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Novel time-saving OGTT sparing HbA1c-HOMA2 based algorithm for the diagnosis of cystic fibrosis-related diabetes

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ABSTRACT

Aims: The diagnosis of cystic fibrosis-related diabetes (CFRD) faces several challenges. We propose a novel screening algorithm to alleviate the burden of cystic fibrosis (CF).
Methods: Through a retrospective cross-sectional single-centre study, HbA1c and HOMA2 indices were assessed in multiple models as alternative diagnostic tools from OGTT data. We sought to establish specific thresholds for CFRD screening with oral glucose tolerance test (OGTT) as gold standard. We evaluated various straightforward or sequential approaches, in terms of diagnostic accuracy while also quantify the potential reduction in OGTTs through these different methods.
Results: HOMA indices were recovered in 72 patients. We devised a composite index that combines HbA1c and HOMA-B: Diabetes Predicting Index in cystic fibrosis (DIPIc) = $(HbA1c(\%) \times 3.455) - (HOMA\text{-}B(\%) \times 0.020) - 19.294$. This index yields the highest screening accuracy according to receiver-operating characteristics curves. Using a stepwise algorithm that incorporates DIPIc decreases the requirement for annual OGTTs. A CFRD exclusion cutoff less than −1.7445 (sensitivity 98 %), in conjunction with a CFRD diagnostic threshold greater than 0.4543 (specificity 98 %) allows for 71 % OGTT sparing.
Conclusion: The composite index DIPIc is a suitable, less invasive screening method for CFRD, which enables to avoid many OGTTs.

1. Introduction

Cystic fibrosis (CF) is a worldwide autosomal recessive inherited disease. While respiratory disorders remain the primary cause of morbidity and mortality in patients with CF (pwCF), advancements in early diagnosis and management have led to increased life-expectancy over recent years [1]. As a result, the prevalence of longer-term chronic complications, such as cystic fibrosis-related diabetes (CFRD), has risen [2].

CFRD is among common non-respiratory comorbidities in pwCF [2], affecting around 20 % of adolescents and 40–50 % of adults [3]. However, CFRD prevalence varies among countries and across age groups, in particular as a result of different screening approaches [4].

Screening for CFRD usually consists of annual 2-hours 75 g oral glucose tolerance test (2 h-OGTT), starting from the age of 10 years since CFRD has an insidious and silent onset [5]. In the absence of other diagnostic criteria (such as polyuria-polydipsia or HbA1c $\geq$ 6.5 %), OGTTs must be repeated after an initial positive test, in order to confirm CFRD diagnosis. OGTTs data correlate with declining lung function over time and increased risk of microvascular complications and premature death [6].

OGTT-based CFRD screening and diagnosis has three major drawbacks. Firstly, OGTT results exhibit substantial variability overtime. Secondly, OGTT screening has practical limitations and is not desirable to many patients, i.e., risk of reactive hypoglycemia, feeling unwell with the glucose load, and fasting requirement. Based on surveys, only 24 % to 67 % of the yearly recommended OGTTs are carried out in the real world [7–10]. Lastly, glycemic thresholds were originally established from cutoffs defining microvascular complications risk in type 2 diabetes mellitus (T2DM), and as a result may not address the specific health issues of pwCFRD, whose primary concerns are nutritional and respiratory problems [11]. Hence, there is considerable heterogeneity across centers regarding the first-line CFRD-screening test and the development of alternative screening method is an important research priority [7,12,13].

HbA1c has been proposed as an alternative CFRD diagnostic tool to

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the OGTT. Applying unadjusted thresholds of the American Diabetes Association (ADA) for HbA1c [14] entails poor sensitivity (Sn) and specificity (Sp) in diagnosing CFRD [15]. A retrospective study of 429 patients suggested that a lower HbA1c threshold (5.8 %) could rule out CFRD, with 93.8 % Sn, while saving 51 % of OGTTs. HbA1c could be a useful pre-screening tool, reducing the need for performing OGTTs [16]. Both adults and children with HbA1c > 6 % had increased risk for incident CFRD and reduced odds of weight gain [17]. Nevertheless, the optimal thresholds and validity of HbA1c for CFRD diagnosis are still debated [18,19].

Continuous glucose monitoring (CGM) is a useful means for CFRD management and identification of high-risk situations for functional decline. Beyond that, numerous authors have emphasized the significance of elevated glucose spikes exceeding 200 mg/dL in the diagnosis of CFRD [10]. Moreover, the importance of the duration exceeding specified glucose thresholds was highlighted. Scully et al. showed that maintaining blood glucose levels above 140 mg/dL for more than 17.5 % of the time or exceeding 180 mg/dL for more than 3.4 % of the time is effective in detecting CFRD compared to OGTT [20]. Consequently, various diagnostic criteria for CGM are currently under investigation, including the percentage of time spent with glucose levels exceeding 140 mg/dL, the area under the curve above 140 mg/dL, and the count of hyperglycemic episodes surpassing 200 mg/dL, particularly as they relate to clinical deterioration. However, as of now, there is insufficient data to establish dependable diagnostic CGM cutoffs for CFRD diagnosis that would help predicting functional decline in pwCF [5,10,21].

Homeostasis Model Assessment (HOMA2) is a widely-used noninvasive means to assess Beta-cell function (BCF) and insulin sensitivity (IS) in individuals with normal glucose tolerance, impaired glucose tolerance (IGT), and T2DM patients [22]. The underlying BCF adjusted for prevailing IS (HOMA-[B × S]), is the product between BCF (HOMA-B) and IS (HOMA-S).

HOMA2 was proposed as screening tool of CFRD in both pediatric and adult populations [23,24]. A two-step approach with HOMA-B < 100 % as threshold was proposed to identify patients requiring OGTT, with Sn 88–91 %; Sp 45–47 %; NPV 89 % in children, and Sn 88 %; Sp 18 %; NPV 90 % adults, respectively) [23,24]. However, these data were not confirmed by Boudreau et al. who showed a Sn of 69 % with a HOMA-B threshold set at 100 % [25].

Based on previous studies [23–28], it was hypothesized that HOMA2 indices could be applied to evaluate glucose homeostasis in CF either alone or in combination. The added value of HOMA-derived BCF indices that take account of individual IS in the diagnosis of CFRD has not yet been evaluated.

We aimed to determine the correlation between HbA1c, HOMA2-BCF and IS, and 2 h-OGTT glucose in adults with CF and to establish effective diagnostic thresholds for HbA1c and HOMA2 indices. We also assessed whether these noninvasive indices best perform when applied individually, either sequentially, or jointly. We then combined these HbA1c and HOMA-B data into a simplified index (Diabetes Predicting Index in CF (DIPIc) with improved diagnostic performance for diagnosing CFRD.

2. Materials and methods

This retrospective study used clinical data extracted between 1996 and 2023 from the electronic medical record from all adult patients with CF followed in the CF reference center of the Cliniques universitaires Saint-Luc in Brussels. All adult patients had a diagnosis of CF based on Farrell's definition: 1) clinical presentation of CF, and 2) sweat chloride testing > 60 mmol/L or sweat chloride testing between 30 and 59 mmol/l + 2 CF-causing CFTR mutation or sweat chloride testing between 30 and 59 mmol/L and CFTR dysfunction showed by CFTR physiologic testing [29]. We considered only the latest OGTT-HOMA. Diabetes was defined according to ADA and the international society for pediatric and adolescent diabetes (ISPAD) criteria. To be included in the diagnostic algorithm, pwCF had to meet the following criteria: having undergone a standardized 75 g 2 h OGTT, with HOMA2 testing from fasting samples data of the OGTT. The HbA1c value closest to the time at which the OGTT was performed, within 2 months, was considered. Exclusion criteria were: ongoing glucose-lowering drug(s), pregnancy, cirrhosis, history of transplantation, recent corticotherapy (oral or intravenous at least one month prior to OGTT-HOMA), or respiratory exacerbation at the time of OGTT-HOMA, the latter defined as intravenous antibiotherapy required for 4 of the following 12 signs or symptoms: sputum changes; new or increased haemoptysis; increased cough; increased dyspnea; malaise, fatigue or lethargy; fever (≥38 °C); anorexia or weight loss; sinus pain or tenderness; change in sinus drainage; change in physical examination of the chest; decrease in lung function of 10 % or more from a previously recorded value; or x-ray changes indicative of a lung infection [30]. Demographic, clinical, and biological characteristics were extracted from the medical file of the patients. Variables collected included: demographic features (age, gender), CFTR channel mutation type, HbA1c (%), 2 h-OGTT fasting plasma glucose and serum insulin, forced expiratory volume in 1 s (FEV_1), FEV_1/Forced vital capacity (FVC), weight and body mass index (BMI).

HOMA2 indices (HOMA-B, HOMA-S, HOMA-[B × S]) were calculated from fasting glucose (mg/dL) and insulinemia (pmol/L) both from the OGTT data. We used the HOMA2 calculator software released by the Radcliffe department of Oxford.

HOMA2 is a mathematical model that evaluates the feedback between glucose and insulin in the body. It uses sets of equations to assess how impaired BCF and IS affect glucose homeostasis. The model establishes an equilibrium point for plasma glucose, insulin, C-peptide, and proinsulin in the fasting state to replicate physiological reality in a reference individual. In HOMA, BCF (%B) and IS (%S) are assigned a normal value of 100 %. To account for individual IS, insulin secretion (HOMA-B) is plotted as a function of IS (HOMA-S), represented as a hyperbolic product area (HOMA-[B × S]) with a standardized normal value of 100 % (corresponding to 10,000 $\%^2$). HOMA-[B × S] represents the underlying residual beta-cell function adjusted for individual IS. Individual BCF loss rate (%.$year^{-1}$) was calculated as the ratio between the hyperbolic product [B × S] loss (100 %-[B × S] (%)) and the age (year) at the time of HOMA modeling. A negative loss rate was considered 0 %.$year^{-1}$.

Glucose assays were conducted on Olympus AU® between 2008 and 2014 and on Roche Cobas® 702 from 2014 onwards. Insulin was measured before 2008 using RIA and thereafter on Diasorin (Liaison® between 2008 and 2014; Liaison® XL since 2014). HbA1c was measured on Tosoh HPLC® from 2008 to 2014 and on Tosoh G8® since 2014. Performance of Roche Cobas® 702 was established against Roche Cobas® 501: slope = 1.003, y-intercept = 0, correlation coefficient = 0.981; coefficient of variability: 0.5–0.7 %. Performance of Diasorin Liaison® XL was established against a reference CLIA method on serum samples: slope = 1.012, y-intercept = -0.46, correlation coefficient = 0.996; coefficient of variability: 1.87–4.95 %. Performance of Tosoh G8 was established against HLC-723G7: slope = 0.9, y-intercept = -0.46, correlation coefficient = 0.996; coefficient of variability: 0.2–0.6 %.

The study protocol was approved by the local ethical committee (2020/23JUI/337).

Statistical analyses were performed with IBM SPSS Statistics® version 27. Numerical variables are expressed as means (±SD) if normally distributed or medians (IQR) for non-normal distribution. Categorical variables are expressed as rates and absolute numbers. Inference tests were performed according to variable type, sample size and, if applicable, to variables distribution. Normality was assessed by Shapiro-Wilk's and Kolmogorov-Smirnov tests. In the event of a mismatch between these two, a non-parametric test was chosen based on visual assessment of Q-Q plots and histograms. To assess differences between groups (shown as boxplots), a Mann-Whitney test was used for non-normal distribution, and a Student's *t* test for normal distribution. Chi-square or Fisher exact tests were used in case of categorical variables.

Correlation between HOMA2 indices, HbA1c, 2 h-OGTT glucose and clinical characteristics were assessed using Pearson test for normal data and Spearman test for non-parametric data. Performances tests were evaluated using receiver-operating-characteristics (ROC) curves and Bayes' theorem nomogram. The initial aim was to establish CFRD diagnostic and exclusion thresholds based on HbA1c and HOMA B-cell function (HOMA B and HOMA-B × S). The idea was to triage sort patients according to these two criteria in order to reduce the need for OGTTs. As it was not feasible to derive diagnostic power from this sequential algorithm, we opted for combining HbA1c and HOMA indices into a single metric for clinical use whose discriminatory performance would be tested by ROC curve method. To generate the DIPIc index, we performed a logistic regression using the backward stepwise method, the usual method for obtaining the most predictive, not causal, variables. Thus, we derived DIPIc by running a stepwise backward logistic regression with a cut-off significance level of 0.10 to identify the best model to predict the probability of having CFRD. The variables introduced into the model were HbA1c, HOMA-S, HOMA-B, HOMA-[B × S], HOMA-IR and the HOMA-[B × S] loss rate.

3. Results

A total of 130 adults pwCF were reviewed: 52 with CFRD (pwCFRD) based on OGTT results and 78 without (pw/oCFRD). HOMA indices and OGTT results were available in 36 pwCFRD and in 56 pw/oCFRD. Among pwCFRD, 2 were excluded due to cirrhosis, 1 had a liver transplant, and 8 patients were < 18 years. Among pw/oCFRD, 8 were excluded due to cirrhosis and 1 due to lack of HbA1c in the EMR. The observation period runs from 1996 to 2023. Eighty-nine percent of HOMAs were performed between 2014 and 2023, 5.5 % between 2008 and 2014, and the remaining 5.5 % between 1996 and 2008. It results in an analyzable cohort of 72 patients (25 pwCFRD and 47 pw/oCFRD, i.e., a 35 % CFRD prevalence).

Age was similar between pwCFRD and pw/oCFRD. Their characteristics are described in Table 1 and illustrated in Fig. 1.

Most HOMA indices and derived data significantly correlated with 2 h-OGTT glucose. HbA1c positively correlated with 2 h-OGTT glucose (n = 70, ρ = 0.663; p < 0.001) and inversely with HOMA-[B × S] (ρ= − 0.331; p = 0.005). HOMA-[B × S] inversely correlated with 2 h-OGTT glucose (n = 70, ρ= − 0.339; p = 0.004). HOMA-[B × S] loss rate positively correlated with 2 h-OGTT glucose (n = 70, ρ = 0.253; p = 0.035) and last available HbA1c (ρ = 0.253; p = 0.034).

HOMA-S, HOMA-B, HOMA-IR, HOMA-[B × S], HOMA-[B × S] loss rate, and HbA1c were subjected to scrutiny as predictor variables within a binary logistic regression model, with backward Wald's stepwise approach to forecast presence or absence of CFRD. The ensuing mathematical expression was derived, yielding an estimated Nagelkerke's R-squared value of 0.618:

DIPIc: (HbA1c (%) × 3.455) - (HOMA-B (%) × 0.020) − 19.294

DIPIc correlated with 2 h-OGTT glucose (ρ = 0.656; p < 0.001). HbA1c, HOMA-B and DIPIc significantly correlated, albeit modestly, with main clinical features of interest in CF (Table 2).

The ROC curves for HbA1c, HOMA-B, HOMA-[B × S] and DIPIc are shown on Fig. 2. ROC AUC for HbA1c was 0.895 (95 % confidence interval (CI) 0.818–0.972; p < 0.0001), with inflection point 6 %, Sn 79 % and Sp 87 %. This threshold would underdiagnose 6 patients and ascribe 6 patients as CFRD despite normal OGTT. Bayes' theorem nomogram (threshold: 6 %) calculates a posterior probability of 73 % in case of positive test and a posterior probability of 13 % in case of negative test. In a stepwise approach with 5.45 % (Sn 96 %) as exclusion threshold, 6.45 % (Sp 98 %) as diagnostic threshold, and the remaining patients undergoing OGTT, 36 % of OGTT would be redundant and thus may have been spared (1 false positive and 1 false negative, respectively).

ROC AUC for DIPIc was significantly larger than that of HbA1c; 0.918 (95 % CI 0.846–0.990; p < 0.001), with inflection point −0.3253, Sn 84 %, and Sp 91.5 %. This threshold would underdiagnose 4 patients and ascribe 4 patients as CFRD despite normal OGTT. A sequential approach with −1.7445 (Sn 96 %) as exclusion threshold and 0.4543 (Sp 98 %) as confirmation threshold would spare 71 % of OGTT (1 false negative and 1 false positive, respectively).

ROC AUC for HOMA-B was 0.743 (95 % CI 0.616–0.870; p = 0.001). The inflection point was 85.15 %, Sn 68 % and Sp 75 %. This threshold would underdiagnose 8 patients and would ascribe 12 patients as CFRD despite normal OGTT. Embedded in a 3 steps sequential algorithm with HbA1c, it would allow the clinician not to resort to OGTT in 58 % of cases with 1 false negative and 1 false positive (HOMA-B < 51.15 % (Sn: 96 %) or > 144.1 % (Sp: 98 %) respectively as thresholds to confirm or rule out diagnosis of CFRD).

ROC AUC for HOMA-[B × S] was 0.683 (95 % CI 0.543–0.822; p = 0.011). The inflection point was 85.8 % with a Sn of 56 % and a Sp of 77 %. This threshold would underdiagnose 11 patients and would ascribe 11 patients as CFRD despite normal OGTT.

Table 3 summarizes different approaches (straightforward method or stepwise algorithm) with their respective Sn, Sp, positive likelihood ratio (+LR), negative likelihood ratio (-LR) and posttest probability if applicable.

Ten patients (21 %) among those without diabetes had a 2 h-OGTT glucose level between 140 and 199 mg/dl. We have no data on 60 min OGTT glucose levels however.

The data were not statistically relevant among patients without diabetes. Using HbA1c or HOMA indices to distinguish NGT from IGT performed either poorly (ROC HbA1c AUC = 0.635 (95 % CI 0.454–0.817; p = 0.194)) or proved clinically useless (ROC HOMA-B

Table 1
Clinical and biological characteristics according to CFRD status at the time of the OGTT.

	pw/oCFRD (n = 47)	pwCFRD (n = 25)	*p-value*
Age (y)	25 (12)	27 (18)	*0.892*
Women (as per birth-assigned sex) (%) (n)	42 (20)	40 (10)	*0.871*
Minimal CFTR channel function (%) (n)	81 (38)	92 (23)	*0.309*
Exocrine pancreatic insufficiency (%) (n)	85 (40)	100 (25)	*0.088*
HEMT (%) (n)	25 (12)	12 (3)	*0.196*
Weight (kg)	61.7 (22.8)	57.6 (18.5)	*0.246*
BMI (kg/m^2)	22.9 (6.2)	21.8 (5.45)	*0.158*
HOMA-B (%)	102.70 (52.2)	71.70 (52.9)	*<0.001*
HOMA-S (%)	92.8 (61.7)	88.1 (118.5)	*0.981*
HOMA-IR	1.1 (0.7)	1.2 (1)	*0.813*
HOMA-B × S (%)	97.0 (33.5)	85.7 (59.9)	*0.011*
HOMA-[B × S] loss rate (%.y^{-1})	0.11 (0.53)	0.71 (1.49)	*0.031*
HbA1c (%)	5.5 ± 0.4	6.5 ± 0.6	*<0.001*
2 h-OGTT glucose (mg/dl)	110 (53)	218 (45)	*<0.001*
DIPIc	−2.3865 (2.66)	1.0850 (2.72)	*<0.001*
FH (%) (n); 2 h-OGTT > 200 mg/dl (%) (n)	–	20 (5); 84 (21)	–
IFG and IGT according to OGTT (%) (n)	4 (2); 21 (10)	32 (8); 8 (2)	–
FEV_1 (% predicted value)	85.2 ± 23.3	77.2 ± 24.2	*0.188*
FEV_1/FVC (%)	72.6 ± 13.9	71.3 ± 11.6	*0.708*

Abbreviations: BMI, body mass index; CFRD, cystic fibrosis-related diabetes; CFTR, cystic fibrosis transmembrane regulator; DM, diabetes mellitus; DIPIc, Diabetes predicting index in cystic fibrosis; FEV_1, forced expiratory volume in one second; FH, fasting hyperglycaemia; FVC, forced vital capacity; HEMT, high effective modulator therapy; HOMA, homeostatic model assessment; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; kg, kilograms; m, meter; n, number; OGTT, oral glucose tolerance test; pwCFRD, patients with cystic fibrosis-related diabetes; pw/oCFRD, patients without cystic fibrosis-related diabetes; y, year(s).
Results are presented as mean ± SD or median (IQR) and rates (absolute number); p value: statistical significance (<0.05 considered statistically significant).

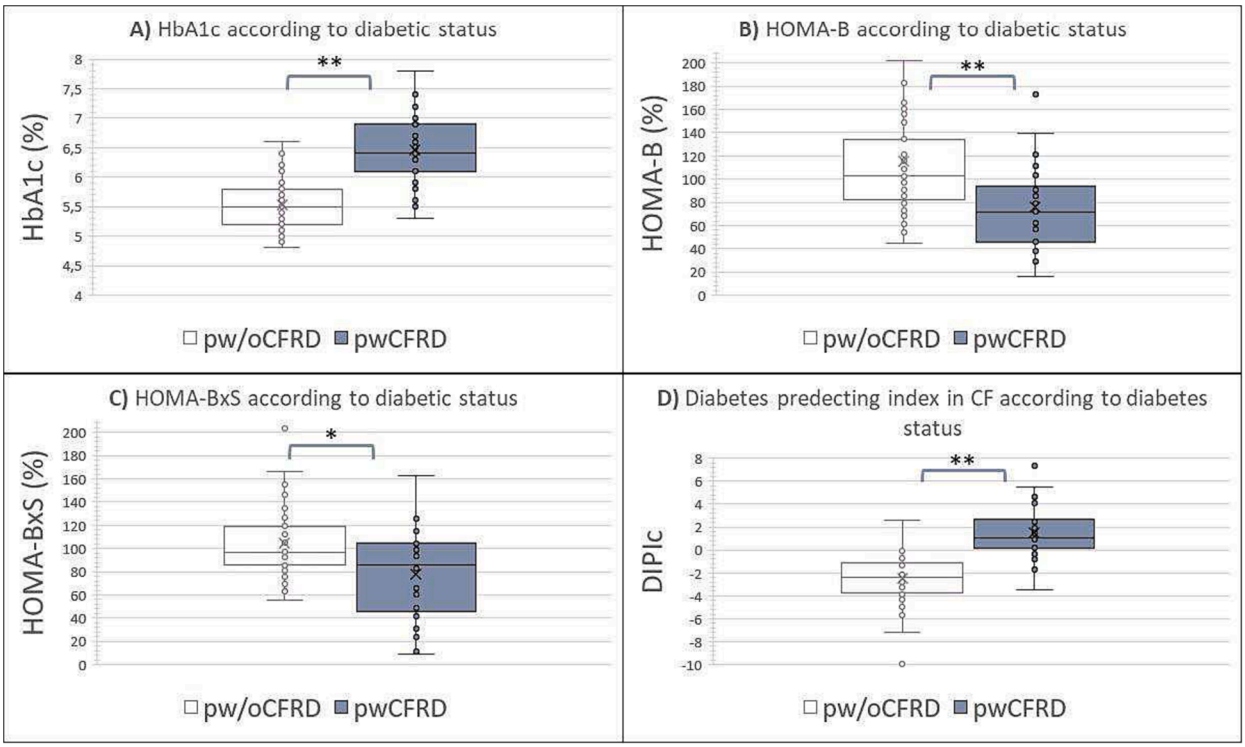

Fig. 1. Boxplots of pw/oCFRD and pwCFRD for the variables HbA1c, HOMA-B, HOMA-B × S and DIPIc. A) Box-and-whiskers plot of HbA1c of pw/oCFRD (white) and pwCFRD (black); the top and bottom of the boxes indicate the 25th and 75th percentile, the midline in the box is the median and the "x" sign represents the mean. The whiskers represent the 5th and 95th percentiles. B) Box-and-whiskers plot of HOMA-B of pw/oCFRD (white) and pwCFRD (black); the top and bottom of the boxes indicate the 25th and 75th percentile, the midline in the box is the median and the "x" sign represents the mean. The whiskers represent the 5th and 95th percentiles. C) Box-and-whiskers plot of HOMA-B × S of pw/oCFRD (white) and pwCFRD (black); the top and bottom of the boxes indicate the 25th and 75th percentile, the midline in the box is the median and the "x" sign represents the mean. The whiskers represent the 5th and 95th percentiles. D) Box-and-whiskers plot of DIPIc of pw/oCFRD (white) and pwCFRD (black); the top and bottom of the boxes indicate the 25th and 75th percentile, the midline in the box is the median and the "x" sign represents the mean. The whiskers represent the 5th and 95th percentiles. Abbreviations: CFRD, cystic fibrosis-related diabetes; DIPIc, Diabetes predicting index in cystic fibrosis; HOMA, homeostatic model assessment; OGTT, oral glucose tolerance test. *: $p < 0.05$; **: $p < 0.001$.

Table 2
Correlations between HOMA indices − 2 h-OGTT result, HbA1c and clinical features.

	HbA1c	HOMA-B	HOMA-S	HOMA-IR	HOMA-B × S	HOMA-B × S loss rate	DIPIc
2 h-OGTT glucose	0.663***	−0.311**	−0.047	0.061	−0.339**	0.253*	0.656***
HbA1c	–	−0.401***	0.019	−0.012	−0.331**	0.251*	–
Weight	−0.225 (p = 0.059)	0.336**	−0.308**	0.281*	−0.180	−0.158	−0.272*
BMI	−0.201 (p = 0.093)	0.313**	−0.325**	0.297*	−0.127	0.096	−0.256*
FEV_1	−0.377***	0.02	−0.025	0.038	−0.103	0.166	−0.277*
FEV_1/FVC	−0.342**	0.01	0.040	−0.033	−0.053	0.106	−0.219 (p = 0.075)

Abbreviations: BMI, body mass index; DIPIc, Diabetes predicting index in cystic fibrosis; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; HOMA, homeostatic model assessment; OGTT, oral glucose tolerance test.
Results are expressed as r = Pearson's coefficient or ρ = Spearman's coefficient.
* $p \leq 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$.

AUC = 0.478 [95 % CI 0.305–0.835; p = 0.835] and ROC HOMA-B × S AUC = 0.495 [95 % CI 0.294–0.695; p = 0.959]). Furthermore, multivariate analysis did not allow building a reliable predictive model based on the HOMA and HbA1c variables. Firstly, the formula generated by the model was complex with multiple variables. Secondly, estimated Nagelkerke's R-squared value yielded only 0.271. Finally, the IGT-predicting index had an AUC of 0.786 (95 % CI 0.644–0.929; p = 0.006) deemed unsatisfactory.

The use of HbA1c or HOMA indices to distinguish NGT from AGT (abnormal glucose tolerance: 2 h-OGTT > 140 mg/dl) was either reliable (ROC HbA1c AUC = 0.826 (95 % CI 0.732–0.921; p < 0.001)) or poor (ROC HOMA-B AUC = 0.665 (95 % CI 0.540–0.790; p = 0.016) and ROC HOMA-B × S AUC = 0.628 (95 % CI 0.497–0.758; p = 0.062).

Using the same methodology to create a metric such as DIPIc for this population in order to distinguish NGT from AGT only came up with an HbA1c-based equation (AGT = HbA1c*2.501–14.586), whereas test's performances were similar to those of isolated HbA1c: AUC 0.826 (95 % CI 0.732–0.921; p < 0.001). Optimal cut off for diagnosis was 1.5455 (Sp: 97 %). Optimal cut off for exclusion of AGT was −1.4558 (Sn: 97 %).

4. Discussion

CFRD is associated with declining pulmonary function, precarious nutritional status, and poor prognosis. Early diagnosis and efficient management are crucial for improving nutritional and pulmonary status, reducing pulmonary exacerbations, and enhancing survival [2,31,32]. Microvascular complications can arise in pwCFRD, due to

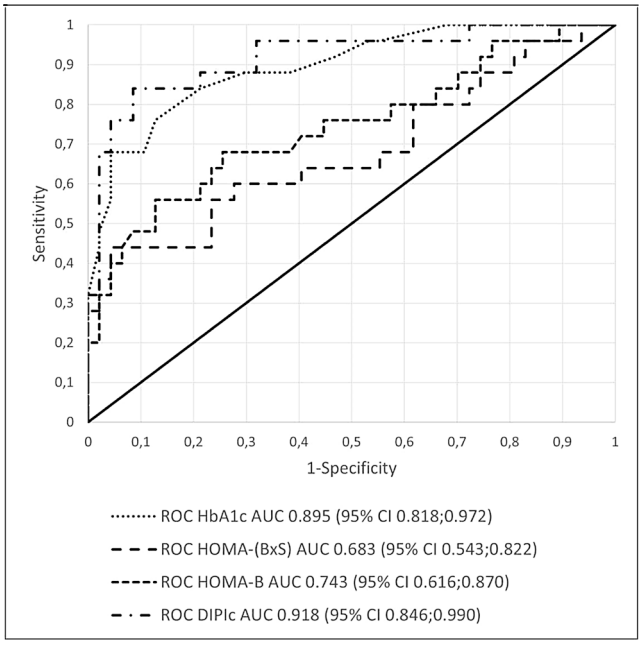

Fig. 2. ROC curves for evaluation of the diagnostic performances of HbA1c, HOMA-B, HOMA-B × S and DIPIc for CFRD. Abbreviations: AUC, area under the curve; CI, confidence interval; ROC, receiver-operating-characteristics.

improved life expectancy and longer glucose exposure. A parallel emergence of cardiovascular risk factors (obesity, dyslipidaemia and hypertension) is also forecast, albeit rarely reported [5]. Longer life expectancy means that a growing number of OGTT screenings for CFRD need be carried out for a given subject, which is time-consuming, unpractical, and potentially costly. HbA1c may have the potential to be employed alongside CGM or HOMA indices to reduce the necessity for OGTT usage [10,33]. Novel simpler screening methods based on easily available data are needed, as regular screening tools and to better predict non-glucose-related CF comorbidities [13].

This study identified a simple method based on indices derived from HOMA and HbA1c to exclude or establish the diagnosis of CFRD. DIPIc performed better than other alternative predictors (HbA1c, HOMA-B, HOMA-[B × S]) to diagnose CFRD. It was also the most effective, used in a 2 steps sequential approach, at reducing the number of OGTTs, thereby helping to ease the burden on pwCF, as compared to other stepwise schemes, such as algorithms based on two (OGTT if HbA1c $\geq$ 5.45 $<$ 6.45 %) or three inputs (OGTT if HbA1c $\geq$ 5.45 $<$ 6.45 % and HOMA-B $\geq$ 51 $<$ 144 % or OGTT if HbA1c $\geq$ 5.45 $<$ 6.45 % and HOMA-[B × S] $\geq$ 62 $<$ 132 %.

DIPIc's cutoffs to rule out and diagnose CFRD are −1.7445 (Sn 96 %) and 0.4543 (Sp 98 %), respectively. Fig. 3 shows that using DIPIc would diagnose 18 patients (25 %) with CFRD and rule out the condition in 33 more (46 %) without resorting to OGTT, leaving 21 patients (29 %) to undergo confirmatory OGTT, i.e., a relative OGTT-sparing of 71 %. As DIPIc outperforms previous diagnostic methods, it thus provides a simple, time- and OGTT-sparing noninvasive means to screen for CFRD. Our results show HbA1c similar cutoffs for opting out of OGTT and OGTT-sparing figures akin to those previously reported, suggesting that our findings are applicable to other settings [19,34]. If the OGTT shows

Table 3
Tests' performances in diagnosing CFRD.

Screening test	Sensitivity (%)	Specificity (%)	Negative likelihood ratio (−LR)	Positive likelihood ratio (+LR)	Post probability if positive test (%)	Post probability if negative test (%)	FN; FP; % OGTT spared (n)
Thresholds for diagnosis based on ROC curve's inflection points (one step strategy)							
HbA1c > 6 %	76	87	0.28	5.95	76	13	FN = 6 FP = 6
DIPIc > −0.3253	84	91	0.17	9.87	84	8	FN = 4 FP = 4
HOMA-B < 85.15 %	68	74	0.43	2.66	59	19	FN = 8 FP = 12
HOMA-[B × S] < 85.8 %	56	77	0.57	2.39	56	23	FN = 11 FP = 11
Stepwise approaches (2 or 3 steps scheme)							
2 steps scheme* HbA1c < 5.45 or > 6.45 %	5.45 = 96 6.45 = 48	5.45 = 47 6.45 = 98	5.45 = 0.08	6.45 = 22.6	–	–	FN = 1; FP = 1; 50 (36)
2 steps scheme** DIPIc < -1.7445 or > 0.4543	−1.7445 = 96 0.4543 = 68	−1.7445 = 68 0.4543 = 98	−1.7445 = 0.06	0.4543 = 32	–	–	FN = 1; FP = 1; 71 (51)
3 steps scheme*** HbA1c (<5.45 or > 6.45 %) followed by HOMA-B (<51.15 or > 144.1 %)	HbA1c 5.45 = 96 HOMA-B 51.15 = 96	HbA1c 6.45 = 98 HOMA-B 144.1 = 98	HbA1c 5.45 = 0.08 HOMA-B 51.15 = 0.17	HbA1c 6.45 = 22.6 HOMA-B 144.1 = 15.04	–	–	FN = 1: FP = 1; 58 (42)
3 steps scheme**** HbA1c (<5.45 or > 6.45 %) + HOMA-[B × S] (<61.67 or > 132.14 %)	HbA1c 5.45 = 96 HOMA-[B × S] 61.67 = 96	HbA1c 6.45 = 98 HOMA-[B × S] 132.14 = 98	HbA1c 5.45 = 0.08 HOMA-[B × S] 61.67 = 0.235	HbA1c 6.45 = 22.6 HOMA-[B × S] 132.14 = 16.92	–	–	FN = 1; FP = 1; 54 (38)

Abbreviations: FN, false negative; FP, false positive; HOMA, homeostasis model assessment; OGTT, oral glucose tolerance test; Sn, sensitivity; Sp, specificity.
*2 steps scheme n°1: CFRD ruled out if HbA1c < 5.45 %; CFRD confirmed if HbA1c > 6.45 %. For patients who do not meet any of these criteria, an OGTT is indicated.
**2 steps scheme n°2: Exclusion of CFRD if DIPIc is below −1.7445 and confirmation of CFRD if it exceeds 0.4543. Patients who do not fulfill any of these conditions should undergo an OGTT.
***3 steps scheme n°1: Exclusion of CFRD if the HbA1c level falls below 5.45 % and confirmation of CFRD when HbA1c exceeds 6.45 %. In cases where neither of these criteria is satisfied, the HOMA-B index should be computed. CFRD can be excluded if the HOMA-B index surpasses 144.1 %, and CFRD is confirmed if it falls below 51.15 %. For patients who do not meet any of these criteria, an OGTT is indicated.
****3 steps scheme n°2: Exclusion of CFRD if the HbA1c level is below 5.45 % and confirmation of CFRD if it exceeds 6.45 %. In cases where neither of these criteria is met, HOMA-[B × S] should be calculated. CFRD can be excluded if the HOMA-[B × S] value surpasses 132.1396 %, and CFRD is confirmed if it falls below 61.67 %. Patients who do not fulfill any of these conditions should proceed to an OGTT.

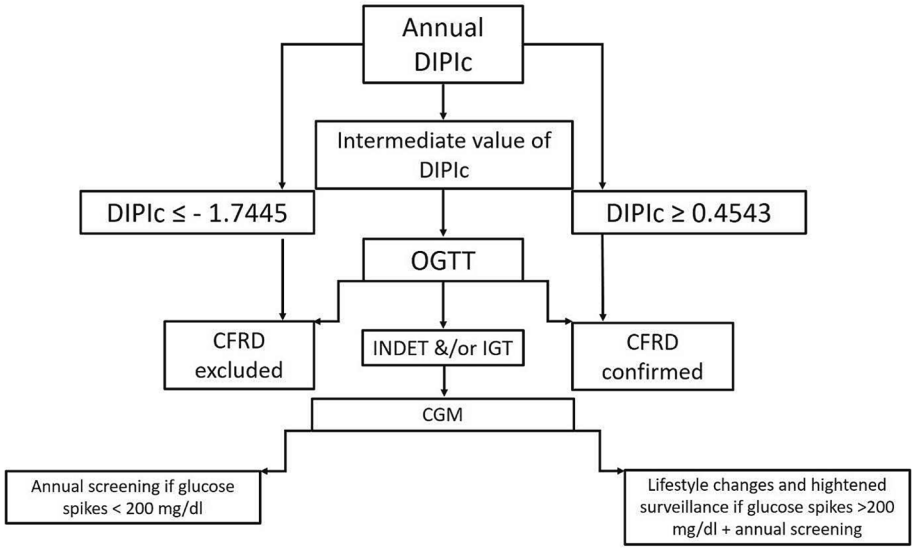

Fig. 3. One Proposed Screening algorithm for CFRD incorporating DIPIc. Abbreviations: CFRD, cystic fibrosis-related diabetes; CGM, continuous glucose monitoring; DIPI(c), Diabetes predicting index in cystic fibrosis; IGT, impaired glucose tolerance; INDET, indeterminate glycemia; OGTT, oral glucose tolerance test. 2 steps algorithm: Exclusion of CFRD if DIPIc is below or equal to −1.7445 and confirmation of CFRD if it exceeds or equal to 0.4543. Patients who do not fulfill any of these conditions should undergo an OGTT with current thresholds. In case of INDET &/or IGT, CGM could be an option to detect patient at risk for clinical decline. If glucose excursions exceed 200 mg/dl, we suggest sporadic lifestyle & dietary measures including physical activities, tighter surveillance for respiratory decline and possibly sporadic use of insulin or repaglinide if dietary indulgences/excesses were committed.

indeterminate glycaemia (1 h-OGTT > 200 mg/dl) or IGT, we suggest as others [1] to initiate a CGM and management accordingly. However, CGM duration is yet to be determined.

HOMA-B is a suitable means for CFRD screening if combined to HbA1c. It performs better than HOMA-[B × S], which was anticipated, given that [B × S] is primarily designed to adjust secretion in the presence of insulin resistance, which is rarely present in CF. The present cohort showed relatively preserved IS, comparable between groups, which is probably why decreased HOMA-B unadjusted to IS predicted CFRD. A HOMA-B value > 100 % was exhibited high Sn and negative predictive value (NPV) to rule out CFRD [23,24]. Using a similar cutoff of 100 %, we did not find such diagnostic performance (Sn 76 %; Sp 50 %, NPV 80 %).

In isolation, HbA1c and HOMA-assessed BCF are insufficient to rule out CFRD. A stepwise approach incorporating HbA1c and/or HOMA2 indices, makes it possible to space out OGTTs with low odds of misdiagnosis.

The drawbacks associated with OGTT in individuals with CF include the duration of the test, the requirement for fasting, the potential risk of hypoglycemia, and the need for repeated sampling. While DIPIc addresses several of these limitations, it still necessitates obtaining a fasting blood sample. Notably, a recent survey revealed that 18 % of participants identified fasting as a significant barrier to OGTT, with 72 % ranking it as the second most substantial shortcoming [7].

Using CGM and GMI could offer an additional option for screening and diagnosis of CFRD, but it will also require in-depth validation to identify which CGM metrics best predict CFRD and CF-specific outcomes [20,21]. There is as yet no data combining longitudinal HOMA indices, including BCF decline (as measures by HOMA-[B × S] loss rate) with GMI and other CGM metrics.

Our study has several limitations. Firstly, unlike HbA1c, which is validated in some diabetes, DIPIc is not validated in any type of diabetes. It requires further external validation. Secondly, assay methods were different across time and due to archiving policies, it is not possible for us to retrieve precisely the methods used before 2008. Nevertheless, the assay methods used were the same in 89 % of patients, and data from only 5.5 % of patients concerned methods used prior to 2008. Thirdly, we based DIPIc on validated OGTT cutoffs for T1 and 2DM, which are possibly not adapted to CFRD. Additionally, while DIPIc could possibly distinguish diabetes from NGT, it cannot detect intermediate situations that 1 h-OGTT level or CGM could highlight. Moreover, we arbitrarily assigned the patients a [B × S] function of 100 % at birth to estimate BCF and cannot ascertain whether a nil [B × S] value *de facto* equates with an endocrine pancreatic function that is immutable. As a result, [B × S] loss rate may have been underestimated in some patients. In addition, HOMA indices must ideally be calculated from the mean (or median) of triplicate pairs of fasting glucose-insulin to decrease analytic variation and impact of pulsatile insulin secretion. Furthermore, a little but not significant difference was observed between the groups in relation to ongoing CFTR modulator therapy during the reviewed OGTTs. Yet, if we considered the penultimate HOMA indices (before CFTR modulators initiation) among patients on CFTR modulator therapy as the time of their last OGTT, the differences in terms of HOMA indices between groups remained unaffected. Besides, a recent study showed no improvement in HOMA indices after initiation of treatment with CFTR modulators [28]. Finally, this study had a retrospective and cross-sectional design. It is clear that the mathematical expression of DIPIc depends solely on our cohort, and broader-scale validation is required. To delve deeper into the relationships between HbA1c, DIPIc, and HOMA-B with lung function and nutritional status, prospective longitudinal studies are warranted.

In conclusion, DIPIc emerges as the noninvasive test with the best performance in diagnosing or ruling out CFRD, both reducing the need for closely spaced OGTTs and the overall burden of CF. For now, OGTT remains the gold standard for CFRD diagnosis despite its limitations. We propose a simple index combining HbA1c with HOMA-B that will need validation in larger longitudinal studies.

CRediT authorship contribution statement

Fabian Lurquin: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Conceptualization. **Sophie Gohy:** Writing – review & editing, Resources. **Michel P. Hermans:** Writing – review & editing, Validation, Supervision. **Vanessa Preumont:** Writing – review & editing, Validation, Supervision, Resources.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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