Annales d'Endocrinologie 84 (2023) 265–271

Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com/en

Original article

Marginal association of fasting blood glucose with the risk of cystic fibrosis-related diabetes

Kathryn J. Potter[a,f], Anne Bonhoure[a,c], Valérie Boudreau[a,b], François Tremblay[d,e], Annick Lavoie[d,e], Maité Carricart[d,e], Peter A. Senior[f], Rémi Rabasa-Lhoret[a,b,c,d,e,*]

[a] *Montreal Clinical Research Institute (IRCM), Montréal, Québec, Canada*
[b] *Department of Nutrition, Faculty of Medicine, Université de Montréal, Montréal, Québec, Canada*
[c] *Division of Experimental Medicine, Faculty of Medicine, McGill University, Montréal, Québec, Canada*
[d] *Department of Medicine, Faculty of Medicine, Université de Montréal, Montréal, Québec, Canada*
[e] *Cystic Fibrosis Clinic, Centre hospitalier de l'Université de Montréal (CHUM), Montréal, Québec, Canada*
[f] *Department of Endocrinology, University of Alberta, Edmonton, Alberta, Canada*

ARTICLE INFO

Article history:
Received 11 July 2022
Accepted 5 September 2022

Keywords:
Cystic fibrosis
Cystic fibrosis-related diabetes
Screening
Diagnosis
Fasting blood glucose
Impaired fasting glucose

ABSTRACT

Objectives. – Cystic fibrosis-related diabetes (CFRD) may be diagnosed by fasting blood glucose ≥ 7.0 mmol/L and/or glucose ≥ 11.1 mmol/L following oral glucose tolerance test (OGTT). We compared the role of fasting and stimulated glucose for diagnosis of CFRD.
Methods. – We performed a cross-sectional review of the prevalence of fasting glycemic abnormalities and Kaplan-Meier survival analysis of risk of progression to CFRD according to baseline fasting glucose in the prospective Montreal Cystic Fibrosis Cohort.
Results. – Isolated fasting hyperglycemia was detected in only 8% of participants at study onset. Eighty percent of subjects had isolated post-challenge hyperglycemia on their first OGTT meeting criteria for CFRD. Kaplan Meier survival analysis demonstrated that impaired fasting glucose (IFG) alone is not a risk factor for CFRD. Subjects with combined IFG and impaired glucose tolerance at baseline (IGT) had the highest risk of progression to CFRD.
Conclusion. – Post-prandial elevations in blood glucose are more common at diagnosis of CFRD. While IGT is a significant risk factor for CFRD, IFG alone is uncommon and does not increase the risk of CFRD. Patients with both IGT and IFG have the highest risk of CFRD.

Abbreviations

ADA	American Diabetes Association
ANOVA	Analysis of variance
ALT	Alanine Aminotransaminase
AST	Aspartate Aminotransaminase
ALP	Akaline Phosphatase
AUC	Area under the curve
BMI	Body mass index
CFRD	Cystic Fibrosis-Related Diabetes
CRP	C-reactive protein
FEV1	Forced expiratory volume in 1 second
FH-	CFRD without fasting hyperglycemia
FH+	CFRD with fasting hyperglycemia
FPG	fasting plasma glucose
G0	CFRD with fasting hyperglycemia
G120	CFRD with 2-hour post-OGTT hyperglycemia
GGT	Gamma Glutamyl transferase
HbA1c	hemoglobin A1c
HOMA-B	Homeostasis model assessment for beta cell secretion
HOMA-IR	Homeostasis model assessment of insulin resistance
IFG	impaired fasting glucose
IGT	impaired glucose tolerance
ISPAD	International Society for Pediatric and Adolescent Diabetes
OGTT	Oral glucose tolerance testing
ROC	Receiver Operator Curve
WHO	World Health Organization

* Corresponding author. IRCM, 110, avenue des Pins, Montréal, QC, Canada H2W1R7.
E-mail address: remi.rabasa-lhoret@ircm.qc.ca (R. Rabasa-Lhoret).

https://doi.org/10.1016/j.ando.2022.09.025
0003-4266/

1. Introduction

Diabetes may be diagnosed by persistent elevation of fasting blood glucose ≥ 7.0 mmol/L, of post-prandial or random blood glucose ≥ 11.1 mmol/L, or both [1–3]. It is unclear whether all patients with cystic fibrosis-related diabetes (CFRD) develop both types of dysglycemia. In 1998, the Cystic Fibrosis (CF) Federation CFRD Consensus Conference distinguished between CFRD patients with and without fasting hyperglycemia (FH: FH + and FH-, respectively) [4]. These terms continue to be applied by the International Society for Pediatric and Adolescent Diabetes (ISPAD), which recommends basal-bolus insulin therapy for FH+ and bolus insulin only for FH- [5]. Conversely, the American Diabetes Association (ADA) does not distinguish between these categories and broadly recommends insulin as therapy for patients with CFRD to maintain nutritional health and pulmonary function [4]. No studies have yet assessed whether basal insulin might provide additional anabolic benefit in patients with CFRD without fasting hyperglycemia.

CFRD is most often diagnosed from post-prandial glucose levels during oral glucose tolerance tests (OGTT) [5,6]. Cross-sectional studies reported 16–47% of patients with CFRD meeting both fasting and post-prandial criteria [6–8]. A 10-year natural history study suggested that fasting hyperglycemia (FH) develops later in the natural history of CFRD [7]; 46% of 54 individuals with CFRD without fasting hyperglycemia on initial OGTT progressed to show fasting glucose ≥ 7.0 mmol/L on serial follow up. Yet, in the University of Michigan observational cohort, there were patient groups who remained FH- for at least a decade [9]. Body mass index and pulmonary function were similar between FH + and FH – groups [9]. Treatment with insulin was important to maintain nutritional status and lung function in both groups. Microvascular complications were only identified in the FH + group.

It remains unclear whether all patients with CFRD progress from FH – to FH + or whether there are distinct subpopulations.

Early diagnosis of CFRD with prompt initiation of insulin is important to maintain nutritional status and optimal lung function [5]. Individuals who can be monitored more frequently may be identified by OGTT screening. Pre-diabetes includes abnormal fasting or post-challenge glucose levels (respectively, impaired fasting glucose: IFG; impaired glucose tolerance: IGT). IGT (defined as a blood glucose 7.8 to 11.0 mmol/L 2 hours after a standard OGTT) is a known risk factor for CFRD [10]. In contrast, prospective studies reported conflicting findings on whether IFG increases CFRD risk [8,11]. Different thresholds have been used to define IFG (World Health Organization (WHO), 6.1 mmol/L [12]; American Diabetes Association (ADA), 5.6 mmol/L, [2]), but neither appears to be sensitive or specific for diagnosis of CFRD [13]. Thus, while IGT is a well-established risk factor, the role of IFG in CFRD pathogenesis is less clearly defined.

In this study, the primary objective was to use prospective data from the Montreal CF cohort (MCFC) to improve our understanding of the role of fasting blood glucose in the diagnosis and pathogenesis of CFRD. We also assessed the efficacy of the ADA and WHO definitions of IFG in CFRD risk prediction. The secondary objective was to compare the role of fasting and post-prandial glucose levels in predicting the development of CFRD.

2. Patients and methods

2.1. Design and setting

Analysis used prospective data from the MCFC. This cohort was established in 2004 and was designed for CFRD screening to study mechanisms of glucose intolerance and its association with CF clinical status in patients without known CFRD. Patients undergo oral glucose tolerance test (OGTT), blood sampling and evaluation of pulmonary function (forced expiratory volume: FEV_1) every 1–2 years until they are diagnosed with diabetes [14].

2.2. Participants

Inclusion criteria comprised age ≥ 18 years, confirmed diagnosis of CF, and at ≥ 2 serial OGTT assessments except in case of de-novo CFRD at initial consultation. Informed consent was obtained for experimentation with human subjects. Patients with de-novo CFRD on baseline screening were referred to an endocrinologist to confirm CFRD diagnosis and were not included in serial follow-up. Exclusion criteria comprised history of any type of diabetes or organ transplantation, pregnancy, recent pulmonary exacerbation, and use of medications that interfere with glucose metabolism (intravenous antibiotics, systemic corticosteroids, or growth hormone) [14]. OGTTs were scheduled when patients were clinically stable, at least 1 month after any pulmonary exacerbation or use of interfering medication.

2.3. Clinical data and blood sample

Age, gender and genotype were collected by chart review. Body weight, standing height, body mass index, and FEV_1 were measured at each consultation on the day of OGTT, as previously described [14]. Pancreatic insufficiency was defined by prescription of enzymatic supplementation. Glycosylated hemoglobin (HbA1c) was measured using fasting serum samples, as described previously [14]. Baseline clinical characteristics are presented in Table 1 for all subjects and for 3 subgroups: never developed diabetes, developed diabetes, identified with diabetes at initial screening. CFRD was defined on the ADA criteria (fasting plasma glucose (FPG) > 7.0 mmol/l and/or 2hr glucose > 11.1 mmol/L). Percentage body fat was obtained by impedance measurement on an electronic scale (Tanita Corporation, Arlington Heights, IL, USA).

2.4. Oral glucose tolerance test (OGTT)

Oral glucose tolerance testing was performed as previously described, with sampling for glucose and insulin at 0, 30, 60, 90 and 120 minutes [14]. Plasma glucose was analyzed on a Glucose Analyzer (YSI 2300 STAT Plus Glucose and Lactate Analyzer; YSI Inc.). Insulin samples were frozen at -80°C then chemically measured in duplicate by immunoturbidimetry (ADVIA I650; Siemens HealthCare). We calculated the area under the curve (AUC) for glucose (AUC_{glu}), insulin (AUC_{ins}) and insulin corrected for glucose ($AUC_{ins/glu}$) for the whole period (0-120 minutes), the early phase (0–30 minutes) and the late phase (30–120 minutes) [15–17]. We also estimated insulin sensitivity according to the Stumvoll index and insulin resistance by HOMA-IR, as previously described [14].

2.5. Statistical analysis

Statistical analysis used GraphPad Prism 8.0 (GraphPad Inc., San Diego, CA). Results are presented as mean ± standard deviation (SD). Analysis of variance (ANOVA) was used to compare groups when appropriate. Post-hoc comparisons were performed using Dunnett's test for multiple comparisons. Kaplan Meier survival analysis was used to compare the proportion of subjects developing diabetes between groups. P-values < 0.05 were considered significant.

3. Results

3.1. Clinical characterization of study subjects

At the time of this analysis, 293 adult subjects were included in the MCFC, as previously described [18]. Subjects had a mean age of

Table 1
Comparison of demographic, clinical and glycemic profiles between subjects who developed CFRD at any point during the study (baseline or prospective) and those who did not.

	Did not develop CFRD over the course of the prospective study	Developed CFRD at any timepoint (baseline or prospective)	P value (t-test)
n	189	100	
Gender (% male)	56%	54%	0.8037
Age (years)	25.3 ± 8.5	25.9 ± 6.7	0.5176
Genotype (homozygous dF508/dF508; heterozygous dF508; other)	47%/43%/10%	53%/38%/9%	0.8543
Pancreatic insufficiency	72%	94%	< 0.0001
Weight (kg)	60.6 ± 10.8	59.3 ± 11.4	0.3259
BMI (kg/m^2)	21.8 ± 3.0	21.6 ± 3.0	0.6442
Fat mass (%)	18.7 ± 7.9	18.4 ± 7.5	0.8259
FEV_1 (%)	74.8 ± 22.0	69.6 ± 21.7	0.0550
CRP	7.4 ± 10.6	5.9 ± 5.7	0.2046
HbA1c (%)	5.6 ± 0.6	6.0 ± 1.0	0.0004
Fasting glucose (mmol/L)	5.3 ± 0.5	5.8 ± 1.0	< 0.0001
Fasting insulin (pmol/L)	10.4 ± 4.9	10.2 ± 5.4	0.7202
2h OGTT glucose (mmol/L)	6.7 ± 1.9	10.7 ± 3.8	< 0.0001
AUC glucose	1019 ± 176	1329 ± 335	< 0.0001
AUC insulin/glucose	5.5 ± 3.1	3.7 ± 2.8	< 0.0001
HOMA-B	132.2 ± 96.9	110.5 ± 95.0	0.0750
HOMA-IR	2.5 ± 1.2	2.6 ± 1.3	0.4292
Stumvoll-ISI	0.1 ± 0.0	0.1 ± 0.0	0.6341

25.5 ± 7.7 years, BMI 21.7 ± 3.0 kg/m^2, and FEV_1 73.2 ± 22.1%. 16% of subjects (48/293) met the criteria for CFRD on baseline screening. An additional 52 developed CFRD over the prospective study period. Mean follow-up was 6.0 ± 3.5 years.

Table 1 compares baseline clinical and demographic characteristics of subjects with CFRD at baseline over the course of the study versus those who never developed CFRD. Those who developed CFRD were more likely to have exocrine pancreatic insufficiency ($P < 0.0001$) and higher fasting and post-challenge glucose levels at baseline ($P < 0.0001$). There was no difference in HOMA-B between groups, but those who developed CFRD tended to have less efficient insulin secretion during OGTT ($AUC_{ins/glu}$; $P < 0.0001$). There were no differences in insulin sensitivity or insulin resistance between groups.

Table 2 compares the criteria for positive CFRD screening at baseline and over the study period. Overall, 80% had an initial positive screen, based on elevated 2-hour post-challenge glucose (G120) only; 8% had a positive screen based on fasting glucose alone (G0); and 12% met both criteria (G0 + G120).

Table 3 compares subjects without diabetes versus those with CFRD based on G0, G120, and G0 + G120.

3.2. Comparison of groups meeting the criteria for CFRD by fasting, post-challenge or combined criteria

Given the small number of subjects meeting the criteria for CFRD based on fasting glucose, we analyzed subjects meeting the criteria based on G0, G120 and G0 + G120 with positive CFRD screen at baseline and positive screen in the prospective follow-up (Table 2). Demographic data were taken at the time of the first positive OGTT screen.

There were significantly more male subjects meeting the criteria for CFRD based on positive fasting glucose ($P = 0.0078$). There was no difference in age, CF genotype, pancreatic exocrine status, weight, BMI, fat mass (%), FEV_1(%), CRP, liver enzymes, or liver function between those with positive screens based on fasting glucose alone (G0), 2-hour OGTT glucose alone (G120), or both (G0 + G120).

Hemoglobin A1c was significantly greater in the G120 group than the G0 + G120 group (G0, 6.1 ± 0.7; G120, 5.9 ± 0.5; G0 + G120, 6.7 ± 1.1; ANOVA, $P = 0.0004$; post-hoc comparison G120 vs G0 + G120, $P = 0.0042$). Area under the OGTT glucose curve (AUC_{glu}) was significantly greater in the G0 + G120 group than in the other groups ($P < 0.0001$ for each comparison). AUC for OGTT insulin corrected for glucose ($AUC_{ins/glu}$) and HOMA-B were significantly different between groups ($AUC_{ins/glu}$: G0, 2.3 ± 1.2; G120, 3.1 ± 1.6; G0 + 120, 1.8 ± 1.7; $P = 0.03$; HOMA-B: G0, 41.4 ± 20.8; G120, 105.6 ± 77.6; G0 + 120, 46.1 ± 20.1; $P = 0.004$). Insulin resistance (HOMA-IR, $P = 0.04$) was greatest and insulin sensitivity (Stumvoll index, $P < 0.0001$) was lowest in the G0 + G120 group.

3.3. Fasting blood glucose increases in association with other measures of dysglycemia, and impaired fasting glucose is associated with decreased insulin secretion and sensitivity

We used baseline data to characterize the relationship between fasting and stimulated glucose and HbA1c, as well as measures of insulin secretion and sensitivity. As shown in Fig. 1 A to D, fasting blood glucose > 6 mmol/L was significantly associated with worsening post-prandial hyperglycemia and HbA1c ($P < 0.0001$). As fasting blood glucose rose, there was an association with lower stimulated and fasting insulin secretion (Figs. 1E, $AUC_{ins/glu}$, and 1F, HOMA-B, both $P < 0.0001$), worsening insulin resistance (HOMA-IR, Fig. 1G, $P = 0.0016$), and decreasing insulin sensitivity (Fig. 1H, $P < 0.0001$).

We also analyzed the relationship between fasting glucose and clinical measures of health in subjects with CF. As shown in Fig. S1, there was no significant association between fasting glucose and FEV_1(%) or BMI. There was, however, a trend for decreasing fat mass as fasting glucose increased (Fig. S1C, $P = 0.0001$).

3.4. Lack of correlation between baseline fasting blood glucose and progression to CFRD

We analyzed the risk of progression to CFRD over the study period in those who did not have CFRD at baseline by Kaplan Meier survival analysis. There was no correlation between fasting blood glucose at baseline and progression to CFRD, as shown in Fig. 2A ($P = 0.6250$). Furthermore, participants who met the criteria for impaired fasting glucose based on ADA criteria (Fig. 2B, $P = 0.9581$) or WHO criteria (Fig. 2C, $P = 0.9946$) at baseline did not show increased risk of progression to CFRD over the study period.

Table 2
Characterization of glycemic abnormalities by cross-sectional and prospective analysis in the Montreal CF Cohort. Diagnosis by fasting and post-challenge criteria: G0 and G120, respectively.

	n	Elevation in G0 only		Elevation in G120 only		Elevation in G0 + G120	
Cross-sectional analysis of subjects diagnosed with CFRD on OGTT at baseline	48	10%	(5/48)	71%	(34/48)	19%	(9/48%)
Glycemic profile at time of diagnosis of CFRD	52	6%	(3/52)	88%	(46/52)	6%	(3/52)
Overall	100	8%	(8/100)	80%	(80/100)	12%	(12/100)

Table 3
Demographic and clinical profiles of MCFC subjects at first positive screen for CFRD based on fasting and post-prandial criteria for CFRD. Subjects were grouped according to positive screen based on fasting glucose (G0), 2-hour post-OGTT glucose (G120), or both (G0 + G120). Data are expressed as mean ± SD.

	CFRD-G0	CFRD-G120	CFRD-G0 + G120	*P* value (ANOVA)
n	8	79	12	
Gender (% male)	88%	46%	83%	0.0078
Genotype	50%/38%/12%	42%/58%/0%	35%/54%/11%	0.6632
Enzymes	100%	95%	100%	0.5900
Age	29.9 ± 9.6	28.5 ± 7.2	30.8 ± 7.5	0.5570
Weight (kg)	62.1 ± 8.2	58.5 ± 11.5	64.1 ± 13.6	0.2570
BMI (kg/m^2)	21.8 ± 2.7	21.8 ± 3.2	21.7 ± 3.8	0.9936
Fat mass (%)	14.0 ± 1.8	19.1 ± 7.5	15.1 ± 6.6	0.0852
FEV_1 (%)	70.8 ± 19.4	66.0 ± 23.0	64.2 ± 25.8	0.8151
CRP	6.1 ± 4.3	7.9 ± 10.2	6.6 ± 6.3	0.8358
AST	20.7 ± 6.7	24.5 ± 7.3	26.5 ± 10.2	0.2888
ALT	26.3 ± 14.5	25.9 ± 14.6	30.2 ± 10.9	0.6624
ALP	83.7 ± 27.0	93.4 ± 33.6	100.5 ± 29.6	0.5603
GGT	32.3 ± 56.8	18.7 ± 14.9	26.3 ± 18.4	0.1702
Albumin	40.1 ± 3.4	39.9 ± 2.9	41.5 ± 3.1	0.2047
Total bilirubin	8.3 ± 5.3	9.5 ± 5.9	14.3 ± 11.8	0.0682
HbA1c (%)	6.1 ± 0.7	5.9 ± 0.5	6.7 ± 1.1	0.0004
Fasting glucose (mmol/L)	7.5 ± 0.4	5.6 ± 0.6	8.0 ± 0.9	< 0.0001
Fasting insulin	8.4 ± 4.2	9.8 ± 5.7	10.4 ± 4.5	0.6652
2h OGTT glucose (mmol/L)	8.8 ± 1.7	13.1 ± 1.7	16.0 ± 2.6	< 0.0001
AUC glucose	1406 ± 206	1437 ± 182	1881 ± 300	< 0.0001
AUC insulin/glucose	2.3 ± 1.2	3.1 ± 1.6	1.8 ± 1.7	0.0306
HOMA-B	41.4 ± 20.8	105.6 ± 77.6	46.1 ± 20.1	0.0044
HOMA-IR	2.7 ± 1.2	2.5 ± 1.5	3.7 ± 1.7	0.0422
Stumvoll-ISI	0.11 ± 0.01	0.10 ± 0.02	0.08 ± 0.02	0.0002

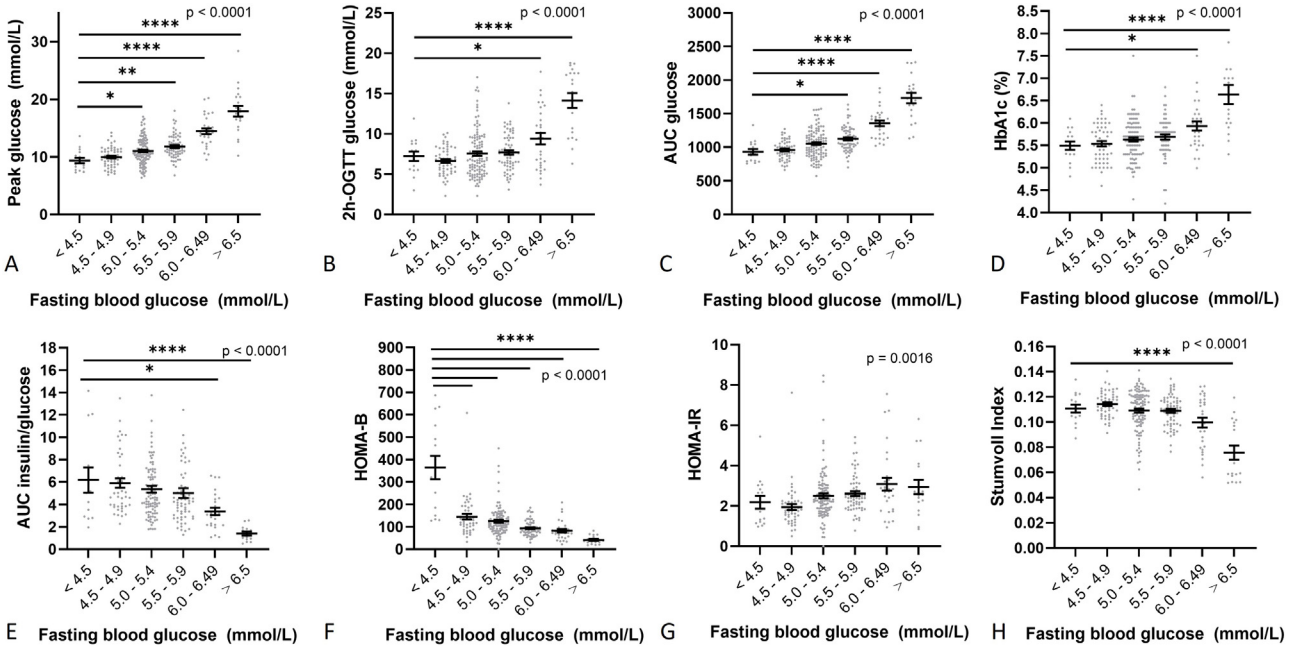

Fig. 1. Stimulated glucose response increases and insulin secretion decreases in association with fasting glucose. Stimulated glucose response is shown in A (A: Peak OGTT glucose, B: 2h-OGTT glucose, C: AUC_{glu}). HbA1c (%) is shown in D. Insulin secretion is shown in E-F (E: $AUC_{ins/glu}$; F: HOMA-B). HOMA-IR, a measure of insulin resistance, is shown in F. The Stumvoll index, a measure of insulin sensitivity, is shown in G. Data are derived from the baseline assessment.

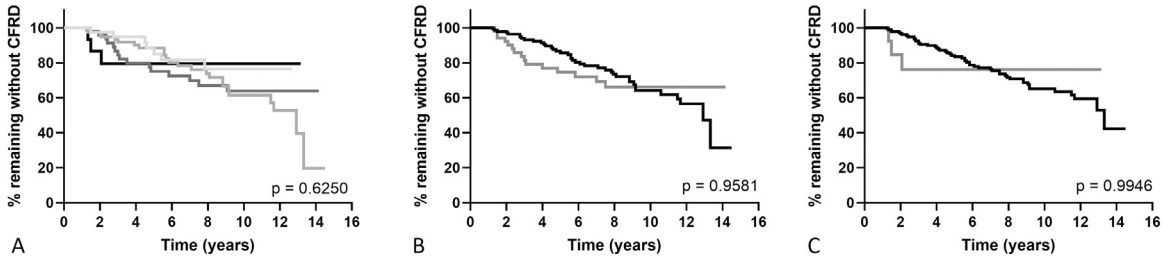

Fig. 2. There was no correlation between baseline fasting blood glucose and risk of progression to CFRD on Kaplan-Meier survival analysis. A) Participants without CFRD at baseline were stratified according to baseline fasting glucose as follows: 4.5-4.9 mmol/L, light gray; 5.0-5.4 mmol/L, medium gray; 5.5-5.9 mmol/L, dark gray; 6.0-6.4 mmol/L, black. B) Stratification according to normal (black line) or impaired fasting glucose (gray line) on the ADA definition (IFG = 5.6-6.9 mmol/L). C) Stratification according to normal (black line) or impaired fasting glucose (gray line) on the WHO definition (IFG = 6.1-6.9 mmol/L).

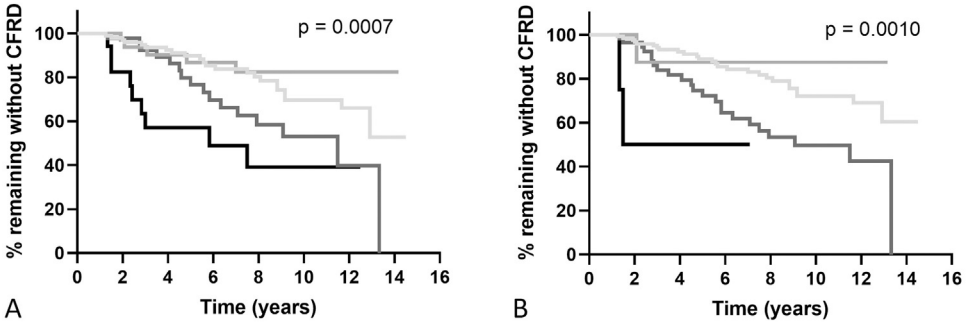

Fig. 3. Subjects with both impaired fasting glucose and impaired glucose tolerance had a greater risk of CFRD. In A), diabetes risk was assessed according to glucose tolerance and fasting glucose on the ADA definition of impaired fasting glucose (IFG; 5.6 – 6.9 mmol/L), and in B, on the WHO definition (IFG; 6.1-6.9 mmol/L).

3.5. Determination of the sensitivity and specificity of ADA- and WHO-defined impaired fasting glucose for the prediction of future CFRD

We compared the sensitivity and specificity of the IFG thresholds for CFRD in the 245 subjects who did not have diabetes at baseline. At a threshold of 5.6 mmol/L, sensitivity for CFRD was 31% and specificity 78%. At a threshold of 6.1 mmol/L, sensitivity was 6% and specificity 92%. The area under the ROC curve was not significant.

3.6. Comparison of IFG, IGT and IFG + IGT profiles for risk of developing CFRD

We performed Kaplan-Meier survival analyses to assess the relationship of IFG and IGT with risk of progression to CFRD. Fig. 3 A and B show that patients with IFG alone did not show increased risk, while IGT was a significant risk factor. Patients with combined IFG + IGT had the highest risk of developing CFRD (Fig. 3A, $P = 0.0070$; Fig. 3B, $P = 0.0010$).

4. Discussion

The present study showed that, at first detection of CFRD, the majority of subjects had isolated post-challenge hyperglycemia. Only a small subgroup had fasting hyperglycemia at first positive screening for CFRD. The only differentiating demographic factor appeared to be male gender, which was more common in case of fasting hyperglycemia. Those with combined fasting and post-challenge hyperglycemia had higher HbA1c levels at diagnosis at CFRD. We clearly showed that impaired fasting glucose, according to both ADA and WHO definitions, was not a risk factor for CFRD unless there was pre-existing impaired glucose tolerance. I.e., as previously demonstrated, IFG is not a sensitive test for CFRD [13]. Above a fasting glucose threshold of 6.0 mmol/L, there was a positive association with post-challenge hyperglycemia, poorer insulin secretion, and lower insulin sensitivity. Finally, although IFG was not an independent risk factor for progression to CFRD, subjects with combined IFG and IGT had a higher risk of progressing to CFRD.

IFG and IGT often occur in isolation and are independent risk factors for type-2 diabetes and cardiovascular disease [2]. Either one may be associated with beta-cell insulin secretion defect [2]. The IFG state is thought to arise from decreased hepatic responsiveness to insulin, leading to mild fasting hyperglycemia [2,19,20]. The early phase of stimulated insulin secretion, however, is also slightly reduced in individuals with IFG [21]. From a clinical perspective, baseline insulin secretion is most accurately reflected by HOMA-B, which is derived from fasting blood glucose and insulin levels [22,23]. IGT is associated with a primary beta cell defect [23] and is more accurately estimated by models based upon post-challenge insulin, such as $AUC_{ins/glu}$. The IFG and IGT states most likely predispose to diabetes by differing contributions of insulin secretory defects and insulin resistance [22]. We demonstrated that IGT and defects in stimulated insulin secretion are important in the pathogenesis of CFRD. We provided additional evidence that IFG does not play a primary role in the development of CFRD. Furthermore, we showed for the first time that patients with combined IFG and IGT had a higher risk of developing CFRD than those with IGT alone. Overall, IFG does not cause CFRD but subjects with both fasting and post-challenge glycemic abnormalities have the highest risk of developing diabetes.

FH is uncommon in CFRD, at least in early stages. In a cross-sectional analysis, Mueller-Brandes et al. found that IFG was not a sensitive test for CFRD and recommended against its use [13]. We came to similar conclusions, using prospective data and a wider-reaching diagnosis of diabetes. The Mueller-Brandes group defined diabetes based on 2 h OGTT results [13], whereas we used fasting or post-prandial hyperglycemia. Our ROC curve analyses showed that neither the ADA nor the WHO definitions of IFG were appropriate screening tests for CFRD.

FH is an important diagnostic criterion in type-2 diabetes because it predicts risk of microvascular complications.

Microvascular complications appear to be associated with FH in CFRD [1,2]. However, prevention of adverse respiratory and nutritional outcomes may be more important in CFRD. Insulin appeared to be important for maintaining respiratory and nutritional health, independently of FH [9]. Furthermore, although most patients developing CFRD will show FH, it is important to identify subgroups of CFRD in order to understand natural history and clinical implications. Patients who meet CFRD-G0 criteria tend to have lower insulin resistance and lower insulin secretion capacity. Those who meet both G0 and G120 criteria have the greatest insulin resistance, lowest insulin secretion capacity and highest HbA1c levels. This cross-sectional analysis of CFRD subtypes suggests one of two phenomena: a subgroup of patients may initially be detected with both fasting and post-prandial hyperglycemia. Alternatively, the G0 + G120 group may be detected at a later stage and have initially presented one glycemic abnormality and have developed worsening glycemic control over time.

In support of this hypothesis, a prospective study by Sterescu et al. showed that 46% of CFRD patients who were FH- on initial OGTT (25/54) progressed to FH + over 10 year's follow-up [7]. Even so, over half of the cohort did not progress to fasting glycemia abnormalities. Studying a small subgroup is difficult in a rare disease. Given the greater insulin resistance in those with fasting dysglycemia, future studies might attempt to determine whether this group has increased genetic susceptibility to T2D. Further study of this subgroup is also important to determine whether fasting dysglycemia predisposes to long-term micro- and/or macro-vascular risk or other respiratory or nutritional complications in patients with CF. If continuous glucose monitoring technology becomes integrated in CFRD screening, future studies might focus on a comparison of fasting and post-prandial glycemic trends to better define sub-populations at risk of CFRD.

4.1. Limitations

This study had limitations despite the large cohort. The results are based only on a French-speaking population in a single region of Canada, and on younger and healthier patients than in other CF cohorts. We are confident that our cohort was well- characterized and comparable for key parameters, such as weight and pulmonary function, to other North American data [24]. We measured fat mass (%) by impedance studies, which tend to show higher intra- and inter-individual variability than BMI. However, we used these data as an adjunct to BMI, to support conclusions derived from the BMI data. Finally, our definition of diabetes was limited to a single fasting glucose assay $\geq$ 7.0 mmol/L or post-prandial glucose $\geq$ 11.1 mmol/L; these values were taken on the same day in standardized conditions.

5. Conclusions

Post-prandial elevation of blood glucose is more common than fasting elevation in patients with CF. IFG is not a sensitive or specific test for diagnosis of CFRD. IFG alone does not increase the risk of CFRD, but patients with both IGT and IFG have a higher risk for than those with IGT alone.

Disclosure of interest

The authors declare that they have no competing interest.

Funding

This work was supported by an operating grant from the Canadian Cystic Fibrosis Foundation (#2883) and the J-A DeSève Diabetes research chair both to RRL.

Author Contributions

Conceptualization: Kathryn Potter, Anne Bonhoure, Valerie Boudreau, Peter Senior, Rémi Rabasa-Lhoret.

Data curation: Valérie Boudreau.

Formal analysis: Kathryn Potter, Anne Bonhoure.

Funding acquisition: Rémi Rabasa-Lhoret.

Investigation: Kathryn Potter, Rémi Rabasa- Lhoret, Peter Senior.

Methodology: Kathryn Potter, Rémi Rabasa- Lhoret, Peter Senior.

Resources: François Tremblay, Maité Carricart, Annick Lavoie, Rémi Rabasa- Lhoret, Peter Senior.

Supervision: Peter Senior, Rémi Rabasa- Lhoret.

Writing – original draft: Kathryn Potter.

Writing – review & editing: Peter Senior, Anne Bonhoure, Valérie Boudreau, François Tremblay, Maité Carricart, Annick Lavoie, Rémi Rabasa- Lhoret.

Formal analysis: Kathryn Potter and Anne Bonhoure.

Acknowledgments

We acknowledge all the patients and the CF and diabetes clinic nurses for their involvement into the Montreal Cystic Fibrosis Cohort.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ando.2022.09.025.

References

[1] Stevens JW, Khunti K, Harvey R, Johnson M, Preston L, Woods HB, et al. Preventing the progression to type 2 diabetes mellitus in adults at high risk: a systematic review and network meta-analysis of lifestyle, pharmacological and surgical interventions. Diabetes Res Clin Pract 2015;107:320–31. Epub 2015/02/02. doi: 10.1016/j.diabres.2015.01.027. PubMed PMID:25638454.

[2] Nathan DM, Davidson MB, DeFronzo RA, Heine RJ, Henry RR, Pratley R, et al. Impaired fasting glucose and impaired glucose tolerance: implications for care. Diabetes Care 2007;30:753–9. Epub 2007/03/01. doi: 10.2337/dc07-9920. PubMed PMID: 17327355.

[3] DeFronzo RA, Abdul-Ghani M. Assessment and treatment of cardiovascular risk in prediabetes: impaired glucose tolerance and impaired fasting glucose. Am J Cardiol 2011;108:3b–24b. Epub 2011/08/10. doi: 10.1016/j.amjcard.2011.03.013. PubMed PMID: 21802577.

[4] Moran A, Brunzell C, Cohen RC, Katz M, Marshall BC, Onady G, et al. 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. Diabetes Care 2010;33:2697–708, http://dx.doi.org/10.2337/dc10-1768. Epub 2010/12/01. PubMed PMID: 21115772; PubMed Central PMCID: PMCPMC2992215.

[5] Moran A, Pillay K, Becker D, Granados A, Hameed S, Acerini CL. ISPAD Clinical Practice Consensus Guidelines 2018: Management of cystic fibrosis-related diabetes in children and adolescents. Pediatr Diabetes 2018;19:64–74, http://dx.doi.org/10.1111/pedi.12732. PubMed PMID: 30094886.

[6] Lanng S, Hansen A, Thorsteinsson B, Nerup J, Koch C. Glucose tolerance in patients with cystic fibrosis: five year prospective study. Bmj 1995;311:655–9, http://dx.doi.org/10.1136/bmj.311.7006.655. PubMed PMID: 7549632; PubMed Central PMCID: PMCPMC2551427.

[7] Sterescu AE, Rhodes B, Jackson R, Dupuis A, Hanna A, Wilson DC, et al. Natural history of glucose intolerance in patients with cystic fibrosis: ten-year prospective observation program. J Pediatr 2010;156:613–7, http://dx.doi.org/10.1016/j.jpeds.2009.10.019. Epub 2009/12/08. PubMed PMID: 19962154.

[8] Frohnert BI, Ode KL, Moran A, Nathan BM, Laguna T, Holme B, et al. Impaired fasting glucose in cystic fibrosis. Diabetes Care 2010;33:2660–4, http://dx.doi.org/10.2337/dc10-0613. PubMed PMID:21115768; PubMed Central PMCID: PMCPMC2992208.

[9] 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, http://dx.doi.org/10.2337/dc09-0586. Epub 2009/06/23. PubMed PMID: 19542209; PubMed Central PMCID: PMCPMC2732133.

[10] Costa M, Potvin S, Hammana I, Malet A, Berthiaume Y, Jeanneret A, et al. Increased glucose excursion in cystic fibrosis and its association with a worse clinical status. J Cyst Fibros 2007;6:376–83,

http://dx.doi.org/10.1016/j.jcf.2007.02.005. Epub 2007/04/06. PubMed PMID: 17409029.
[11] 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 2014;13:80–5, http://dx.doi.org/10.1016/j.jcf.2013.06.001. Epub 2013/07/03. PubMed PMID: 23809507.
[12] Gómez-Pérez FJ, Aguilar-Salinas CA, López-Alvarenga JC, Perez-Jauregui J, Guillen-Pineda LE, Rull JA. Lack of agreement between the World Health Organization Category of impaired glucose tolerance and the American Diabetes Association category of impaired fasting glucose. Diabetes Care 1998;21:1886–8, http://dx.doi.org/10.2337/diacare.21.11.1886. Epub 1998/11/05. PubMed PMID: 9802737.
[13] Mueller-Brandes C, Holl RW, Nastoll M, Ballmann M. New criteria for impaired fasting glucose and screening for diabetes in cystic fibrosis. Eur Respir J 2005;25:715–7, http://dx.doi.org/10.1183/09031936.05.00068104. Epub 2005/04/02. PubMed PMID: 15802348.
[14] Coriati A, Belson L, Ziai S, Haberer E, Gauthier MS, Mailhot G, et al. Impact of sex on insulin secretion in cystic fibrosis. J Clin Endocrinol Metab 2014;99:1767–73, http://dx.doi.org/10.1210/jc.2013-2756. Epub 2014/01/23. PubMed PMID: 24446654.
[15] Maki KC, McKenney JM, Farmer MV, Reeves MS, Dicklin MR. Indices of insulin sensitivity and secretion from a standard liquid meal test in subjects with type 2 diabetes, impaired or normal fasting glucose. Nutr J 2009;8:22, http://dx.doi.org/10.1186/1475-2891-8-22. Epub 2009/05/30. PubMed PMID: 19476649; PubMed Central PMCID: PMCPMC2694824.
[16] Colomba J, Boudreau V, Lehoux-Dubois C, Desjardins K, Coriati A, Tremblay F, et al. The main mechanism associated with progression of glucose intolerance in older patients with cystic fibrosis is insulin resistance and not reduced insulin secretion capacity. J Cyst Fibros 2019;18:551–6, http://dx.doi.org/10.1016/j.jcf.2019.01.009. Epub 2019/02/04. PubMed PMID: 30711385.
[17] Lavie M, Fisher D, Vilozni D, Forschmidt R, Sarouk I, Kanety H, et al. Glucose intolerance in cystic fibrosis as a determinant of pulmonary function and clinical status. Diabetes Res Clin Pract 2015;110:276–84, http://dx.doi.org/10.1016/j.diabres.2015.10.007. Epub 2015/10/29. PubMed PMID: 26508676.
[18] Colomba J, Rabasa-Lhoret R, Bonhoure A, Bergeron C, Boudreau V, Tremblay F, et al. Dyslipidemia is not associated with the development of glucose intolerance or diabetes in cystic fibrosis. J Cyst Fibros 2020;19:704–11, http://dx.doi.org/10.1016/j.jcf.2020.04.004. Epub 2020/04/25. PubMed PMID: 32327389.
[19] Yip WCY, Sequeira IR, Plank LD, Poppitt SD. Prevalence of Pre-Diabetes across Ethnicities: A Review of Impaired Fasting Glucose (IFG) and Impaired Glucose Tolerance (IGT) for Classification of Dysglycaemia. Nutrients 2017;9, http://dx.doi.org/10.3390/nu9111273. Epub 2017/11/23. PubMed PMID: 29165385; PubMed Central PMCID: PMCPMC5707745.
[20] Ivers NM, Jiang M, Alloo J, Singer A, Ngui D, Casey CG, et al. Diabetes Canada 2018 clinical practice guidelines: Key messages for family physicians caring for patients living with type 2 diabetes. Can Fam Physician 2019;65:14–24. Epub 2019/01/25. PubMed PMID: 30674509; PubMed Central PMCID: PMCPMC6347316.
[21] Abdul-Ghani MA, Tripathy D, DeFronzo RA. Contributions of beta-cell dysfunction and insulin resistance to the pathogenesis of impaired glucose tolerance and impaired fasting glucose. Diabetes Care 2006;29:1130–9, http://dx.doi.org/10.2337/diacare.2951130. Epub 2006/04/29. PubMed PMID: 16644654.
[22] Meyer C, Pimenta W, Woerle HJ, Van Haeften T, Szoke E, Mitrakou A, et al. Different mechanisms for impaired fasting glucose and impaired postprandial glucose tolerance in humans. Diabetes Care 2006;29:1909–14, http://dx.doi.org/10.2337/dc06-0438. Epub 2006/07/29. PubMed PMID: 16873801.
[23] Kahn SE. The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of Type 2 diabetes. Diabetologia 2003;46:3–19, http://dx.doi.org/10.1007/s00125-002-1009-0. Epub 2003/03/15. PubMed PMID: 12637977.
[24] Quon BS, Sykes J, Stanojevic S, Marshall BC, Petren K, Ostrenga J, et al. Clinical characteristics of cystic fibrosis patients prior to lung transplantation: An international comparison between Canada and the United States. Clin Transplant 2018;32:e13188, http://dx.doi.org/10.1111/ctr.13188. Epub 2018/01/03. PubMed PMID: 29292522; PubMed Central PMCID: PMCPMC6120341.