Open Journal of Pathology, 2016, 6, 32-40
Published Online January 2016 in SciRes. http://www.scirp.org/journal/ojpathology
http://dx.doi.org/10.4236/ojpathology.2016.61006

Clinical Outcome of CF Patients with CF Related Diabetes: Do We Need to Change Our Policy?

An Jacobs[1], Francois Vermeulen[2], Kris de Boeck[2], Kristina Casteels[3], Marijke Proesmans[2*]

[1]KU Leuven, Belgium Department of Pediatrics, University Hospital of Leuven, Leuven, Belgium
[2]Pediatric Pulmonology, University Hospital of Leuven, Leuven, Belgium
[3]Pediatric Endocrinology, University Hospital of Leuven, Leuven, Belgium
Email: marijke.proesmans@uzleuven.be

Received 23 December 2015; accepted 19 January 2016; published 25 January 2016

Abstract

Background: Many studies have shown that CFRD has a negative impact on CF prognosis. Current guidelines advise to screen for CFRD with an OGTT yearly from the age of 10 - 12. In our center we do not routinely screen for CFRD because the OGTT is cumbersome and not an ideal screening test. We therefore want to exclude unfavourable clinical evolution due to late diagnosis. Methods: 23 CF patients with diagnosis of CFRD < 18 years old were matched to a control patient. Clinical evolution (BMI, lung function, and chronic infection treatment burden) was analyzed starting 2 years before until 2 years after diagnosis of CFRD. Results: In the 2 years before diagnosis of CFRD, BMI and LF were similar for both groups while need for IV AB treatment was higher in the CFRD group. In the 2 years following diagnosis and treatment, LF decline was worse in the CFRD despite more IV AB treatments. BMI was still comparable. We conclude that clinical status was comparable between cases and controls in the 2 years preceding the diagnosis of CFRD. However, the need for IV antibiotic treatment seems to precede the faster lung function decline after CFRD diagnosis.

Keywords

Cystic Fibrosis, Cystic Fibrosis Related Diabetes, Clinical Outcome

1. Introduction

Cystic fibrosis (CF) is a life-shortening, multi-organ disease, caused by mutations in the CF transmembrane conductance regulator (CFTR) gene. This gene encodes an ion channel highly expressed in the apical membrane

*Corresponding author.

How to cite this paper: Jacobs, A., Vermeulen, F., de Boeck, D., Casteels, K. and Proesmans, M. (2016) Clinical Outcome of CF Patients with CF Related Diabetes: Do We Need to Change Our Policy? *Open Journal of Pathology*, **5**, 32-40.
http://dx.doi.org/10.4236/ojpathology.2016.61006

of epithelial cells [1]. CFTR mutations resulting in dysfunction of the ion channel lead to disturbed epithelial water balance resulting in viscous secretions in exocrine organs like the airways and the pancreas. The main cause of death in CF is respiratory failure secondary to chronic lung infection. Chronic sinusitis, exo- and endocrine pancreatic dysfunction and male infertility are other CF disease manifestations.

CF related diabetes (CFRD) is one of the most common comorbidities of this disease [2] with about 50% of CF patients developing diabetes by the age of 30 years old. While it is rare in childhood, CFRD risk increases from adolescence on wards [3]. Many studies have shown that CFRD has a negative impact on CF prognosis, with worse nutritional status, more severe lung disease and higher mortality [4]-[12]. Even the prediabetic stage may lead to clinical decline [4] [9] [11] [13] [14]. In more recent reports the negative impact of CFRD were less pronounced most likely because of improved CF treatment [7] [15].

The pathophysiology of CFRD is complex. Thick viscous secretions cause obstruction of the exocrine pancreatic ducts with secondary pancreatic fibrosis and fatty infiltration [16]. This progressive pancreatic damage further leads to destruction of islet architecture and delayed and diminished insulin secretion [3]. Recent data suggest that impaired insulin secretion may also be a direct consequence of the mutated CTFR [17]. Insulin insufficiency is the primary defect but insulin resistance may be a contributing factor. Although CFRD thus shares features of both type 1 and type 2 diabetes, it is a separate entity based on pathophysiological and clinical differences [3]. At present insulin is the only recommended therapy for CFRD [2] [16], but this increases the overall CF treatment burden significantly.

Current guidelines [3] [16] [18]-[20] advise to screen on yearly basis for CFRD with an OGTT from the age of 10 - 12 years old. CFRD diagnosis is established if the glucose level is more than 200 mg/dl after two hours in an oral glucose tolerance test (OGTT) [16]. Although in the UK these guidelines are well followed [21], some do not support routine screening [22]. Recent insights suggest that glucose tolerance in CF ranges from normal glucose tolerance (NGT), over impaired glucose tolerance (IGT), to CFRD with(out) fasting hyperglycaemia [15] and the severity of the impaired glucose metabolism may fluctuate over time. Glucose tolerance will be abnormal long before the OGTT will reach the threshold of CFRD diagnosis. Therefore CFRD is not a clear-cut phenomenon that starts at a certain point in time. Moreover, the correlation between the OGTT and the glucose profile during an average day is very weak [23].

In our center, we do not perform yearly CFRD screening with OGTT but rather use this test as a low threshold for diagnostic purposes whenever a patient with CF between the age of 10 and 18 years old has an unstable evolution. In order to evaluate the impact of this practice on patient evolution, we decided to study the clinical evolution before and after diagnosis of CFRD in our pediatric cohort.

2. Methods

2.1. Study Design

This is a retrospective case-control study using the hospital patient registry from the pediatric CF database. Patients born between 1-1-1997 to 31-12-2012, diagnosed with CFRD and treated with insulin before the age of 18 years were included. Each patient diagnosed with CFRD patients was matched with a CF patient without CFRD based on gender, genotype, year of birth, age at CF diagnosis and chronic *P. aeruginosa* infection. Exclusion criteria were death within the follow up period, and lung transplantation before time zero.

2.2. Study Sample

Possible indications for OGTT apart from diabetic symptoms are: insufficient growth or weight gain increased respiratory symptoms or increased treatment need, vague complaints of fatigue or malaise. The pediatric CF cohort in our center counted 127 children (<18 years old) in 1997 and decreased to 118 children in 2012 (excluding transplanted CF patients).

2.3. Data Collection

We collected patient data two years before the start of insulin treatment (=time zero), until two years after. For the matched group, time zero was set at the same age as time zero of the index case. For CFRD patients receiving a lung transplant within the two year period after start of insulin, data after the transplantation were excluded.

The following parameters were used. For lung function, FEV1 was expressed as % predicted (FEV1%pred)

according to Wang *et al.* [24]. FEV1%pred decline for each year was calculated by the slope of the regression line through the best FEV1% predicted of each quartile.

Infection status was registered for *Pseudomonas aeruginosa* (PA), other Gram negative bacteria (for example *Achromobacter xylosoxidans*), *Methicillin Resistant Staphylococcus aureus* (MRSA] and *Aspergillus* spp in each year. Chronic Pseudomonas infection was defined according to the Leeds criteria [25]. The Leeds criteria groups 'never', 'intermittent', 'free off' were grouped as 'non-chronic'. The same definition was applied for other Gram-negative bacteria. MRSA and *Aspergillus* spp infections were defined as 'positive' in case of one or more positive cultures were obtained.

Corticosteroid use was classified as "any" systemic steroids *versus* no systemic steroids over the year. Intravenous (IV) antibiotic use was counted as the number of days IV antibiotics per year, and the number of IV treatment courses per year.

Biometric data are given as BMIz-score. Best, worst and mean BMI z-score per year were included.

Diagnosis of CFRD was based on OGTT (glycaemia after 120 minutes > 200 mg/dl) or on a typical clinical presentation with polyuria, polydipsia, glycosuria, in the face of fastinghyperglycaemia.

For all patients the highest HbA1c value for each year was registered. For the OGTT fasting glycaemia and glycaemia after two hours were registered.

The Ethics Committee of the University Hospitals Leuven acknowledged that the study is carried out according to the prevailing ethical standards.

2.4. Statistics

Data were analysed with the non-parametric independent samples median test, using SPSS (IBM Corp., Released 2011, IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY). Categorical parameters like gender, transplantation and death were assessed using chi square test. Statistical significance was considered at p-values < 0.05. Lung function decline was calculated as a linear regression through the best value of FEV1 of each quarter of a year. No decline was calculated if only 2 consecutive lung function values were available, in order to avoid falsely steep regression lines.

3. Results

3.1. Baseline Characteristics

Data were analysed for 23 CFRD patients and the same number of matched non CFRD patients. All patients were pancreatic insufficient. Baseline characteristics are presented in **Table 1**. Baseline disease characteristics were similar in both groups apart from median HbA1C at time of diagnosis which was higher in the CFRD group ($p < 0.001$).

All control patients had at least one OGGT excluding CFRD in the study period (Year − 2 to Year + 2): 6/11 patients had at least 1 OGTT in the J-2 to time 0 period and 9/11 patients at least one test in the period time 0 to Year + 2 (median glycaemia at 2 hours 126 mg/dl IQR 106 - 160).

3.2. Lung Function

Best FEV1 % predicted of each quartile of the four years' timeline did not significantly differ between CFRD and control patients (see figure 1). Lung function declinetwo years before start of insulin treatment was not different: a median (IQR) of −0.85% (−1.44% - −0.16%) for the CFRD group and −0.33% (−1.40% - 0.13%) for the controls ($p = 1.00$). Despite start of insulin treatment, we notice a significantly faster lung function decline in the CFRD group compared to the control group (median (IQR) −0.67% (−1.62 - 0.11%) *versus* 0.10% (−0.91 - 0.46%) over a period of 2 years.

3.3. Infection Status

The incidence of chronic infection with *Pseudomonas aeruginosa* or with other Gram negative bacteria was similar for both groups because this was one of the matching criteria (**Table 2**). When we looked at all the gram negative bacteria together, the number of positive cultures per year tended to be higher in the CFRD group, in comparison with the controls (data not shown). The incidence of MRSA infections was 7% in the CFRD group versus 10% in the control group and did not significantly differ.

Table 1. Baseline characteristics. Continuous variables are expressed as median (IQR).

	CFRD N = 23	Matched controls N = 23	p-value
Current age	21.2 years (16.7 - 23.6)	20.7 years (16.0 - 23.5)	1.00
Gender F/M	14/9	14/9	1.00
Age at CF diagnosis	0.1 years (0 - 0.5)	0.1 years (0 - 0.1)	0.167
Age at CFRD diagnosis	14.0 years (13.4 - 17.0)	/	/
FEV1 % predicted at time zero	71.6 (59.2 - 89.2)	82.3 (57.8 - 92.5)	0.095
BMI Z-score at diagnosis	−0.89 (−2.23 - 0.42)	−0.71 (−1.29 - 0.16)	0.628
HbA1c at diagnosis	6.30 % (6.2% - 6.7%)	5.75% (5.5% - 6.1%)	<0.001
OGTT at time zero: fasting glycaemia	96 mg/dl (85 - 106)	/	/
OGTT at time zero: glycaemia at 120'	214 mg/dl (192 - 233)	/	/
F508 Homozygote	17/23	15/23	0.522
F508 Heterozygote/class I-III	5/23	8/23	0.326
No F508 deletion	1/23	0/23	0.321

Table 2. Overview of chronic versus non chronic infection status of *P. aeruginosa* and other gram negative bacteria, over the four years' timeline.

		CFRD +		CFRD −		p-value
		Non chronic	Chronic	Non chronic	Chronic	
Y − 2	**P. aeruginosa**	11	12	15	8	0.234
	Other Gram-bacteria	10	13	14	9	0.238
Y − 1	**P. aeruginosa**	14	9	16	7	0.536
	Other Gram-bacteria	10	13	13	10	0.376
Y + 1	**P. aeruginosa**	12	11	14	9	0.552
	Other Gram-bacteria	8	15	12	11	0.234
Y + 2	**P. aeruginosa**	14	9	18	5	0.200
	Other Gram-bacteria	11	12	16	7	0.134

3.4. Medication Use

The number of IV antibiotic days per year increased in both groups over the years but was always significantly higher in the CFRD group (**Table 3**).

The number of patients treated with oral steroids varied significantly from year to year in the CFRD group (between 4/23 or 17.4% to 6/23 or 26.1%), as well as in the control group (from 1/23 or 4.5% to 4/23 or 18.2%) in the control group. This was not different between groups. All years combined, 18/92 (19.6%) of CFRD group used steroids which is higher than the control group: 8/88 (9%) (p = 0.0458).

3.5. Nutritional Status

The median BMI z-score per year was comparable in both groups for each year (−0.77, −0.88, −0.89, −1.18 for the CFRD group, −0.94, −0.73, −0.72, −0.90 for the control group).

3.6. HbA1c

Median HbA1c rose in the CFRD group from 6.1% in year −2, to 6.4% in the fourth year. In the control group median HbA1 increased from 5.75% to 5.9%. The highest HbA1cper patient was significantly higher in the

Table 3. Overview of use of IV antibiotics per year, expressed as number of IV antibiotics days. Medians (range).

		CFRD+	CFRD-	p-value
Median (IQR) of IV antibiotic days	**Y − 2**	18 (12 - 43)	5 (0 - 16)	0.072
	Y − 1	26 (13 - 58)	1.5 (0 - 15)	0.022
	Y + 1	40 (15 - 58)	7 (0 - 18)	0.004
	Y + 2	33 (15 - 64)	0 (0 - 36)	0.016
	Y − 2 and Y − 1	45 (18 - 101)	7 (0 - 24)	0.002
	Y + 1 and Y + 2	59 (44 - 122)	15 (0 - 59)	0.016

CFRD group compared to the control group for the first three years of the timeline: medians in year −2 were 6.1% vs. 5.75% ($p = 0.03$), in year −1 6.2% vs. 5.8% ($p < 0.001$), and in year +1 6.3% vs. 5.75% ($p<0.001$). Only in the fourth year-that is the second year after start of insulin treatment-this difference was no longer significantly different (medians 6.4% vs. 5.9%; $p = 0.10$).

3.7. Transplantation and Mortality

There was no significant difference in transplantation between cases and controls (4 out of 23 for the CFRD group, 3 out of 23 for the controls, $p = 0.681$). Concerning mortality: 3 out of 23 in the CFRD group died (at 4, 9 and 10 years after time zero), 1 out of 23 for the controls died 7 years after time zero ($p = 0.295$).

4. Discussion

Since we do not systematically screen for CFRD with OGTT, we decided to study the clinical evolution of CF patients diagnosed with CFRD before the age of 18 years in our CF clinic using a case control approach. FEV1 (expressed as best FEV % predicted per quartile) did not significantly differ between the two groups over a time period starting 2 years before up to the diagnosis of CFRD. Despite start of insulin treatment FEV1 decreased faster in the CFRD group in the 2 years after the diagnosis. In a large data set from the European Epidemiologic Registry of Cystic Fibrosis (ERCF) (7566 CF patients), mean FEV1 % was significantly lower in pediatric patients diagnosed with CFRD [5]. Other studies also documented this negative effect on lung function [9] [10] [12]. In an older study [4] also using a matched control design, lung function was already worse in the 4 years preceding the diagnosis of CFRD. Faster lung function decline has been reported before diagnosis in a retrospectively cohort of 457 CF patients [26]. A large part of CFRD patients in our series have a relatively preserved lung function with a median (IQR) FEV1% at start of 82% (66-93%) which may partially explain the difference with older studies.

Chronic infection with *P. aeruginosa* and other gram negative bacteria was overall rare in the CFRD group and control patients were matched for this. Isolation of MRSA and *Aspergillus* spp were rather infrequent and not significantly different. We did not find literature to compare these data with.

Biometric evolution did not differ between both groups and this is in agreement with other recent data [15] where BMI z-score did not differ between those with and without CFRD. As in other multidisciplinary CF teams, there is a strong emphasis on dietary measures with close and intensive dietary follow-up by the dietician aimed at maintaining hyper caloric intake after CFRD diagnosis.

Our study cohort was not appropriate to estimate mortality. An extensive retrospective multicentre cohort study of 4234 CF patients showed that diabetes is a clear determinant of mortality [6]. Patients included were aged 0 - 65 years old and data are based on UK registry data form 1996-2005. Also other data on mortality date back at least 10 years [7]-[9].

The only difference between patients and controls in the years preceding the CFRD diagnosis was burden of therapy which may be an indication of disease severity. Higher need for therapy is one of the clinical reasons to plan an OGTT in our clinic. However, higher need for IV antibiotic treatment persisted after start of insulin treatment. We did not find other data on need for antibiotic treatment in CFRD to compare our data with.

Prescription of oral steroids(which in our centre reflects mostly occurrence of allergic bronchopulmonary as-

pergillosis) was higher in the CFRD patients only when grouping all the years. Oral steroid use may increase insulin resistance and therefore worsen glucose intolerance.

European (2005) as well as American guidelines (2010] [18] [19] recommend annual CFRD screening with an OGTT, starting at the age of 10 - 12 years old. There is however controversy about annual screening using OGTT [22]. The prerequisites for screening are that the natural course of the disease is well known, an adequate screening test is available and earlier diagnosis and treatment improves prognosis. There is consensus that random glucose, HbA1c and fasting glucose have insufficient sensitivity and specificity to be used for CFRD screening [27]. The problem is that the OGTT hardly performs better. Concerning specificity, glucose tolerance in CF patients is variable over time and a diabetic OGTT at one time point may revert to 'non diabetic' in a large proportion of patients or *vice versa* [4] [28] Additionally, the test sensitivity is low because discordance has been documented between OGTT results and glucose profile during normal feeding (as can be measured by-home glucose monitoring). Only the latter will tell the clinician if and how the patients should be treated [19] [20]. Continuous glucose monitoring would even be more informative [19] [29]. However, current data are insufficient to link GCM results to treatment needs and long term outcome. Most patients with CF have some degree of intermittent glucose elevation but it is not known whether they all need treatment [30]-[35].

The rationale to screen is that CFRD has a negative impact on disease course and increases mortality [4]-[12] while treatment may partially reverse these negative effects [4] [7] [13] [15] [36]. The rationale to use the OGTT is that there is no other easy and adequate screening test. Clinical harm may however already occur before the OGTT reaches the diabetic level (and thus before start of insulin treatment] [4] [9] [11] [13] [14]. Even modest increases in glycaemia may cause an increase in glucose concentration in the bronchial mucosae. This may facilitate the growth of respiratory pathogens and thus aggravate chronic endobronchial infection [37] because pathogens like *S. aureus* and *P. aeruginosa* utilise glucose as a growth substrate [38]. Furthermore, insulin insufficiency compromises nutritional status and loss in BMI has a negative impact on lung function [39].

There are little data on the benefit of treating the prediabetic status with insulin [40] [41] and doing so would add significant burden of therapy and risk for hypoglycaemia. Small uncontrolled studies suggest that treatment with insulin or oral antidiabetic drugs improves weight and clinical status in IGT CF adolescents [40]-[44].

So the arguments pro screening are the following: no early or specific symptoms and treatment improves prognosis. Arguments a*gainst screen*ing are: OGTT is cumbersome and time consuming, OGTT is not a good screening test (OGGT fluctuates over time and normal OGTT does not rule out post prandial hyperglycaemia), respiratory decline may occur already before abnormal OGTT. Additionally, no firm data are available that earlier therapy based on screening (ideally with CGM) in otherwise stable CF patients improves prognosis. Finally, there is a cost issue: at the age of 12 years, CFRD prevalence is around 7%. Therefore in 93% of children this test is futile. The cost of this test in a day care setting in our center is 330 euros.

In our CF clinic, we do not screen annually and the OGTT is used as diagnostic instead of screening tool. We do realise that because diabetes symptoms are often mild and a specific, diagnosis may be made too late. A recent study form Brazil suggested that from 52 screened patients, 10 had CFRD based on the OGTT while only 8 had a diagnosis based on clinical suspicion [45]. Although we do not have similar data for our center, we believe that the percentage of missed patients in our center will be lower due to our very low level of suspicion. This is supported by the finding that we currently have a comparable CFRD prevalence in our pediatric CF centre, in comparison to prevalence of the Belgian CF Register (5% vs. 2.5%). In a retrospective US study on 872 CF patients followed at the University of Minnesota [15], there was a CFRD prevalence of 2% in the group of children less than 10 years old, and 19% in de adolescent group.

Limitations of our study are the small cohort, the retrospective design, and the fact that we did not always find a perfect match for each CFRD patient fulfilling all of the matching criteria. The strengths of our study are the homogenous treatment of the patients and the extensive documentation of clinical status including airway pathogens and therapy burden.

5. Conclusions

Based on the results presented here we have no indication that the diagnosis of CFRD is made too late since lung function and weight are comparable for cases and controls. However, the higher treatment burden with IV antibiotics in the CFRD group and faster decline of lung function at follow-up might be avoided by earlier diagnosis.

These data are presented as a plead for more studies into optimized screening tests together with more studies on when and how to treat (pre) CFRD. As soon as more data are available on how to use continuous glucose monitoring as a screening tool for CFRD diagnosis and treatment decision, we are keen to change or clinical practice in order to optimise the treatment of our CF patients [23] [27].

References

[1] Zielenski, J. (2000) Genotype and Phenotype in Cystic Fibrosis. *Respiration*, **67**, 117-133. http://dx.doi.org/10.1159/000029497

[2] O'Riordan, S.M., Dattani, M.T. and Hindmarsh, P.C. (2010) Cystic Fibrosis-Related Diabetes in Childhood. *Hormone Research in Paediatrics*, **73**, 15-24. http://dx.doi.org/10.1159/000271912

[3] Moran, A., Becker, D., Casella, S.J., Gottlieb, P.A., Kirkman, M.S., Marshall, B.C., *et al.* (2010) Epidemiology, Pathophysiology, and Prognostic Implications of Cystic fibrosis-Related Diabetes: A Technical Review. *Diabetes Care*, **33**, 2677-2683. http://dx.doi.org/10.2337/dc10-1279

[4] Lanng, S., Thorsteinsson, B., Nerup, J. and Koch, C. (1992) Influence of the Development of Diabetes Mellitus on Clinical Status in Patients with Cystic Fibrosis. *European Journal of Pediatrics*, **151**, 684-687. http://dx.doi.org/10.1007/BF01957574

[5] Koch, C., Rainisio, M., Madessani, U., Harms, H.K., Hodson, M.E., Mastella, G., *et al.* (2001) Presence of Cystic Fibrosis-Related Diabetes Mellitus Is Tightly Linked to Poor Lung Function in Patients with Cystic Fibrosis: Data from the European Epidemiologic Registry of Cystic Fibrosis. *Pediatric Pulmonology*, **32**, 343-350. http://dx.doi.org/10.1002/ppul.1142

[6] Chamnan, P., Shine, B.S., Haworth, C.S., Bilton, D. and Adler, A.I. (2010) Diabetes as a Determinant of Mortality in Cystic Fibrosis. *Diabetes Care*, **33**, 311-316. http://dx.doi.org/10.2337/dc09-1215

[7] Bismuth, E., Laborde, K., Taupin, P., *et al.* (2008) Glucose Tolerance and Insulin Secretion, Morbidity, and Death in Patients with Cystic Fibrosis. *Journal of Pediatrics*, **152**, 540-545.

[8] Milla, C.E., Billings, J. and Moran, A. (2005) Diabetes Is Associated with Dramatically Decreased Survival in Female but Not Male Subjects with Cystic Fibrosis. *Diabetes Care*, **28**, 2141-2144. http://dx.doi.org/10.2337/diacare.28.9.2141

[9] Milla, C.E., Warwick, W.J. and Moran, A. (2000) Trends in Pulmonary Function in Patients with Cystic Fibrosis Correlate with the Degree of Glucose Intolerance at Baseline. *American Journal of Respiratory and Critical Care Medicine*, **162**, 891-895. http://dx.doi.org/10.1164/ajrccm.162.3.9904075

[10] Rosenecker, J., Hofler, R., Steinkam, P.G., *et al.* (2001) Diabetes Mellitus in Patients with Cystic Fibrosis: The Impact of Diabetes Mellitus on Pulmonary Function and Clinical Outcome. *European Journal of Medical Research*, **6**, 345-350.

[11] White, H., Pollard, K., Etherington, C., Clifton, I., Morton, A.M., Owen, D., *et al.* (2009) Nutritional Decline in Cystic Fibrosis Related Diabetes: The Effect of Intensive Nutritional Intervention. *Journal of Cystic Fibrosis*, **8**, 179-185. http://dx.doi.org/10.1016/j.jcf.2008.12.002

[12] Sims, E.J., Green, M.W. and Mehta, A. (2005) Decreased Lung Function in Female but Not Male Subjects with Established Cystic Fibrosis-Related Diabetes. *Diabetes Care*, **28**, 1581-1587. http://dx.doi.org/10.2337/diacare.28.7.1581

[13] Nousia-Arvanitakis, S., Galli-Tsinopoulou, A. and Karamouzis, M. (2001) Insulin Improves Clinical Status of Patients with Cystic-Fibrosis-Related Diabetes Mellitus. *Acta Paediatrica*, **90**, 515-519.

[14] Rolon, M.A., Benali, K., Munck, A., Navarro, J., Clement, A., Tubiana-Rufi, N., *et al.* (2001) Cystic Fibrosis-Related Diabetes Mellitus: Clinical Impact of Prediabetes and Effects of Insulin Therapy. *Acta Paediatrica*, **90**, 860-867.

[15] Moran, A., Dunitz, J., Nathan, B., Saeed, A., Holme, B. and Thomas, W. (2009) Cystic Fibrosis-Related Diabetes: Current Trends in Prevalence, Incidence, and Mortality. *Diabetes Care*, **32**, 1626-1631. http://dx.doi.org/10.2337/dc09-0586

[16] O'Riordan, S.M., Robinson, P.D., Donaghue, K.C. and Moran, A. (2009) Management of Cystic Fibrosis-Related Diabetes in Children and Adolescents. *Pediatric Diabetes*, **10**, 43-50. http://dx.doi.org/10.1111/j.1399-5448.2009.00587.x

[17] Ode, K.L. and Moran, A. (2013) New Insights into Cystic Fibrosis-Related Diabetes in Children. *Lancet Diabetes Endocrinology*, **1**, 52-58. http://dx.doi.org/10.1016/S2213-8587(13)70015-9

[18] Moran, A., Brunzell, C., Cohen, R.C., Katz, M., Marshall, B.C., Onady, G., *et al.* (2010) 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*, **33**, 2697-2708. http://dx.doi.org/10.2337/dc10-1768

[19] Kerem, E., Conway, S., Elborn, S. and Heijerman, H. (2005) Standards of Care for Patients with Cystic Fibrosis: A European Consensus. *Journal of Cystic Fibrosis*, **4**, 7-26. http://dx.doi.org/10.1016/j.jcf.2004.12.002

[20] UK Cystic Fibrosis Trust Diabetes Working Group (2004) Management of Cystic Fibrosis Related Diabetes Mellitus.

[21] Wickens-Mitchell, K.L., Gilchrist, F.J., Mckenna, D., Raffeeq, P. and Lenney, W. (2014) The Screening and Diagnosis of Cystic Fibrosis-Related Diabetes in the United Kingdom. *Journal of Cystic Fibrosis*, **13**, 589-592. http://dx.doi.org/10.1016/j.jcf.2014.01.008

[22] Walshaw, M. (2009) Routine OGTT Screening for CFRD—No Thanks. *Journal of the Royal Society of Medicine*, **102**, 40-44. http://dx.doi.org/10.1258/jrsm.2009.s19009

[23] Hameed, S., Jaffe, A. and Verge, C.F. (2015) Advances in the Detection and Management of Cystic Fibrosis Related Diabetes. *Current Opinion in Pediatrics*, **27**, 525-533. http://dx.doi.org/10.1097/MOP.0000000000000251

[24] Wang, X., Dockery, D.W., Wypij, D., Fay, M.E. and Ferris Jr., B.G. (1993) Pulmonary Function between 6 and 18 Years of Age. *Pediatric Pulmonology*, **15**, 75-88. http://dx.doi.org/10.1002/ppul.1950150204

[25] Lee, T.W., Brownlee, K.G., Conway, S.P., Denton, M. and Littlewood, J.M. (2003) Evaluation of a New Definition for Chronic *Pseudomonas aeruginosa* Infection in Cystic Fibrosis Patients. *Journal of Cystic Fibrosis*, **2**, 29-34. http://dx.doi.org/10.1016/S1569-1993(02)00141-8

[26] Schaedel, C., De Monestrol, I., Hjelte, L., *et al.* (2002) Predictors of Deterioration of Lung Function in Cystic Fibrosis. *Pediatric Pulmonology*, **33**, 483-491. http://dx.doi.org/10.1002/ppul.10100

[27] Waugh, N., Royle, P., Craigie, I., *et al.* (2012) Screening for Cystic Fibrosis-Related Diabetes: A Systematic Review. *Health Technology Assessment*, **16**, 1-6. http://dx.doi.org/10.3310/hta16240

[28] Sterescu, A.E., Rousseau-Harsany, E., Farrell, C., Powell, J., David, M. and Dubois, J. (2006) The Potential Efficacy of Omega-3 Fatty Acids as Anti-Angiogenic Agents in Benign Vascular Tumors of Infancy. *Medical Hypotheses*, **66**, 1121-1124. http://dx.doi.org/10.1016/j.mehy.2005.12.040

[29] Leclercq, A., Gauthier, B., Rosner, V., *et al.* (2014) Early Assessment of Glucose Abnormalities during Continuous Glucose Monitoring Associated with Lung Function Impairment in Cystic Fibrosis Patients. *Journal of Cystic Fibrosis*, **13**, 478-484. http://dx.doi.org/10.1016/j.jcf.2013.11.005

[30] Dobson, L., Sheldon, C.D. and Hattersley, A.T. (2004) Understanding Cystic-Fibrosis-Related Diabetes: Best Thought of as Insulin Deficiency? *Journal of the Royal Society of Medicine*, **97**, 26-35.

[31] Hameed, S., Morton, J.R., Jaffe, A., *et al.* (2010) Early Glucose Abnormalities in Cystic Fibrosis Are Preceded by Poor Weight Gain. *Diabetes Care*, **33**, 221-226. http://dx.doi.org/10.2337/dc09-1492

[32] Jefferies, C., Solomon, M., Perlman, K., Sweezey, N. and Daneman, D. (2005) Continuous Glucose Monitoring in Adolescents with Cystic Fibrosis. *The Journal of Pediatrics*, **147**, 396-398. http://dx.doi.org/10.1016/j.jpeds.2005.05.004

[33] Khammar, A., Stremler, N., Dubus, J.C., Gross, G., Sarles, J. and Reynaud, R. (2009) Value of Continuous Glucose Monitoring in Screening for Diabetes in Cystic Fibrosis. Archives de Pédiatrie, **16**, 1540-1546. http://dx.doi.org/10.1016/j.arcped.2009.09.007

[34] Martin-Frias, M., Ferreiro, A.L., Alcol, E.C., Gomez, M.A.A., Valverde, R.Y. and Castellanos, R.B. (2009) Continuous Glucose Monitoring System in the Screening of Glucose Disorders in Cystic Fibrosis. *Anales de Pediatria*, **70**, 120-125.

[35] Moreau, F., Weiller, M.A., Rosner, V., *et al.* (2008) Continuous Glucose Monitoring in Cystic Fibrosis Patients According to the Glucose Tolerance. *Hormone and Metabolic Research*, **40**, 502-506. http://dx.doi.org/10.1055/s-2008-1062723

[36] Mohan, K., Israel, K.L., Miller, H., Grainger, R., Ledson, M.J. and Walshaw, M.J. (2008) Long-Term Effect of Insulin Treatment in Cystic Fibrosis-Related Diabetes. *Respiration*, **76**, 181-186. http://dx.doi.org/10.1159/000110206

[37] Brennan, A.L., Gyi, K.M., Wood, D.M., *et al.* (2007) Airway Glucose Concentrations and Effect on Growth of Respiratory Pathogens in Cystic Fibrosis. *Journal of Cystic Fibrosis*, **6**, 101-109. http://dx.doi.org/10.1016/j.jcf.2006.03.009

[38] Garnett, J.P., Baker, E.H. and Baines, D.L. (2012) Sweet Talk: Insights into the Nature and Importance of Glucose Transport in Lung Epithelium. *European Respiratory Journal*, **40**, 1269-1276. http://dx.doi.org/10.1183/09031936.00052612

[39] Steinkamp, M.P., O'mahony, O.A., Brogley, M., *et al.* (2009) Treatment-Dependent Androgen Receptor Mutations in Prostate Cancer Exploit Multiple Mechanisms to Evade Therapy. *Cancer Research*, **69**, 4434-4442. http://dx.doi.org/10.1158/0008-5472.CAN-08-3605

[40] Bizzarri, C., Lucidi, V., Ciampalini, P., Bella, S., Russo, B. and Cappa, M. (2006) Clinical Effects of Early Treatment with Insulin Glargine in Patients with Cystic Fibrosis and Impaired Glucose Tolerance. *Journal of Endocrinological Investigation*, **29**, RC1-RC4. http://dx.doi.org/10.1007/BF03345538

[41] Mozzillo, E., Franzese, A., Valerio, G., *et al*. (2009) One-Year Glargine Treatment Can Improve the Course of Lung Disease in Children and Adolescents with Cystic Fibrosis and Early Glucose Derangements. *Pediatric Diabetes*, **10**, 162-167. http://dx.doi.org/10.1111/j.1399-5448.2008.00451.x

[42] Dobson, L., Hattersley, A.T., Tiley, S., Elworthy, S., Oades, P.J. and Sheldon, C.D. (2002) Clinical Improvement in Cystic Fibrosis with Early Insulin Treatment. *Archives of Disease in Childhood*, **87**, 430-431. http://dx.doi.org/10.1136/adc.87.5.430

[43] Hameed, S., Morton, J.R., Field, P.I., *et al*. (2012) Once Daily Insulin Detemir in Cystic Fibrosis with Insulin Deficiency. *Archives of Disease in Childhood*, **97**, 464-467. http://dx.doi.org/10.1136/adc.2010.204636

[44] Kolouskova, S., Zemkova, D., Bartosova, J., *et al.* (2011) Low-Dose Insulin Therapy in Patients with Cystic Fibrosis and Early-Stage Insulinopenia Prevents Deterioration of Lung Function: A 3-Year Prospective Study. *Journal of Pediatric Endocrinology and Metabolism*, **24**, 449-454. http://dx.doi.org/10.1515/jpem.2011.050

[45] Noronha, R.M., Damaceno, N., Muramatu, L.H., Monte, O. and Calliari, L.E. (2014) Importance of Screening with Oral Glucose Tolerance Test for Early Diagnosis of Cystic Fibrosis-Related Diabetes Mellitus. *Pediatric Diabetes*, **15**, 309-312. http://dx.doi.org/10.1111/pedi.12094