. Other authors have no conflicts of interest to declare.

### Acknowledgements

The authors wish to acknowledge the excellent staff at the clinical research unit at the ACTSI as well as AS's outstanding research coordinators who assisted in data collection.

This work was supported by the Cystic Fibrosis Foundation (CFFSTECEN07A0), and supported in part by VA award HSR&D IIR 07-138, (L.S.P.), FDA RO1FD003527 (A.S. and L.S.P.), U01 DK1U01DK098246 (L.S.P.) and Cystic Fibrosis Foundation award PHILLI12A0 (L.S.P.). It is also supported by the National Center for Advancing Translational Sciences of the National Institutes of Health under award number UL1TR000454. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The sponsors had no role in the design and conduct of the

study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

LM researched the data and drafted the manuscript, QH and QL analyzed the data and reviewed/edited the manuscript, LSP reviewed/edited the manuscript and AS conceived of the project, oversaw the recruitment of the subjects and the study visits and reviewed/edited the manuscript.

### References

- [1] Moran A, Dunitz J, Nathan B, Saeed A, Holme B, Thomas W. Cystic fibrosis-related diabetes: current trends in prevalence, incidence, and mortality. *Diabetes Care* 2009;32:1626–31.
- [2] Koch D, Rainisio M, Madessani U, Harms HK, Hodson ME, Mastella G, et al. Presence of cystic fibrosis-related diabetes mellitus is tightly linked to poor lung function in patients with cystic fibrosis: data from the European Epidemiologic Registry of Cystic Fibrosis. *Pediatr Pulmonol* 2001;32:343–50.
- [3] Marshall BC, Butler SM, Stoddard M, Moran AM, Liou TG, Morgan WJ. Epidemiology of cystic fibrosis-related diabetes. *J Pediatr* 2005;146:681–7.
- [4] Milla CE, Warwick WJ, Moran A. Trends in pulmonary function in patients with cystic fibrosis correlate with the degree of glucose intolerance at baseline. *Am J Respiratory and Critical Care Medicine*.
- [5] Chamman P, Shine BS, Haworth CS, Bilton D, Adler AI. Diabetes as a determinant of mortality in cystic fibrosis. *Diabetes Care* 2010;33:311–6.
- [6] Lanng S, Thorsteinson B, Nerup J, Koch C. Influence of the development of diabetes mellitus on clinical status in patients with cystic fibrosis. *Eur J Pediatr* 1992;151:684–7.
- [7] Lanng S, Thorsteinson B, Nerup J, Koch C. Diabetes mellitus in cystic fibrosis: effect of insulin therapy on lung function and infections. *Acta Paediatr* 1994;83:849–53.
- [8] Clinical care guidelines for cystic fibrosis-related diabetes: a position statement of the American Diabetes Association and a clinical practice guideline of the Cystic Fibrosis Foundation, endorsed by the Pediatric Endocrine Society. Moran A. Division of Pediatric Endocrinology, University of Minnesota, Minneapolis, Minnesota, USA. *Diabetes Care* Dec 2010;33(12):2697–708.
- [9] Dobson L, Sheldon CD, Hattersley AT. Conventional measures underestimate glycaemia in cystic fibrosis patients. *Diabet Med* 2004;21:691–6.
- [10] Brodsky J, Dougherty S, Makani R, Rubenstein RC, Kelly A. Elevation of 1-hour plasma glucose during oral glucose tolerance testing is associated with worse pulmonary function in cystic fibrosis. *Diabetes Care* Feb 2011;34(2):292–5.
- [11] Kahn SE, Prigeon RL, McCulloch DK, Boyko EJ, Bergman RN, Schwartz MW, et al. Quantification of the relationship between insulin sensitivity and B-cell function in human subjects: evidence for a hyperbolic function. *Diabetes* 1993;42:1663–72.
- [12] Utzschneider KM, Prigeon RL, Faulenbach MV, Tong J, Carr DB, Boyko EJ, et al. Oral Disposition Index predicts the development of future diabetes above and beyond fasting and 2-h glucose levels. *Diabetes Care* 2009;32:776–8.
- [13] Genuth S, Alberti KG, Bennett P, Buse J, DeFronzo R, Kahn R, et al. Follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care* 2003;26:3160–7.
- [14] Bergman RN, Phillips LS, Cobelli C. Physiologic evaluation of factors controlling glucose tolerance in man: measurement of insulin sensitivity and B-cell glucose sensitivity from the response to intravenous glucose. *J Clin Invest* 1981;68:1456–67.
- [15] Moreau F, Weiller MA, Rosner V, Weiss L, Hasselmann M, Pinget M, et al. Continuous glucose monitoring in cystic fibrosis patients according to the glucose tolerance. *Horm Metab Res* 2008;40:502–6.
- [16] Schmid K, Fink K, Holl RW, Hebestreit H, Ballmann M. Predictors for future cystic fibrosis-related diabetes by oral glucose tolerance test. *J Cyst Fibros* Jun 2013;13:00106–9.
- [17] Abdul-Ghani MA, Abdul-Ghani T, Ali N, DeFronzo RA. One-hour plasma glucose concentration and the metabolic syndrome identify subjects at high risk for future type 2 diabetes. *Diabetes Care* 2008;31:1650–5.
- [18] Elder DA, Wooldridge JL, Dolan LM, D'Alessio DA. Glucose tolerance, insulin secretion, and insulin sensitivity in children and adolescents with cystic fibrosis and no prior history of diabetes. *J Pediatr* 2007;151(6):653–8.

- [19] Yung B, Noormohamed FH, Kemp M, Hooper J, Lant AF, Hodson ME. Cystic fibrosis-related diabetes: the role of peripheral insulin resistance and beta-cell dysfunction. *Diabet Med* 2002;19:221–6.
- [20] Bismuth E, Laborde K, Taupin P, Velho G, Ribault V, Jennane F, et al. Glucose tolerance and insulin secretion, morbidity, and death in patients with cystic fibrosis. *J Pediatr* 2008;152(4):540–5 [e1].
- [21] Utzschneider KM, Prigeon RL, Tong J, Gerchman F, Carr DB, Zraika S, et al. Within-subject variability of measures of beta cell function derived from a 2 h OGTT: implications for research studies. *Diabetologia* 2007;50:2516–25.
- [22] Hammana I, Potvin S, Tardif A, Berthiaume Y, Coderre L, Rabasa-Lhoret R. Validation of insulin secretion indices in cystic fibrosis patients. *J Cyst Fibros* Dec 2009;8(6):378–81.
- [23] George L, Bacha F, Lee S, Tfayli H, Andreatt E, Arslanian S. Surrogate estimates of insulin sensitivity in obese youth along the spectrum of glucose tolerance from normal to prediabetes to diabetes. *J Clin Endocrinol Metab* 2011;96:2136–45.