ELSEVIER
Journal of Cystic Fibrosis xx (2017) xxx – xxx
Journal of Cystic Fibrosis
www.elsevier.com/locate/jcf

Original Article

Glucose trajectories in cystic fibrosis and their association with pulmonary function

Quitterie Reynaud [a,b,*], Muriel Rabilloud [c,d,e], Sylvain Roche [c,d,e], Stéphanie Poupon-Bourdy [b,f], Jean Iwaz [c,d,e], Raphaële Nove-Josserand [a,b], Emilie Blond [g,h], Martine Laville [i,j], Cathy Llerena [k], Sébastien Quetant [l], Philippe Reix [m], Sandrine Touzet [b,f], Isabelle Durieu [a,b]

[a] *Centre de Référence de la Mucoviscidose Adultes, Service de Médecine Interne, Hospices Civils de Lyon, F-69495 Pierre Bénite, France*
[b] *Université de Lyon, Équipe d'Accueil Health Services and Performance Research (HESPER) 7425, F-69003 Lyon, France*
[c] *Service de Biostatistique-Bioinformatique, Hospices Civils de Lyon, F-69003 Lyon, France*
[d] *Université Lyon 1, F-69100 Villeurbanne, France*
[e] *CNRS UMR 5558, Laboratoire de Biométrie et Biologie Évolutive, Équipe Biostatistique-Santé, F-69100 Villeurbanne, France*
[f] *Pôle IMER, Hospices Civils de Lyon, F-69003 Lyon, France*
[g] *Service de Biochimie et Biologie Moléculaire, Hospices Civils de Lyon, F-69495 Pierre Bénite, France*
[h] *Université de Lyon, INSERM U1060, Laboratoire CarMen, F-69003 Lyon, France*
[i] *Service d'Endocrinologie, Diabétologie et Nutrition, Hospices Civils de Lyon, F-69495 Pierre Bénite, France*
[j] *Université de Lyon, Fédération Hospitalo-Universitaire DO-IT, F-69003 Lyon, France*
[k] *Centre de ressources et de compétences de la mucoviscidose, Département de Pédiatrie, CHU de Grenoble, F-38100 Grenoble, France*
[l] *Centre de ressources et de compétences de la mucoviscidose, Clinique Universitaire de Pneumologie, Pôle Thorax et Vaisseaux, CHU Grenoble, F-39700 La Tronche, France*
[m] *Centre de Référence pédiatrique de la Mucoviscidose, Service de Pneumologie pédiatrique, Hôpital Femme-Mère-Enfant, Hospices Civils de Lyon, F-69500 Bron, France*

Received 26 December 2016; revised 11 August 2017; accepted 26 September 2017
Available online xxxx

Abstract

Background: The prevalence of cystic fibrosis-related diabetes is increasing. This condition is potentially responsible for respiratory decline.
Methods: At inclusion, then yearly (over three years), 111 children and 117 adults with cystic fibrosis had oral glucose tolerance and insulin tests at one (G1) and 2 h (G2). KmL analysis identified homogeneous G1 and G2 glucose trajectories. A linear mixed model quantified the relationships between trajectories and FEV1 changes.
Results: In children, there were three G1 and four G2 trajectories and FEV1 decrease was not significantly different between G1 or G2 trajectories. In adults, two G1 and four G2 trajectories were identified and FEV1 change was estimated at −0.85/year (95% CI: [−1.54; −0.17], p = 0.01) whatever the G1 trajectory and found significantly faster in the high and increasing G2 trajectory (−2.1/year, [−3.9; −0.2], p = 0.03).
Conclusions: In case of persistent G2 abnormality, physicians should be alert for clinical deterioration and intensify patient surveillance.

Keywords: Cystic fibrosis-related diabetes; Oral glucose tolerance test; Pulmonary function; Body mass index

1. Introduction

In cystic fibrosis (CF) patients, CF-related diabetes (CFRD) is a highly prevalent non-respiratory comorbidity. Its increasing prevalence may be linked to the increase in screening rates and

* Corresponding author at: Centre de Référence de la Mucoviscidose, Département de Médecine Interne, Hospices Civils de Lyon, Centre Hospitalier Lyon Sud, F-69495 Pierre-Bénite, France.
E-mail address: quitterie.reynaud@chu-lyon.fr (Q. Reynaud).

https://doi.org/10.1016/j.jcf.2017.09.010

the extension of life expectancy. By the start of the current decade, CFRD was affecting 9% of CF patients aged 5 to 9 years, 26% of those aged 10 to 20 years, and up to 50% of those aged ≥30 [1,2]. Similar prevalence rates were given by the last report of the French CF Registry (2014) [3].

In CF, an annual 75 g oral glucose tolerance test (OGTT) for screening CFRD is now standard care in patients aged ≥10 years. The diagnosis of CFRD is currently recommended by the American Diabetes Association despite some limitations [4]. The strict diagnostic criterion of CFRD is still one OGTT made when patients are clinically stable and confirmed three months later whereas recent studies in CF patients have shown that glucose homeostasis is highly variable over time [5,6]. A recent study suggested a role for decreased insulin sensitivity in the deterioration of glucose tolerance [7].

Screening for CFRD is important because it may be partly responsible for deterioration of pulmonary function [8]. This explains the recourse to OGTT and other markers and thresholds of glucose abnormality as early predictors of CFRD development and clinical deterioration; however, the relative importance of these predictors and their link with the decline of the forced expiratory volume in 1 s (FEV1) are still unclear. In recent cross-sectional studies [9,10], the elevation of 1-h fasting plasma glucose during 75 g-OGTT has been shown associated with poor pulmonary function and, more recently, new subgroups of patients with indeterminate glucose tolerance (INDET) had reduced pulmonary functions [11]. Though, none of these studies has taken into account the high changes of glucose homeostasis over time.

The aim of the present study was to identify patterns of glucose homeostasis change over time in children and adults with CF and explore a possible link between these patterns and pulmonary function.

2. Methods

2.1. Study design and population

This multicenter prospective cohort study considered first all CF patients aged ≥10 years who attended four CF centers (two adult and two pediatric centers) in the French Rhône-Alpes Region between 2009 and 2011. After excluding CF patients with pancreatic insufficiency (defined by the need for pancreatic enzyme supplementation), patients with current antidiabetic treatment (insulin or oral antidiabetic), patients with previous or planned pulmonary transplantation, and pregnant or breastfeeding women, the study kept 228 CF patients as participants: 111 children (aged 10 to 18 years at inclusion) and 117 adults (>18 years).

The main participant characteristics collected at inclusion were: sex, age, genotype, body mass index (BMI) in adults, BMI Z-scores in children, and FEV1. The participants were examined at inclusion then yearly over a three-year follow-up period as part of routine follow-up visits. At each examination, the physicians collected, among other data: weight, height, FEV1, and OGTT results. FEV1 values were expressed as percentage of the predicted normal value given by Knudson formula [12]. All measurements of the same variable were carried out the same way over the whole study period.

The institutional review board of each participating hospital authorized the study in accordance with the current ethical standards. Printed information about the study was given to each participant or legal surrogate and his/her signed informed consent obtained. The study ClinicalTrials.gov Identifier is NCT01072708.

2.2. Oral glucose tolerance testing

Each OGTT was carried out after an overnight fast before a routine clinical visit. The participant was given glucose (1.75 g per kg bodyweight, maximum 75 g); then plasma glucose and insulin were measured at start (G0), 1 h (G1), and 2 h (G2). Insulin was measured with BI-INS-IRMA kit (CisBio Bioassays, Codolet, France).

At the time of OGTT, all participants were clinically stable with no recent pulmonary exacerbation or symptoms of acute infection. Individuals treated with long-term low-dose oral corticosteroids were included in the study. Patients were kept in the cohort and the analysis whenever they had at least two OGTT measurements on two different visits, including those who required insulin treatment, met strict CFRD criteria but were left untreated, underwent pulmonary transplantation, or died during follow-up.

According to conventional criteria (American Diabetes Association and Cystic Fibrosis Foundation) [1] patients diagnosed with fasting hyperglycemia at any moment during the three-year follow-up received an antidiabetic treatment (insulin). Patients with abnormal OGTTs (impaired glucose tolerance, CFRD without fasting hyperglycemia) were monitored at home with three daily glycemic controls including before- and after-meal glucose level controls during a minimum of 7 days. Patients with after-meal glucose levels <10 mmol/L were left untreated. In case of clinical worsening, OGTT was repeated and patients found with abnormal OGTT were given insulin when justified.

2.3. Statistical analysis

The participants' characteristics at inclusion were described using the mean ± standard deviation or the median (range) for quantitative variables and the absolute + relative frequency in each category for qualitative variables.

A longitudinal cluster analysis method, KmL [13], was used to split the participants into several homogeneous subgroups of G1 and G2 glycemia changes over three years of follow-up. The method allows identifying subgroups of participants that follow similar patterns of glucose changes over time, herein called "glucose trajectories". For a given number of subgroups (2, 3, or 4), the optimal partition was obtained by maximizing the between-subgroup variance. The number of subgroups retained was determined according to Calinski & Harabasz criterion [14].

A graphical interface was also used to allow an a posteriori choice of the subgroups according to their clinical significance

Please cite this article as: Reynaud Q, et al, Glucose trajectories in cystic fibrosis and their association with pulmonary function, J Cyst Fibros (2017), https://doi.org/10.1016/j.jcf.2017.09.010