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Original Article

Influence of macrolides, nutritional support and respiratory therapies in diabetes and normal glucose tolerance in cystic fibrosis. A retrospective analysis of a cohort of adult and younger patients

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ABSTRACT

Aim: The development of cystic fibrosis related diabetes is associated with increased morbidity and mortality, worse nutritional status and lung function decline. It is known that patients with cystic fibrosis have a chronic inflammation status and that β pancreatic cells are very sensitive to oxidative stress. So these inflammatory mediators could contribute to the onset of progressive pancreatic fibrosis and, hence, to impair glucose metabolism. So, it could be hypothesized that the treatment with macrolides would protect and preserve β-cell function by decreasing pro-inflammatory cytokines and free oxidative radicals.
Methods: We retrospectively analyzed a cohort of 64 patients affected of cystic fibrosis, older than 14 years, by using the first pathological 2-h oral glucose tolerance test; peripheral insulin resistance was calculated using the homeostasis model assessment for insulin resistance (HOMA – IR) and pancreatic β-cell function was estimated according to Wareham. The influence of macrolides, microbiological colonization, nutritional support and related clinical parameters were analyzed.
Results: Comparing CFRD without FPG and NGT, and after adjustment for microbial colonization, the significance of the use of macrolides was lost ($p = 0.1$), as a risk or protective factor for any of the studied groups. Non-significative associations were found in the use of macrolides, inhaled corticosteroids and nutritional support therapies within the different disorders of carbohydrate metabolism.
Conclusions: The anti-inflammatory and immunomodulating effect of macrolides did not seem to affect the β cell function or insulin resistance in patients with cystic fibrosis. The use of inhaled corticosteroids or nutritional supplements have not any influence in the carbohydrate metabolism. Further prospective studies are needed to analyze a potential protective role of macrolides in the development of carbohydrate metabolism alterations in cystic fibrosis.

1. Introduction

Nowadays there is an important scientific evidence showing that the diagnosis of cystic fibrosis related diabetes (CFRD) in patients with cystic fibrosis (CF) is associated with an increasing mortality. In fact, it is estimated that the risk of death attributable to diabetes is between 31% and 55%, regardless of other complications of CF [1]. Therefore, an early diagnosis and an appropriate therapeutic management are essential in these patients.

CFRD has an underlying insulin deficiency which promotes a negative protein balance, leading to an increased catabolism and weight loss, which contribute to the morbidity and mortality of these patients [2]. Thus, weight loss and lung function decline are probably the two most important items of prognosis (in terms of clinical conditions) in CF patients. It is known that a gradual decline in weight, body mass index (BMI) and lung function could

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precede to the CFRD diagnosis between 1 and 4 years [3]. The lung function decline is greater in CFRD than in normoglycemic patients and this decrease correlates directly with the degree of insulinopenia and severity of abnormal carbohydrate metabolism [4]. Severe lung disease (defined as force expiratory volume in 1 s percent predicted (FEV1%) <40%) may be associated with poor glycemic control in subjects with diabetes. Finally, the presence CFRD involves a higher frequency of lung disease exacerbations and an increase in the prevalence of pathogens in sputum [4,5].

For all these reasons, there is a greater emphasis on the early diagnosis and identification of predictors factors for the development of CFRD. Regarding these factors, some of them have been already identified: female gender, age, type of genetic mutation, exocrine pancreatic insufficiency, the degree of lung function deterioration, use of corticosteroids and the presence of other CF complications, as liver disease and lung transplantation [4,6].

Moreover, it is known that β pancreatic cell is very sensitive to oxidative imbalance, and its expression of antioxidants (superoxide dismutase, catalase, glutathione peroxidase) is lower than in other tissues. So it is an easy target to free oxidative radicals and inflammatory cytokines such as TNF-α, IL-6, IL-8. These inflammatory mediators activate certain cell signaling pathways in the β cell that may contribute to the development of fibrosis. Thus, progressively, it would reduce the production of insulin [7].

However, scarce data exist about the influence of respiratory support therapies and its possible role in the development of CFRD, and other disturbances of glucose, and particularly, about their immunomodulatory effect. The primary objective of the present work is to ascertain if these support therapies could decrease these inflammatory state and, consequently, have some influences in the glucose metabolism disturbances in CF. And particularly, if treatment with macrolide antibiotics could preserve the β cell function by lowering proinflammatory cytokines and free radicals, and thus, could be a protector factor for the development of carbohydrate metabolism disorders.

2. Methods

A single-center, observational, cross-sectional and retrospective study was conducted. Data concerning the year of diagnosis of any abnormal glucose metabolism were selected. A database was designed for the collection of the studied variables in patients followed up during the years 2011 and 2012 in the multidisciplinary CF unit of the university hospital Ramón y Cajal. For data collection was used both electronic files and those deposited in the archives of the center, besides microbiological and biochemical data sets in electronic formats.

Patients were diagnosed of CF according to the criteria of the Spanish Society of Pneumology and Thoracic Surgery (SEPAR) guidelines, which was based on the Rosenstein and Cutting (1998) recommendations and those proposed by the European Cystic Fibrosis Society (ECFS).

Patients were included if they fulfilled the next criteria: age ≥ 14 years old, a first pathological 2-h oral glucose tolerance test (2hOGTT) in a stable phase of the disease, respiratory function and anthropometric parameters in the same period of time in which 2hOGTT was done. In those patients with a non-pathological 2hOGTT, previous data of the last performed test were also collected.

The exclusion criteria was age under 14 years, incomplete data of 2hOGTT (those that did not allow a correct interpretation of the curve), no matched records of the lung function and nutritional parameters in the same period of time, pregnancy, viral infections (HIV, HVC, HVB), organ transplantation (lung, liver) at the time or prior to the 2hOGTT diagnosis curve.

The 2hOGTT was performed following the guidelines of the World Health Organization for a period of stability of lung disease of at least 6 weeks. This test is routinely carry out as an annual method of screening in these patients from 10 years of age, in accordance with the recommendations of the *U.S. Cystic Fibrosis Foundation* [8] and the *International Society of Pediatric & Adolescent Diabetes* [9]. The study groups were defined according to the proposed criteria of CFRD and other disturbances of glucose metabolism by *North American CF Consensus Conference* (2010) and *American Diabetes Association* (ADA) [8,10,11].

Lung function test was measure using a spirometry system according to the modified procedures (1987) of the *National Institute for Ocupational Safety and Health* and the *American Thoracic Society*. The results of the forced expiratory volume in one second (FEV1) were expressed as percentage of predicted for age, sex, ethnicity, weight and height, as recommended by SEPAR.

HOMA-IR is a simple method to estimate the peripheral insulin resistance requiring only values of fasting blood glucose and basal insulin (G_0 (mmol/L) × I_0/22,5) [12]. The pancreatic β cell function was calculated by the next ratio: the increase of insulin at 30 min (I_{30}–I_0 mU/L) between the plasma glucose levels obtained at 30 min of 2hOGTT [13].

Data recorded for the analysis were: vitamin and nutritional supplements, therapy with macrolides, microbiological colonization by *Staphylococcus aureus* and *Pseudomonas aeruginosa*, respiratory support therapies with antibiotics and inhaled bronchodilators containing corticosteroids, inward length of stay and number of exacerbations in the study period, and additional respiratory support during exacerbations.

Qualitative variables are expressed in their respective frequencies. Continuous variables with normal distribution were expressed with their respective means and standard deviation (SD), according to the normal distribution in the Kolmogorov–Smirnov test; those which do not comply with this distribution were reported in medians and interquartile range (IQR, P_{25}–P_{75}).

For the cohort analysis, the cases with normal glucose tolerance (NGT) were selected as the control group. Differences with other categories of carbohydrates metabolism alterations were analyzed according to the test of the Pearson Chi-square (or Fisher's exact test, as appropriate). Adjustments were made according to Mantel-Haenszel, in the most significant variables. Odds ratios (OR) were calculated for each condition, if the number of cases in each box do allowed it. For those continuous variables with no normal distribution, the nonparametric Mann–Whitney test was selected.

For all analyzes were considered significant a value of $p < 0.05$ (bilateral). Statistical analysis were performed using the statistical package SPSS, version 18.0 (Chicago, IL, USA).

3. Results

The general characteristics of the series are summarized in Table 1.

The mean age at the study entry was 26.84 years (SD 9.46), while the median age of diagnosis of CF was 1 year (IQR 1-6.5) – so the calculated mean disease progression was 20.43 years. A total of 36 males (56.3%) and 28 females (43.8%) were included. Of the total cases, 17 had an age range between 14 and 20 years.

Upon the completion of the curve (2hOGTT) in the diagnosis year, in almost all patients (90.3%) had been identified in sputum any bacterial strain colonization (36.1% had meticillin-sensitive *S. aureus*, 34.4% over two bacterial species and 21.3% *P. aeruginosa*).

After the 2hOGTT, NGT was detected in 26.7% (n = 16) of cases. CFRD without fasting hyperglycaemia (FPG) was detected in 18.3% (n = 11). There were no cases of CFRD with FPG. Indeterminate