AGE AND EXOCRINE PANCREATIC ENZYME REQUIREMENTS ARE MAJOR DETERMINANTS FOR CARBOHYDRATE METABOLISM IMPAIRMENT IN CHILDREN AFFECTED WITH CYSTIC FIBROSIS

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Introduction:

- The development of diabetes in patients affected with cystic fibrosis (cystic fibrosis related diabetes [CFRD]) is associated to a poorer nutritional status, respiratory function and an increase in mortality rate.
- Screening for CFRD is recommended from 10 years of age onwards, however prediabetic conditions could develop before that age. The clinical relevance of these conditions in CF and the eventual indication of screening before age 10 is not fully addressed.

Objectives:

1. To characterize the prevalence and degree of glucose metabolism impairment in 50 patients affected with cystic fibrosis (CF).
2. To explore the eventual role of genetic, clinical and therapeutic parameters as predictors of CFRD or prediabetic status.
3. To analyze whether the study of glucose and insulin levels both, fasting and throughout the oral glucose tolerance test (OGTT) and continuous subcutaneous glucose monitoring (CSGM) can afford any additional information related of these disorders.

Patients and methods:

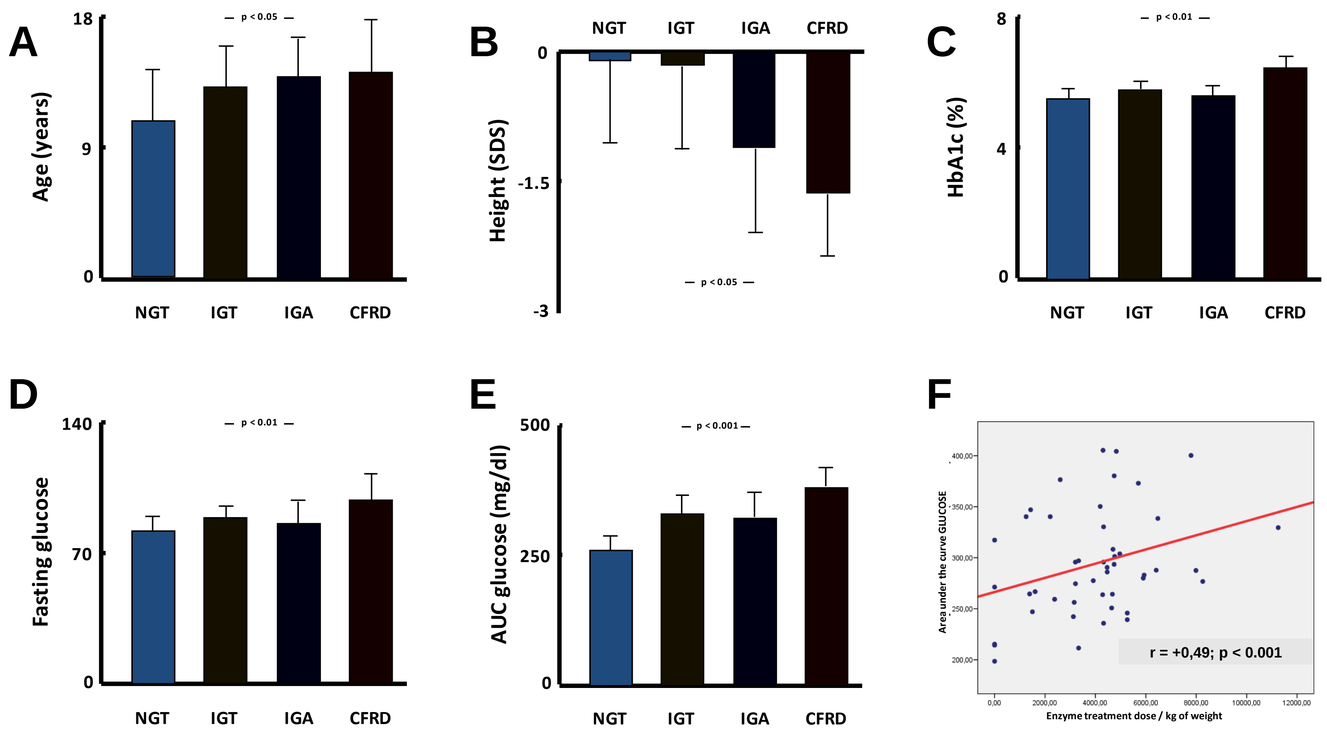
- Fifty CF patients aged above 5 years (27 males/23 females; mean age 12.27 ± 3.72 years), free from disease exacerbation (no need for steroid nor other acute treatments in the previous 8 weeks) were studied. Information on genetic (*CFTR* mutations) and clinical background (hospital admissions, bacterial colonizations, growth velocity and change in BMI in the previous year) was collected. At enrollment, height & weight [Waterlow indexes], and enzyme replacement dose were recorded and a pulmonary function test performed (considering standardized forced vital capacity [FVC] and forced expiratory volume [FEV-1] for analysis).
- Glycohaemoglobin (HbA1c), C reactive protein [CRP] and nutritional parameters were measured and an OGTT (for glucose and insulin [0, 30, 60 and 120´]) performed. Patients with impaired glucose metabolism (IFG, impaired fasting glucose: ≥100 mg/dl; IGT, impaired glucose tolerance: ≥144 mg/dl at 120´; IGA, indeterminate glucose alteration: ≥ 200 mg/dl at 30´or 60´ or CFRD: ≥ 200 mg/dl at 120´ or ≥126 mg/dl fasting [twice]) were offered continuous subcutaneous glucose monitoring for 7 days (CSGM, accepted by n=16), recording the time above 144 mg/dl and number of hyperglycemia peaks (>200 mg/dl). Glucose and insulin area under the curve (AUC) in the OGTT were calculated (0.25xfasting value+ 0.5x30´value +0.75x60´value +0.5x30´value).

Results:

- Twenty eight patients (56%) showed normal glucose tolerance (NGT), one (2%) IFG, 13 (26%) IGT, 3 (6%) CFRD and 5 (10%) (IGA).
- Older age and lower height were observed in patients according to the severity of their glucose metabolism (GM) defect (NGT < IGT < IGA < CFRD) (p<0,05, Table, Figures A & B). Significant differences in HbA1c, fasting and AUC glucose between groups were found (Table, Figures C, D & E) with HbA1c levels correlating with AUC-glucose (r=+0.49; p<0.001) and time of glucose >144mg/dL during CSGM (r=+0.57; p<0.05), but also with 120 minutes glycemia (r=+0.54; p<0.001) and not with fasting or AUC-insulin.
- Group comparison showed no differences in the prevalence of different *CFTR* mutations, lung function (FVC and FEV1), nutritional status (Waterlow index for weight) or the number of disease exacerbation episodes in the previous year (Table). No differences were observed in nutritional parameters (A, E, D vitamin, albumin, lipid profile) either.
- Exocrine enzyme replacement dose (per kg) significantly correlated with AUC-glucose (Figure F), but not with AUC-insulin .

	NGT	IGT	IGA	CFRD	p value
Age (years)	10.9 (±3.7)	13.3 (±3.0)	14.6 (±2.6)	14.9 (±3.6)	0.034 *
Height (SDS)	-0.11 (±1.0)	-0.16 (±1.0)	-1.10 (±1.0)	-1.63 (±0.7)	0.047 *
Growth velocity (SDS)	-0.87 (±2.5)	1.53 (±3.64)	3.77 (±8.1)	-1.71 (±2.7)	0.067
Height Waterlow index (%)	98.7 (±4.9)	99.1 (±4.1)	96.0 (±3.7)	92.0 (±2.7)	0.079
FEV1 (Z-Score)	-1.98 (±1.49)	-1.65 (±1.02)	-2.05 (±2.00)	-1.08 (±1.37)	0.566
FVC (Z-Score)	-1.51 (±1.45)	-0.84 (±0.97)	-1.02 (±0.78)	-0.79 (±0.76)	0.457
Exacerbations (last year)	3.7 (±2.7)	2.7 (±2.1)	2.8 (±2.1)	2.3 (±0.9)	0.930
Enzime dose (IUx1000/kg/day)	3.83 (±2.69)	4.16 (±2.28)	3.61 (±2.04)	4.94 (±2.79)	0.369
Ferritin (ng/ml)	29.1 (±10.9)	28.1 (±11.8)	43.2 (±19.0)	34.0 (±12.0)	0.343
CRP (mg/dL)	0.44 (±0.3	0.40 (±0.1)	1.52 (±2.0)	0.33 (±0.23)	0.673
HbA1c (%)	5.52 (±0.30)	5.8 (±0.25)	5.58 (±0.32)	6.43 (±0.37)	0.002 *
Fasting glucose (mg/dL)	82.15 (±7.6)	89.15 (±5.8)	85.8 (±11.6)	98.67 (±13.9)	0.016 *
Fasting insulin (mg/dL)	5.45 (±2.4)	8.94 (±5.6)	6.60 (±2.9)	9.03 (±1.4)	0.075
AUC glucose	260.2 (±31.6)	328.4 (±37.9)	322.5 (±47.3)	381.5 (±35.8)	0.000 *
AUC insulin	60.3 (±28.7)	100.5 (±63.6)	71.1 (±43.2)	87.5 (±26.9)	0.148

• Table: Variable comparison between groups (excluding impaired fasting glucose [IFG] due to n=1).
• *Abbreviations*: AUC: Area under the curve; CFRD: Cystic fibrosis related diabetes; CRP: C reactive protein; FEV-1: Forced espiratory volume; FVC: Forced vital capacity; IGA: Indeterminate glucose alteration; IGT: Impaired glucose tolerance; IU: International units; NGT: Normal glucose tolerance; NS: Non significant; SDS: Standard deviation [Z] score.



• Figures: Comparison between groups (excluding impaired fasting glucose [IFG] due to n=1).
• *Abbreviations*: AUC: Area under the curve; CFRD: Cystic fibrosis related diabetes; IGA: Indeterminate glucose alteration; IGT: Impaired glucose tolerance; NGT: Normal glucose tolerance; SDS: Standard deviation [Z] score.

Conclusions:

- 1) Insulin and glucose AUC analysis do not afford additional information to fasting/120minutes glucose determination in CF.
- 2) HbA1c is useful as an indicator of the time in hyperglycemia also in CF patients.
- 3) Older ages and greater enzyme intake are correlated to worse glucose metabolism status in CF patients.