Positive impact of insulin treatment on clinical trend in cystic fibrosis patients: a retrospective study

Andrea Giugno¹, Salvatore Leonardi², Donatella Lo Presti¹, Tiziana Timpanaro¹
Giuseppe Parisi², Maria Papale², Novella Rotolo², Sara Manti², Manuela Caruso-Nicoletti¹

¹Centro di Endocrinologia e Diabetologia Pediatrica, Università di Catania; AOU Policlinico-San Marco, Catania, Italy;
²UOC Broncopneumologia Pediatrica e Fibrosi Cistica, Università di Catania; AOU Policlinico-San Marco, Catania, Italy

Abstract. Background and aim: Cystic fibrosis-related diabetes is a complication of cystic fibrosis (CF). Our study aimed to evaluate the effects of insulin therapy in overt diabetics or pre-diabetics CF patients on BMI and respiratory function. Methods: We selected a sample of 17 insulin-treated patients (Group T) and a sample of 17 CF control patients with normal glucose metabolism (Group C). Group T was also subdivided into overt-diabetic patients and pre-diabetic patients (IGT, INDET). For treated patients, an observation period was established from the first insulin administration to 12 months. For control patients, a comparable year of observation was chosen. Data regarding BMI, FVC, FEV1, and PEF were collected at time 0, and at time 12. The number of hospital admissions for infectious episodes during the year of observation and the preceding year was recorded for Group T patients. Results: The results showed a significant increase in BMI in treated patients compared to control, especially for overt diabetics. The study of spirometric parameters showed a significant improvement in PEF, the main effort-dependent respiratory index, especially for over-diabetics, suggesting a hypothetical positive impact of the insulin anabolic action on the magnitude of expiratory effort. In contrast, the study of infectious episodes revealed a significant reduction in hospital admissions in pre-diabetic treated patients. Conclusions: Overall, our study focuses on the importance of glycemic monitoring during the early stages of CF disease and the advantage of insulin treatment in the early stages of glucose alteration. (www.actabiomedica.it)

Key words: Cystic Fibrosis, Diabetes, Insulin therapy, CFRD, respiratory function, BMI

Introduction

Cystic Fibrosis (CF) is one of the most common life-threatening autosomal recessive disorders in the Caucasian population (1). Although the advances made in the management of CF have allowed a significant increase in the survival of these patients, an increased incidence of long-term complications has been observed (2), representing, to date, a critical point in the management of CF patients.

CFRD is occurring in 40-50% of CF patients (5), and its prevalence increases by 5% for patients over 10 years old and 9% for patients over 20 years old (4). The secretion of altered pancreatic juice, more acid and rich in protein, leads to the obstruction of the pancreatic ducts, and determines an increase in intraductal pressure, inflammation, amyloid deposition, fatty infiltration, pancreatic damage, and parenchymal atrophy (5). The role of insulin resistance in the pathogenesis of CFRD is controversial. Some authors suggest that patients with impaired glucose tolerance have increased peripheral insulin resistance, which is related to worse clinical status, malnutrition, and impaired lung function (27). All these alterations, disrupting the
pancreatic islets’ alpha and beta cells, cause damages ranging from pancreatic insufficiency to insulin and glucagon deficiency (6).

CFRD causes neuropathy, gastropathy, retinopathy, and diabetic nephropathy, similar to other forms of diabetes (7). The onset of diabetes in CF patients worsens the patient’s overall clinical condition, affecting nutritional/weight status, pulmonary function, and short- and long-term microvascular complications (8-10), but there isn’t clear evidence of the impact of insulin deficiency on hospital admissions for respiratory infections. Indeed, in the scientific community, there isn’t a common consensus about the treatment of pre-diabetic stages.

In this study, we aimed to evaluate the impact of insulin treatment on weight status, respiratory function, and respiratory infectious status in CFRD patients and CF patients in whit early stages of glucose alteration.

Materials and methods

Patients

All CF patients followed at our Regional Reference Center for Cystic Fibrosis are periodically evaluated in collaboration with our Pediatric Endocrinology Unit to monitor glucose metabolism and other endocrine complications of CF. Follow-up of glucose metabolism includes: fasting blood glucose, glycated hemoglobin, and five points OGTT (see “methods”). For the study, we retrospectively recruited a group of seventeen patients on insulin therapy (Group T). We then selected a sample of 17 CF patients without evidence of glycemic abnormalities, comparable for age and sex at Group T, which was used in the study as a control group (Group C). Informed consent was obtained from each patient to use the collected data for this study.

Group T consists of 17 subjects, 10 males and 7 females, with a mean age of 23.8 ± 9.2 years, 7 homozygotes DF508 / DF508, 9 heterozygous DF508 / other, 1 other/other; twelve patients out of 17 (70.6%) have pancreatic insufficiency. The average age at which insulin therapy was started for these patients is 19.6 ± 8 years. Fourteen patients started treatment with insulin glargine at different dosages; for 3 of them (T8, T15, and T16) insulin aspart alone or in combination with long-acting insulin was prescribed. Group T was then divided into two subgroups based on the value of HbA1c at time 0. According to the guidelines, glycated hemoglobin over 6.5% allows the diagnosis of CFRD (18), this value was used to form the two subgroups: pre-diabetic (HB1AC at time 0 <6.5%) and diabetic (HB1AC at time 0 ≥ 6.5%). Pre-diabetics were classified as IGT, INDET, or IGT / INDET based on the values of the OGTT at time 0. The pre-diabetics were 9 out of 17; 7 males and 2 females, with a mean age of 21.67 ± 9.4 years; 6 of them were classified as IGT, 3 as IGT / INDET. Diabetics were 8 out of 17; 3 males and 5 females, with a mean age of 26.13 ± 8.9 years.

Group C consists of 17 patients, 9 males and 8 females, with a mean age of 25.9 ± 15.3 years at the time of the study, 13 heterozygous DF508 / other, 4 other/other; 8 patients out of 17 (47%) have pancreatic insufficiency. Demographic, clinical, and genetic data are summarized in Table 1.

Methods

Fasting blood glucose is measured at each patient’s access to the Cystic Fibrosis Center; HbA1c is performed 2-4 times a year. According to guidelines (18) OGTT is performed in all CF patients from 10 years old, once a year, in absence of pathological signs, following standard procedure. OGTT identifies several diagnostic sub-categories, on the basis of one hour plasma glucose (PG1) and two hours plasma glucose (PG2): Impaired glucose tolerance (IGT)
Acta Biomed 2022; Vol. 93, N. 5: e2022295

(140 < PG2 < 200 mg/dl); indeterminate glycemia (INDET) (PG1 > 200 mg/dl, PG2 < 140 mg/dl); CFRD (PG2 > 200 mg/dl) (11). Spirometry examinations were performed with a standard spirometer (CosmedSrL). For each spirometry, the forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), and forced expiratory flow (PEF) have been studied. The FVC corresponds to the forced vital capacity, and is the total volume of air expelled after a forced exhalation starting from a maximal inspiration; FEV1 is the volume of air expelled in the first second of a forced exhalation starting from a maximal inspiration; it is the most significant and reproducible parameter of spirometry; PEF is peak expiratory flow, and corresponds to the maximum flow emitted in forced expiration. Infectious respiratory episodes were recorded for Group T patients. They were calculated as the number of hospital admissions due to respiratory infectious exacerbations.

Hb1Ac was measured using the high-performance liquid chromatographic (HPLC) method.

Study protocol

For each patient in Group T, an observation period was established starting with the first insulin administration (time 0) and ending after 12 months (time 12). BMI, FVC, FEV1, and PEF were collected at time 0 and at time 12. Hospital admissions for respiratory infections occurred in the year preceding time 0, and in the following year (study period), were recorded.

For Group C patients, a comparable year of observation was chosen. BMI, FVC, FEV1, and PEF were collected at time 0 (beginning of the observation year), and at time 12 (after 12 months).

Statistical analysis

BMI and spirometry parameters were compared:

- At Time 0 to evaluate the differences between the two groups;
- At Time 0 and Time 12 to evaluate the variation over time for each Group;
- At Time 12 to evaluate the differences between the groups at the end of the study period;

The Delta (Time 12 - time 0) was calculated to compare the extension of the variations between the two Groups.

The same analysis was performed for the diabetic vs pre-diabetic subgroups.

Hospital admissions were compared for Group T between episodes collected in the year preceding time 0 and in the following year, to evaluate the variation after starting therapy.

For statistical analysis Student’s t-test was used for paired data in the comparison between values of the same group of patients; Student’s t for unpaired data in the comparison between different groups of patients.

Statistical significance was assumed for p-value <0.05, with a 95% confidence interval.

Data and graphics were processed using GraphPad Prism software (© 1922-2022 Graphpad Software, Inc. All rights reserved).

Results

All subjects completed the study and were considered in the final analysis. Patients in Group T and Group C did not differ significantly in age and sex. All patients with homozygous DF508 mutation were in group T (7 of 17).

BMI

Means, medians, and standard deviations of Group C and T BMI are collected in Table 2. BMI, at time 0,

| Group C | BMI time 0 | BMI time 12 | Group T | BMI time 0 | BMI time 12 |
|---------|------------|-------------|---------|------------|-------------|
| Mean    | 20,2       | 20,3        | Mean    | 17,1       | 18,1        |
| Median  | 19,6       | 18,7        | Median  | 16,5       | 17,5        |
| S.T.    | ± 4,4      | 4,1         | S.T.    | ± 2,3      | ± 2,2       |
shows that at time 0 the differences between the two groups were statistically significant for each of the three values; FVC, FEV1, and PEF were lower in Group T (Figure 2a); at time 12 these differences remain significant, but the gap was shortened (Figure 2b). P-values are shown in the figure.

Indeed, at the time 12, group T showed an improvement/increase in all three spirometry parameters, although only PEF had a statistically significant increase (Figure 3, p-value 0,0221). Conversely, spirometry parameters in Group C did not show any statistically significant variation. The observed trend was confirmed by comparing the delta (time 12-time 0) of the two groups for each parameter. This comparison shows a statistically significant difference only for PEF.

Pre diabetics vs diabetics comparison show a similar increase in both subgroups, although PEF showed a statistically significant difference between Group T and Group C (p-value 0,014); at time 12 months BMI showed an increase and a decrease in Group T and Group C, respectively (Figure 1). BMI of Group T was significantly increased at time 12 (p-value 0,0006). The delta BMI (BMI time 12-BMI time 0) in the two groups was significantly different (p-value 0,0084).

Pre diabetics vs diabetics comparison for BMI did not show significant differences, both at times 0 and 12. However, the delta BMI showed a greater increase in BMI in the subgroup of diabetic patients (P = 0.05).

**Respiratory function**

Means, medians, and standard deviations of Group C and T spirometry parameters are collected in Table 3. A comparison of the 3 spirometry parameters shows that at time 0 the differences between the two groups were statistically significant for each of the three values; FVC, FEV1, and PEF were lower in Group T (Figure 2a); at time 12 these differences remain significant, but the gap was shortened (Figure 2b). P-values are shown in the figure.

Figure 1. BMI Group T and Group C at times 0 and 12. The figure shows a statistical significance difference between group T and C at time 0, and a statistically increase in BMI in group T between time 0 and time 12.
Table 3. Means, medians, and standard deviations of Group C and T spirometry parameters.

| Group   | FVC % time 0 | FVC% time 12 | FEV1 % time 0 | FEV1% time 12 | PEF % time 0 | PEF% time 12 |
|---------|--------------|--------------|---------------|---------------|--------------|--------------|
| **Mean** | 99,4         | 96,8         | 96,8          | 92,9          | 95,6         | 92,6         |
| **Median** | 100,1       | 98,2         | 92,2          | 91,4          | 97,9         | 88           |
| **S.T.**   | ± 20,6       | ± 23,6       | ± 27,8        | ± 28,6        | ± 25,3       | ± 30,7       |
| **Group T** |             |              |               |               |              |              |
| **Mean** | 70,8         | 74,9         | 56,2          | 58,2          | 55,5         | 64,8         |
| **Median** | 68,3         | 77,5         | 46,5          | 56            | 46,5         | 61,2         |
| **S.T.**   | ± 23,3       | ± 20,8       | ± 26,7        | ± 22,6        | ± 28,2       | ± 22,3       |

Figure 2. A) to the left, Group T vs Group C spirometry parameters at time 0. The figure shows a statistically significant difference for each parameter in time 0 between Group T and C; A) to the right, Group T vs Group C spirometry parameters at time 12. Differences remain significant, but the gap was shortened.
Instead, the pre-diabetics vs diabetics comparison shows that pre-diabetics responded to treatment with a statistically significant reduction in hospital admissions in the year of treatment compared to the previous year, unlike the diabetic group (Figure 5, p-value 0.0207). Also, the delta was significantly different (p-value 0.0458).

Discussion

Cystic fibrosis patient is a complex patient and the alteration of glucose metabolism is a frequent...
Cystic fibrosis severely affects nutritional status with different mechanisms. CF patients often experience a condition of malnutrition, complicated by exocrine pancreatic insufficiency. This pathological state occurs when less than 5-10% of digestive enzymes are produced, and its prevalence is very high (85-90% of subjects) increasing with age and severity of the mutations; it contributes to malnutrition causing maldigestion/malabsorption. (14)

In addition, CF patients need a caloric intake of 120-150% of the average energy needs about age and sex, due to the persistent inflammatory state, recurrent infections, and respiratory muscle strain associated with dyspnea and polypnea. (15)

Insulin has a very central role in anabolic phenomena, in particular muscle and adipose tissue development. Insulin deficiency determines a metabolic switch, aggravating the already compromised nutritional status and the clinical status of the patient. Indeed, CF patients referred for lung transplantation with a BMI less than 18 kg/m² are at high risk of a complication linked to a worsening of the disease. An Italian study of 24 patients between 2 and 5.9 years of age showed that 33% of subjects had different degrees of glucose intolerance, oscillating between “indeterminate glucose tolerance” (INDET) and CFRD. (12). Its onset is associated with pancreas impairment and often follows pancreatic insufficiency, which is associated with the most serious genotypes of the underlying disease (4,13) as our data show: in fact, all subjects with homozygous DF508 / DF508 mutation belong to group T, none was in group C. Diabetes developing in already compromised patients negatively influences their pathophysiology and management (8)

Therefore, adequate management of CF patients with alterations in glucose metabolism could have a positive impact on their overall clinical condition. Our study aimed to focus on the effects of insulin treatment in patients with diabetes or prediabetes on nutritional status, evaluated by BMI, and respiratory performance. A major limitation of the study is the smallness of the sample examined, especially in the subdivision between diabetics and prediabetes. Another limitation was the difficulty of collecting a control group homogeneous to group T.

Cystic fibrosis severely affects nutritional status with different mechanisms. CF patients often experience a condition of malnutrition, complicated by exocrine pancreatic insufficiency. This pathological state occurs when less than 5-10% of digestive enzymes are produced, and its prevalence is very high (85-90% of subjects) increasing with age and severity of the mutations; it contributes to malnutrition causing maldigestion/malabsorption. (14)

In addition, CF patients need a caloric intake of 120-150% of the average energy needs about age and sex, due to the persistent inflammatory state, recurrent infections, and respiratory muscle strain associated with dyspnea and polypnea. (15)

Insulin has a very central role in anabolic phenomena, in particular muscle and adipose tissue development. Insulin deficiency determines a metabolic switch, aggravating the already compromised nutritional status and the clinical status of the patient. Indeed, CF patients referred for lung transplantation with a BMI less than 18 kg/m² are at high risk of
death over the next 12 months. (16-18) Randomized studies have shown an increase in BMI in adult patients with CFRD following insulin therapy. (19). In our study, patients candidates for therapy started from a significantly worse weight stage than controls suggesting that insulin deficiency might have contributed already to the deficit of their weight state. We confirmed the beneficial effect of insulin therapy on weight since the BMI of these patients significantly increased after one year of treatment. Instead, we observed a slight decrease, probably due to the progression of the underlying disease, in the year of observation of the control group. At the end of the study period, the initial significant difference between the two groups was not present, confirming the importance of insulin replacement to avoid further worsening of weight deficit.

Lung disease affects the quality of life, prognosis, and survival of CF patients more than any other clinical manifestation; therefore, we also wanted to evaluate if diabetes and pre-diabetic stages could have a deleterious impact on pulmonary pathology. We studied pulmonary disease through two modalities:

**Figure 5.** To the left, pre-diabetics hospital admissions pre and post-therapy; to the right, diabetics hospital admissions pre and post-therapy (N: number of annual episodes). The figure shows a statistically significant reduction in hospital admissions in pre-diabetics after therapy.
respiratory function expressed through spirometry indices, and respiratory infectious episodes. The spirometry parameters obtained from the analysis at high volumes (within the first 25% of the FVC) are defined as “effort dependent” because they depend on the expiratory effort. They include FEV1, and above all PEF. Indeed, PEF is measured in the early phase of exhalation (about 150ms of time) at high volumes, so it reflects the diameter of the major airways, and the extent of the intrathoracic pressure developed. Insulin deficiency can contribute to aggravating the restrictive component of the disease, by a different mechanism demonstrated in the literature, such as diabetic pulmonary microangiopathy, an increased concentration of glucose in bronchial secretions, a deficit of the lung structural protein component, and development of reactive oxygen species (20-24). Moreover, insulin deficiency could contribute to the reduced development of the thoracic muscles necessary to perform a maximal forced expiration.

In our study, we compared FVC, FEV1, and PEF at times 0 and 12 in the two groups, T and C. Data at time 0 showed statistically significant differences between the two groups for each of the three parameters. The spirometry of group C was substantially normal, unlike the spirometry of group T. This confirms that diabetic or pre-diabetic CF patients have a more compromised respiratory function than CF patients with normal glucose metabolism. After 12 months of insulin treatment, all the values increased; however, FVC and FEV1 showed a clear improvement trend, but only the PEF, showed a statistically significant increase. The data on PEF is interesting new data because leading to speculation on a potential role of insulin deficiency on the muscular component of respiratory dynamics, reflected by a deficit of the more effort-dependent spirometry parameter. Further studies could clarify this hypothesis, for example by studying respiratory muscle performance indices such as MIP (maximal inspiratory pressure, or P1max) and MEP (maximal expiratory pressure, Pmax). At the end of the 12 months of treatment, spirometry indices were still lower compared to controls, but they improved while Group C showed a slight tendency to worsen.

Data on hospital admissions for respiratory infectious episodes are interesting because they worsen lung function and the quality of life of CF patients. The data were analyzed for treated patients using two observation periods: the previous year and the one following the start of insulin therapy. The median of the episodes decreases from 2 episodes per year to 1; moreover, patients without hospitalization doubled in the treatment year. The reason for the lack of statistical significance of these data can be explained by the small sample size and the heterogeneity between pre-diabetics and diabetics in the response to therapy, as will be seen forward.

An open question in the scientific community is when to start treating these patients. Some studies are favorable to the early beginning of therapy, but there is still a debate. (12,25)

Clinical practice guidelines suggest starting follow-up for diabetes from 10 years old in CF patients, performing an annual OGTT, to identify early stages of glucose alteration (26). In particular, the INDET stage gets great interest because it is an early indicator of the alteration of glucose homeostasis, and it is not entirely clear how to manage this category. We divide group T into two subgroups of pre-diabetic and diabetic based on a lower, equal to, or greater than 6.5% glycated hemoglobin before starting therapy, considered cut-off to diagnose diabetes according to guidelines. So we obtained two groups of a few patients, which represents a critical aspect of the study. The results were discordant for the different parameters studied. BMI study presented two populations both responsive to treatment, with significant weight increase; however, BMI increase was greater in the diabetic patients. The study of spirometry indices demonstrated a similar improvement of FVC and FEV1 in the two sub-groups, but the response on PEF showed a significantly greater improvement in diabetic patients compared to pre-diabetics. The number of hospital admissions instead showed an opposite trend, with a significantly higher response in the pre-diabetic subgroup, with a median decreasing from 2 to 0 hospital admission for a year. In reverse, diabetics did not show any change in the number of infectious episodes before and after treatment.

These results show that diabetic patients responded to insulin therapy better for weight gain and PEF; pre-diabetics responded better in terms of
reduction of hospital admissions for respiratory infections. The best response of the diabetic group in terms of BMI and PEF reinforces the hypothesis of their indirect connection because better nutritional status could correlate with the increased strength of the patients, and therefore with a better performance of the expiring muscles, reflected by PEF. So diabetic patients, with a lower starting BMI, in worse clinical conditions, and treated with higher insulin doses may respond better in terms of BMI and developed force (PEF), compared to a pre-diabetic patient. The best response of pre-diabetics in terms of hospital admissions (especially if this data could be confirmed in larger groups and longer times) would suggest an indication for early treatment of CF patients in prediabetic stages, considering how much they affect the quality of life, the respiratory function and general clinical conditions of CF patient.

In conclusion, we propose that early insulin treatment of CF patients with abnormal glucose metabolism improves nutritional state and is probably useful in improving respiratory performance and reducing the frequency of hospitalization due to infectious exacerbation. For this purpose, a multicenter trial would be useful to define and standardize modalities and clinical indications of early insulin treatment in prediabetic CF patients.

**Conflict of Interest:** Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patient/licensing arrangement, etc.) that might pose a conflict of interest in connection with the submitted article.

**Informed Consent:** Informed consent was obtained from each patient to use the collected data for this study.

**Ethics Approval:** The study obtained the approval of the ethics committee of the University of Catania according to protocol number 212/2018.

**Research Funding:** This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

**Financial Disclosure:** The authors have no financial relationship relevant to this article to disclose.

**Author Contributions:** All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

**References**

1. Spoonhower KA, Davis PB. Epidemiology of Cystic Fibrosis. Clin Chest Med 2016 Mar;37(1):1-8. DOI: 10.1016/j.ccm.2015.10.002.
2. Fitz Simmons SC. The changing epidemiology of cystic fibrosis. J Pediatr. 1993 Jan;122(1):1-9. DOI: 10.1016/s0022-3476(05)83478-x.
3. Lang S, Hansen A, Thorsteinsson B, Nerup J, Koch C. Glucose tolerance in patients with cystic fibrosis: five-year prospective study. BMJ. 1995 Sep 9;311(7006):655-9. DOI: 10.1136/bmj.311.7006.655.
4. 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 Sep;32(9):1626-31. DOI: 10.2337/dc09-0586.
5. O’Sullivan BP, Freedman SD. Cystic fibrosis. Lancet. 2009 May 30;373(9678):1891-904. DOI: 10.1016/S0140-6736(09)60327-5.
6. Iannucci A, Mukai K, Johnson D, Burke B. Endocrine pancreas in cystic fibrosis: an immunohistochemical study. HumPathol. 1984 Mar;15(3):278-84. DOI: 10.1016/s0046-8177(84)80191-4.
7. Schwarzenberg SJ, Thomas W, Olsen TW, et al. Microvascular complications in cystic fibrosis-related diabetes. Diabetes Care. 2007 May;30(5):1056-61. DOI: 10.2337/dc06-1576.
8. Milla CE, Warwick WJ, Moran A. Trends in pulmonary function in patients with cystic fibrosis correlate with the degree of glucose intolerance at baseline. Am J Respir Crit Care Med. 2000 Sep;162(3 Pt 1):891-5. DOI: 10.1164/ajrccm.162.3.9904075.
9. O’Riordan SM, Robinson PD, Donaghue KC, Moran A; ISPAD Clinical Practice Consensus. Management of cystic fibrosis-related diabetes. Pediatr Diabetes. 2008 Jul 28;9(4Pt1):338-44.DOI:10.1111/j.1399-5448.2008.00437.x.
10. Hameed S1, Jaffé A, Verge CF. Cystic fibrosis related diabetes (CFRD)--the end stage of progressive insulin deficiency. Pediatr Pulmonol. 2011 Aug;46(8):747-60. DOI: 10.1002/ppul.21495.
11. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2020 -American Diabetes Association-Diabetes Care 2020 Jan;43(1 Suppl):S14-S31.
12. Mozillo E, Raia V, Fattorusso V, et al. Glucose derangements in very young children with cystic fibrosis and pancreatic insufficiency. Diabetes Care 2012;35:e78 doi: 10.2337/dc12-0459.
13. Kerem E, Corey M, Kerem BS, Rommens J, Markiewicz D, Levison H, et al. The relation between genotype and phenotype in cystic fibrosis—analysis of the most common mutation (delta F508). N Engl J Med. 1990 Nov 29;323(22):1517-22. DOI: 10.1056/NEJM199011293232203.
14. Li L, Somerset S. Digestive system dysfunction in cystic fibrosis: challenges for nutrition therapy. Dig Liver Dis. 2014 Oct;46(10):865-74. doi: 10.1016/j.dld.2014.06.011. Epub 2014 Jul 19. PMID: 25053610.

15. Pencharz, P. B., and P. R. Durie. “Pathogenesis of Malnutrition in Cystic Fibrosis, and Its Treatment.” Clinical Nutrition (Edinburgh, Scotland) 19, no. 6 (December 2000): 387–94. doi:10.1054/cnlu.1999.0079.

16. Hirche TO, Knoop C, Hebestreit H, Shimmin D, Solé A, Elborn JS et al. TO; ECORN-CF Study Group. Practical guidelines: lung transplantation in patients with cystic fibrosis. Pulm Med. 2014;2014:621342. DOI: 10.1155/2014/621342. Epub 2014 Mar 30. Erratum in: Pulm Med.2015;2015:698460.

17. Snell GI, Bennetts K, Bartolo J, Levvey B, Griffiths A, Williams T, et al. M. Body mass index as a predictor of survival in adults with cystic fibrosis referred for lung transplantation. J Heart Lung Transplant. 1998 Nov;17(11):1097-103.

18. Lederer DJ, Wilt JS, D’Ovidio F, Bacchetta MD, Shah L, Ravichandran S, et al. Obesity and underweight are associated with an increased risk of death after lung transplantation. Am J Respir Crit Care Med. 2009 Nov 1;180(9):887-95. DOI: 10.1164/rcrm.2009-0025OC.

19. Moran A, Pekow P, Grover P, Zorn M, Slovis B, Pilewski J et al.; Cystic Fibrosis Related Diabetes Therapy Study Group. Insulin therapy to improve BMI in cystic fibrosis-related diabetes without fasting hyperglycemia: results of the cystic fibrosis-related diabetes therapy trial. Diabetes Care. 2009 Oct;32(10):1783-8. DOI: 10.2337/dc09-0585.

20. Pitocco D, Fusco L, Conte EG, Zaccardi F, Condoluci C, Scavone G et al. The diabetic lung--a new target organ? Rev Diabet Stud. 2012 Spring;9(1):23-35. doi: 10.1900/RDS.2012.9.23.

21. Wood DM, Brennan AL, Philips BJ, Baker EH. Effect of hyperglycemia on glucose concentration of human nasal secretions. Clin Sci (Lond). 2004 May;106(5):527-33. DOI: 10.1042/CS20030333.

22. Brennan AL, Gyi KM, Wood DM, Johnson J, Holliman R, Baines DL, et al. Airway glucose concentrations and effect on growth of respiratory pathogens in cystic fibrosis. J Cyst Fibros. 2007 Apr;6(2):101-9. DOI: 10.1016/j.jcf.2006.03.009.

23. Hunt WR, Zughai ER, Guentert DE, Shenep MA, Koval M, McCarty NA et al. Hyperglycemia impedes lung bacterial clearance in a murine model of cystic fibrosis-related diabetes. Am J Physiol Lung Cell Mol Physiol. 2014 Jan 1;306(1):L43-9. DOI: 10.1152/ajplung.00224.2013. Epub 2013 Oct 4.

24. Langs, Thorsteinsson B, Nerup J, Koch C. Diabetes mellitus in cystic fibrosis: effect of insulin therapy on lung function and infections. Acta Paediatr. 1994 Aug;83(8):849-53. DOI: 10.1111/j.1651-2227.1994.tb13156.x.

25. Bizzarri C, Lucidi V, Ciampalini P, Bella S, Russo B, Cappa M. Clinical effects of early treatment with insulin glargine in patients with cystic fibrosis and impaired glucose tolerance. J Endocrinol Invest. 2006 Mar;29(3):RC1-4. DOI: 10.1007/BF03345538.

26. Moran A, Brunzell C, Cohen RC, Katz M, Marshall BC, Onady G et al.; CFRD Guidelines Committee. 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 Dec;33(12):2697-708. DOI: 10.2337/dc10-1768.

27. Tofé S, Moreno JC, Máiz L, Alonso M, Escobar H, Barrio R. Insulin- secretion abnormalities and clinical deterioration related to im- paired glucose tolerance in cystic fibrosis. Eur J Endocrinol 2005, 152: 241-7.

Correspondence:
Received: 12 February 2022
Accepted: 4 March 2022
Andrea Giugno, Centro di Endocrinologia e Diabetologia Pediatrica, Università di Catania; AOU Policlinico-San Marco Via S.Sofia n.78, 95123 Catania, Italy
E-mail: andrea.giugno@hotmail.com