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Original Article

Early assessment of glucose abnormalities during continuous glucose monitoring associated with lung function impairment in cystic fibrosis patients

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Abstract

Background: Cystic fibrosis-related diabetes (CFRD) is correlated with a decline in lung function. Under certain circumstances, oral glucose tolerance test (OGTT) screening, used to diagnose CFRD, fails to reveal early glucose tolerance abnormalities. In this situation, continuous glucose monitoring (CGM) could be a useful tool for evaluating early abnormalities of glucose tolerance in CF patients. We aimed to study the CGM glucose profile in CF patients with normal OGTT screening results and to evaluate lung function and nutritional status according to the CGM glucose profile.

Methods: We assessed glycemic control, the CGM glucose profile, nutritional status, lung function antibiotic courses and colonization (*P. aeruginosa* and *S. aureus*) in CF patients, aged 10 years and over, with normal screening OGTT results (blood glucose at T120 min < 7.8 mmol/l). Two groups were identified according to the max CGM glucose value: Group 1 < 11 mmol/l and Group 2 ≥ 11 mmol/l.

Results: Among the 38 patients with normal OGTT, 12 (31.6%) were in Group 2. Compared to Group 1, Group 2 patients exhibited a significant impairment in lung function: FEV_1, 68.2 ± 25.6% vs. 87.3 ± 17%, p = 0.01 and FVC, 86.1% ± 19.4% vs. 99.3% ± 13.4%, p = 0.021, as well as a higher rate of colonization by *P. aeruginosa*: 83.3% vs. 44%, p = 0.024. Nevertheless, there were no differences in nutritional status (BMI standard deviation score: p = 0.079; prealbumin: p = 0.364).

Conclusions: CGM reveals early abnormalities of glucose tolerance that remain undiagnosed by OGTT screening and are associated with worse lung function and a higher prevalence of *P. aeruginosa* colonization in patients with CF.

Clinical trial registration number: NCT00476281.

Keywords: Cystic fibrosis; OGTT; CGM; Lung function; Early glucose tolerance abnormalities

1. Background

Because the life expectancy of cystic fibrosis (CF) patients has increased over the past few decades, cystic fibrosis-related diabetes (CFRD) has become a common complication of CF

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(50% of patients over 30 years old) [1]. CFRD is also known to be associated with an impairment of lung function [2,3] and weight loss [4]; both are associated with higher mortality rates [5–7].

For the early detection of CFRD and improvements in its treatment, OGTT is recommended in the North American Cystic Fibrosis Foundation criteria [1] to be performed yearly on patients older than 10 years of age. However, some authors have shown that the standard methods of glycemic assessment, random or fasting glucose concentrations, and/or OGTT underdiagnosed CFRD [8–10]. Consequently, early glucose abnormalities remained undetected. Moreover, it is known that patients who will later develop CFRD present a decrease in their lung function and weight standard deviation score (SDS) during the preceding 12 months [11].

CGM is a new method that can be used to evaluate the blood glucose profile over several days. It was used to control the efficiency of insulin pump therapy or the self-management of type 1 diabetic patients at home [12–14]. It has also been evaluated in children, adolescents and adults with CF [15,16], and its use has been proposed to study early glucose tolerance abnormalities [17–19]. As a result, it could be a useful tool to diagnose early glucose abnormalities that are not revealed by OGTT.

We designed this study to assess CGM glucose profiles in CF patients with normal OGTT. Nutritional status, lung function and infection parameters were studied in CF patients according to their CGM glucose profile.

2. Methods

2.1. Study design and patients

A total of 83 CF patients (42 males and 41 females) with fasting glycemia < 6.9 mmol/l who were at least 10 years old (age range: 12.4–57.3 years) were followed at the CF center of Strasbourg University Hospital (France) and enrolled in a prospective monocentric cross-sectional cohort study between March 2009 and September 2012. The CF diagnosis in these patients was based on clinical features and on positive CF genotype. The subjects were excluded if they had been diagnosed with diabetes or liver disease, had undergone a lung transplant or were taking steroids. Each patient underwent blood tests (HbA1c and prealbumin), OGTT, CGM, respiratory and nutritional evaluation. The evaluations were performed while the patients were in a clinically stable state, with at least 1 month having passed since any respiratory exacerbation and in the absence of a restricted-calorie diet. The protocol was approved by the local ethics committee (n.2007/09), and each patient or their legal representative provided written informed consent. The study protocol was conducted in accordance with the Declaration of Helsinki.

2.2. Metabolic evaluation

The OGTT screening was performed at the CF center on the morning after an unrestricted diet and typical physical activity. As recommended by the World Health Organization criteria [20] and the North American Cystic Fibrosis Foundation criteria [1], plasma glucose and C-peptide levels were measured at 0 and 120 min after drinking a glucose solution at a dose of 1.75 g/kg (up to a maximum of 75 g). The patients were classified according to the level of glycemia they presented at 2 h: normal glucose tolerance (NGT), glycemia at 2 h < 7.8 mmol/l; impaired glucose tolerance (IGT), 7.8 mmol/l ≤ glycemia at 2 h < 11 mmol/l; and CFRD, glycemia at 2 h ≥ 11 mmol/l.

The HbA1c (hemoglobin A1c) level was determined before performing the OGTT (%) using high-performance liquid chromatography (Variant 2, Bio-Rad, Marnes-La-Coquette, France).

Within three months after the OGTT was performed, patients remained stable in terms of weight, did not show pulmonary exacerbations requiring steroid intake, and had the CGM device installed at the outpatient clinic (Medtronic, and Sylmar, CA, USA). This device remained in situ in the home environment for 72 h for all of the subjects. They consumed their typical diet and entered a minimum of four self-monitored blood glucose values for daily CGM calibration. Various parameters were assessed: average glucose (mmol/l), maximum glucose (mmol/l), AUC of glucose values ≥ 7.8 mmol/l (mmol/l/day), duration of glucose values ≥ 7.8 mmol/l over the course of 72 h (%) and peak number of interstitial glucose values ≥ 11 mmol/l. We defined two groups based on the presence (Group 1) or absence (Group 2) of at least one interstitial glucose value higher than 11 mmol/l during the CGM recording.

2.3. Nutritional status

Patients were weighed and measured, and their BMI [weight in kilograms/height in meters squared] was calculated. The age- and gender-specific z-scores for BMI SDS (SD: standard deviation) were computed relative to the French reference population [21]. A blood sample was taken just before the OGTT to determine the prealbumin level (g/l).

2.4. Lung function

The patients performed spirometry with FEV_1 and FVC measurements (Vmax spirometer, VIASYS, Healthcare Respiratory Technologies, Canada), which was adjusted in percentage according to the age, gender, height and weight, as recommended by the ERS (European Respiratory Society) and the North American (American Thoracic Society) guidelines [22]. The number of intravenous antibiotic courses in one year was quantified for each subject. The bacterial species in sputum specimens (*P. aeruginosa* and *S. aureus*) were identified according to the North American guidelines [23].

2.5. Statistical analysis

All of the data were extracted from the CGM sensor to a personal computer with the aid of a communication device, which allowed downloading and reviewing (MiniMed Solutions Software, version 1.7a). The mean and SD of the interstitial glucose concentrations were derived for all of the CGM