

ORIGINAL ARTICLE

Insulin resistance, β -cell dysfunction and differences in curves of plasma glucose and insulin in the intermediate points of the standard glucose tolerance test in adults with cystic fibrosis[☆]



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Received 1 June 2014; accepted 8 August 2014

Available online 19 February 2015

KEYWORDS

Diabetes;
Cystic fibrosis;
Insulin resistance;
 β -cell function;
2-h oral glucose
tolerance test

Abstract

Background: Diabetes has become a co-morbidity with a negative impact on nutritional status, lung function and survival in cystic fibrosis.

Objective: To identify any changes in intermediate points after a 2-h oral glucose tolerance test (OGTT), pancreatic β -cell dysfunction, and insulin resistance in cystic fibrosis-related diabetes.

Methods: It was carried out a retrospective analysis in a cohort of 64 patients affected of cystic fibrosis, older than 14 years, using the first pathological OGTT. Peripheral insulin resistance was measured using the homeostasis model assessment for insulin resistance (HOMA-IR), and pancreatic β -cell function was calculated according to Wareham. Time to maximum plasma insulin and glucose levels and area under the curve (AUC_{0–120}) were also measured.

Results: Twenty-eight women and 36 men with a mean age of 26.8 years were enrolled, of whom 26.7% had normal glucose tolerance (NGT), 18.3% cystic fibrosis-related diabetes without fasting hyperglycemia (CFRD w/o FPG), 10% indeterminate (INDET), and 45% impaired glucose tolerance (IGT). HOMA-IR values were not significantly different between the diagnostic categories. Patients with any pathological change had worse β -cell function, with a significant delay in insulin secretion, although there were no differences in total insulin production (AUC_{0–120}). Time to maximum glucose levels was significantly shorter in NGT patients as compared to other categories, with glucose AUC_{0–120} being higher in the different diagnostic categories as compared to NGT.

[☆] Please cite this article as: Cano Megías M, González Albarrán O, Guisado Vasco P, Lamas Ferreiro A, Máiz Carro L. Resistencia insulínica, disfunción de la célula β pancreática y diferencias en los puntos intermedios de las curvas de glucemia e insulina tras una sobrecarga oral estándar de glucosa en adultos con fibrosis quística. Endocrinol Nutr. 2015;62:91–99.

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PALABRAS CLAVE

Diabetes;
Fibrosis quística;
Resistencia a la insulina;
Función de célula β ;
Test de tolerancia oral a la glucosa a las 2 horas

Conclusions: In over half the cases, peak blood glucose levels during a standard OGTT are reached in the intermediate time points, rather than at the usual time of 120 min. Patients with cystic fibrosis and impaired glucose metabolism have a delayed insulin secretion during the standard OGTT due to loss of first-phase insulin secretion, with no differences in total insulin production. Absence of significant changes in HOMA-IR suggests that β -cell dysfunction is the main pathogenetic mechanism.

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Resistencia insulínica, disfunción de la célula β pancreática y diferencias en los puntos intermedios de las curvas de glucemia e insulina tras una sobrecarga oral estándar de glucosa en adultos con fibrosis quística

Resumen

Fundamento: La diabetes se ha convertido en una comorbilidad prevalente que tiene un impacto negativo sobre el estado nutricional, la función pulmonar y la supervivencia en la fibrosis quística.

Objetivo: Identificar alteraciones en los puntos intermedios del test de tolerancia oral a la glucosa de 2 h (OGTT), la disfunción de la célula β pancreática y la resistencia insulínica en la diabetes relacionada con la fibrosis quística.

Métodos: Analizamos de forma retrospectiva una serie de 64 pacientes mayores de 14 años, mediante los datos del primer OGTT patológico durante su seguimiento. Se determinaron la resistencia insulínica, usando el modelo HOMA-IR, la función de la célula β pancreática según Wareham, el tiempo en alcanzar la concentración máxima plasmática de insulina y glucosa y el área bajo la curva (AUC_{0-120}).

Resultados: Se incluyeron 28 mujeres y 36 varones. La media de edad de la serie fue de 26,8 años. El 26,7% tenía una tolerancia normal (TGN), un 18,3% diabetes sin alteración de la glucosa en ayunas (CFRD sin FPG), el 10% una alteración indeterminada (INDET) y el 45% intolerancia hidrocarbonada (IGT). En los valores del HOMA-IR no se encontraron diferencias entre ningún grupo. Los casos con alguna alteración diagnóstica tenían una peor función de la célula β , con un retraso significativo en la secreción de insulina, aunque no hubo diferencias en su producción total (AUC_{0-120}). El tiempo en alcanzar el pico máximo de glucosa era significativamente menor en los TGN frente al resto de categorías, siendo el AUC_{0-120} de glucosa mayor en las distintas categorías diagnósticas frente a TGN.

Conclusiones: En más de la mitad de los casos el pico máximo de glucemia en la OGTT se alcanza en puntos intermedios y no en el tiempo clásico de 120 min. La secreción precoz de insulina está retrasada en los pacientes con fibrosis quística y alteraciones en el metabolismo de la glucosa, sin llegar a observarse diferencias en la producción total de la misma. La ausencia de alteraciones significativas en el HOMA-IR sugiere que la disfunción de la célula β es el principal mecanismo patogénico.

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Introduction

Cystic fibrosis (CF) is the fatal genetic disease with autosomal recessive inheritance most common among Caucasians. CF results from a mutation in the gene that encodes the protein called cystic fibrosis transmembrane conductance regulator (CFTR), located in the long arm of chromosome 7 (7q31.2). More than 1500 mutations have been identified, but the most common one is the deletion of phenylalanine at position 508 ($\Delta F508$), which affects approximately 94% of subjects; no other mutation occurs in more than 5% of individuals.^{1,2} The incidence of CF in Spain ranges from one per 2810–8028 live newborns, depending on the different prevalence of the $\Delta F508$ mutation.^{3,4} The survival

rate of patients with CF has significantly improved in the last decades as the result of advances in respiratory and nutritional medical care, which has allowed for a life expectancy of between 30 and 40 years.⁵ Cystic fibrosis-related diabetes (CFRD) and other carbohydrate metabolism changes are among the most common current comorbidities, although the first cases reported of CFRD and impaired glucose tolerance (IGT) in CF date back to 1955.⁵ The prevalence of CFRD increases with age: 9% at 5–9 years, 26% at 10–20 years, and up to 50% at around 30 years. From 15 to 30 years of age, the proportion of patients with normal glucose tolerance (NGT) decreases almost linearly, but this is difficult to estimate because glucose tolerance varies from year to year in patients with CF.^{6–10} The risk of death attributable

to diabetes in CF ranges from 31% to 55% regardless of other complications of CF.¹¹ However, the overall mortality rate has decreased in recent years from 6.7 (1992–1997) to 3.5 (2003–2008) per 100 person-years.¹² The early diagnosis of CFRD and adequate therapeutic management are therefore essential in the monitoring of these patients, not only in childhood, but also as a determinant clinical factor for prognosis in adolescence and adulthood.

The oral glucose tolerance test (OGTT) is the diagnostic test of choice because basal fasting plasma glucose (FPG) levels used as the only screening test would leave undiagnosed more than 2/3 of patients with CFRD.¹³ However, a blood glucose peak at 120 min may be absent in a high number of patients with CF, and it is therefore considered necessary to draw samples every 30 min during this test. It has been noted that subjects with CF but no CFRD have peak blood glucose levels at 30, 60, and 90 min, but blood glucose levels similar to healthy controls both at baseline and 120 min,¹⁴ and that these more subtle changes may have clinical relevance.^{15,16} Thus, in recent years various authors have suggested that blood glucose levels at 60 and 90 min may be more sensitive for detecting glucose intolerance in these patients.¹⁴ The US Cystic Fibrosis Foundation¹⁷ and the International Society of Pediatric & Adolescent Diabetes¹⁸ do not differentiate between CFRD with or without FPG because it has recently been suggested that treatment of both would involve benefits for nutritional status and lung function.^{19,20}

The study objectives were to assess OGTT curve changes (particularly, at these intermediate points), insulin resistance, and pancreatic β -cell function between patients with NGT and the different diagnostic categories of carbohydrate metabolism changes in a cohort of adolescent and adult patients with CF.

Material and methods

Subjects

A number of variables were collected from patients with CF followed up by the multidisciplinary cystic fibrosis unit of Hospital Universitario Ramón y Cajal during 2011–2012. Patients were diagnosed with CF using the criteria of Rosenstein and Cutting (1998) and the European Cystic Fibrosis Society.

Patients recruited into the study met the following criteria: diagnosis of CF, age older than 14 years, and annual screening for diabetes using OGTT. Exclusion criteria included: age under 14 years and incomplete OGTT data, the absence of records of lung function and nutritional parameters coinciding in time, pregnancy, HIV, HCV and/or HBV infection, and organ transplant at the time or before OGTT.

Methods

Data were collected from clinical histories, both electronic and those kept in hospital files. Data from the year of diagnosis of the first pathological screening OGTT, i.e. with some of the diagnostic categories defined by the American Diabetes Association (ADA),¹⁷ were analyzed. In patients with

no pathological OGTT, data from the most recently performed OGTT were collected.

The study was approved by the local ethics committee (registry number 063/12).

Oral glucose tolerance test

The OGTT consists of the administration of an oral solution containing 1.75 g/kg of glucose (maximum dose 75 g) dissolved in water. Blood samples are subsequently drawn to measure insulin and glucose levels at baseline and 30, 60, 90, and 120 min.

Study groups were defined based on the criteria for CFRD and other glucose metabolism changes—IGT and indeterminate glucose tolerance (INDET)—of the North American CF Consensus Conference (2010) and the American Diabetes Association (ADA).^{12,17} The OGTT was performed during a stable phase of the disease lasting at least 6 weeks—defined as the absence of intercurrent infections, systemic corticosteroid and/or antibiotic therapy, or hospitalization—and as an annual screening method from the age of 10 years, as recommended by the US Cystic Fibrosis Foundation¹⁷ and the International Society of Pediatric & Adolescent Diabetes.¹⁸

Plasma glucose levels were measured using the glucose oxidase method (Beckman Glucose Analyser; Beckman Instruments, Fullerton, CA, USA). Serum insulin levels were measured using a solid-phase chemiluminescent immuno-metric assay (IMMULITE 2000, Siemens Medical Solutions Diagnostics, Los Angeles, CA, USA). Maximum intra-assay and inter-assay coefficients were 5.5% and 7.3% for insulin. Analytical sensitivity of the assay for insulin was 2 mU/L. Blood glucose values are given in mg/dL, and insulin levels in mU/L.

Insulin resistance was tested using the homeostasis model HOMA-IR, which only requires basal glucose and insulin levels (G_0 [mmol/L] $\times$ I_0 /22.5)²¹. Pancreatic β -cell function (mU/mmol) was assessed as the ratio of insulin increase at 30 min ($I_{30} - I_0$ mU/L) to glucose at 30 min during the OGTT (in mmol/l) based on the model of Wareham et al.²² and on the methodology of Yung et al.²³

Respiratory function tests were performed using a spirometry system following the procedures modified in 1987 by the National Institute for Occupational Safety and Health and the American Thoracic Society. The results of the forced expiratory volume in 1 s (FEV1) are given as the percentage of the predicted value for age, sex, race, weight, and height according to the recommendations of the Spanish Society of Pneumology and Thoracic Surgery (SEPAR).

Statistical analysis

Quantitative variables are given as their respective frequencies, and normally distributed continuous variables as mean (and standard deviation). Variables not normally distributed are given as median and interquartile range (IQR, $I_{p25-p75}$). The normal distribution of variables was verified using a Kolmogorov–Smirnov test.

A bimodal Student's *t* test for independent data was used as a parametric test in continuous variables with a normal distribution. A Mann–Whitney *U* test was used for normally distributed variables, except in cases where a logarithmic

Table 1 Clinical, genetic, and lung function characteristics of patients undergoing oral glucose tolerance test and with blood glucose disorders related to cystic fibrosis.

	No.	Patients (%)	Mean (SD)
Age at study entry (years)	63		26.8 (9.5)
Age at diagnosis of cystic fibrosis (years)	61		1 (<i>I</i> _{p25–p75} 5.5) ^a
Sex	64		
Male		36 (56.25)	
Female		28 (43.75)	
Mutational status $\Delta F508$	64		
Heterozygous		48 (75)	
Homozygous		15 (23.4)	
Unknown		1 (1.6)	
Normal glucose tolerance (NGT)	60	16 (26.7)	
Cystic fibrosis-related diabetes with no impaired basal blood glucose (CFRD without FPG)	60	11 (18.3)	
Indeterminate tolerance (INDET)	60	6 (10)	
Carbohydrate intolerance (IGT)	60	27 (45)	
Lung disease	62	61 (98.4)	
Exocrine pancreatic disease	62	46 (74.2)	
BMI	61		20.3 (3.3)
Total FEV1 (%)	61		69.5 (20.4)
FVC %	61		75.1 (19)

^a Median and IQR.

data transformation showed a better fit of the model in the comparison of the different diagnostic categories in the area under the curve (AUC_{0-120}) and in time to reach peak plasma insulin and glucose concentration (T_{max} in minutes). Times to peak insulin and glucose concentration were calculated assuming a Gaussian distribution of data in the OGTT.

A value of $p < 0.05$ (two-sided) was considered significant in all tests. Statistical analyses were performed using software SPSS version 18.0 (Chicago, IL, USA) and MedCalc Statistical Software version 13.1.2 (MedCalc Software bvba, Ostend, Belgium; <http://www.medcalc.org>; 2014).

Results

Mean patient age at study entry was 26.8 years (SD 9.5). The sample consisted of 64 patients, of which 60 were finally included in the analysis. Table 1 shows the general characteristics of the sample.

NGT after the OGTT was found in 26.7% ($n = 16$). CFRD without FPG was detected in 18.3% ($n = 11$) of patients. There were no cases of CFRD with FPG. The INDET category was found in 10% ($n = 6$), and IGT in 45% ($n = 27$) of patients. In no patient was impaired FPG detected.

Glycemic status and glucose and insulin response in the OGTT

Peak blood glucose level was reached at 30 min in 10.9% of patients, at 60 min in 50%, at 90 min in 15.6%, and at 120 min in 6.3% of patients. Peak insulin level was found at 120 min in 40.6% of patients, while 25% reached it at 90 min, 10.9% at 60 min, and 3.1% at 30 min of the OGTT.

A comparison of patients with NGT and those with CFRD criteria without FPG (Table 2; Fig. 1) showed a statistically significant difference in mean plasma glucose levels from minute 30 of the test ($p = 0.018$), a difference that persisted in the next measurements at 60, 90, and 120 min

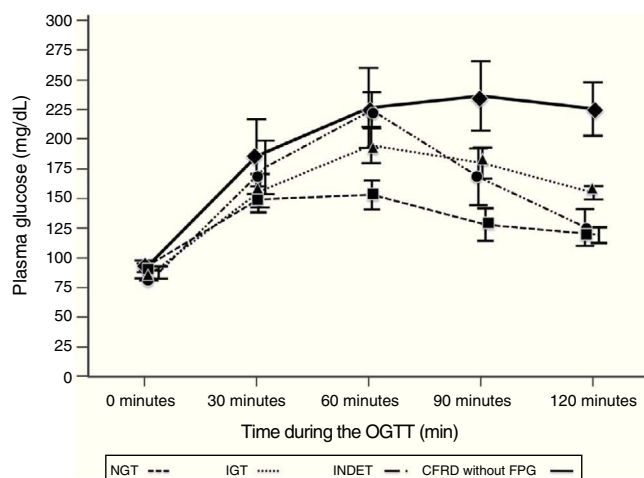


Figure 1 Mean glucose concentration in mg/dL after an oral glucose tolerance test in patients with cystic fibrosis and different diagnostic categories of carbohydrate metabolism disorders. NGT vs CFRD without FPG: $p = 0.018$ at 30 min; $p < 0.001$ at 60, 90, and 120 min. NGT vs IGT: $p < 0.001$, at 60, 90, and 120 min; $p = NS$ at 30 min. NGT vs INDET: $p = NS$ at 30 and 120 min; $p < 0.001$ at 60 min and $p = 0.016$ at 90 min. CFRD without FPG: cystic fibrosis-related diabetes with no impaired fasting blood glucose; IGT: impaired glucose tolerance; INDET: indeterminate glucose tolerance; NGT: normal glucose tolerance.

Table 2 Differences in the OGTT curve between NGT and the different categories of carbohydrate disorders.

	NGT	CFRD without FPG	t (95% difference interval)	p	IGT	t (95% difference interval)	p	INDET	t (95% difference interval)	p
Basal glucose	81.13 (7.16)	93.36 (14.14)	-1.78 (-18.19, 1.71)	0.1	89.85 (9.61)	-1.7 (-10.33, 0.88)	0.1	88 (4.86)	-0.9 (-9.53, 3.78)	0.38
Basal insulin	5.09 (3.87)	3.74 (2.48)	- (-1.78, 4.49)	0.23	4.16 (3.33)	- (-1.32, 3.19)	0.32	3.72 (2.13)	- (-2.14, 4.89)	0.86
Glucose 30 min	151.67 (21.89)	185.3 (43.84)	-2.55 (-60.92, -6.35)	0.02	160 (34.43)	-0.84 (-28.35, 11.69)	0.41	172.83 (20.73)	-2.03 (-42.99, 0.66)	0.06
Insulin 30 min	42.03 (21.83)	20.58 (15.23)	2.47 (3.36, 39.56)	0.02	24.1 (23.5)	2.41 (2.91, 32.96)	0.02	28.13 (15.35)	1.42 (-6.65, 34.45)	0.17
Glucose 60 min	149.75 (24.6)	226.4 (47.22)	-5.46 (-105.65, -47.65)	<0.001	200.35 (36.78)	-4.86 (-71.63, -29.57)	<0.001	219.33 (13.89)	-6.49 (-91.96, -47.21)	<0.001
Insulin 60 min	56.19 (25.65)	47.4 (60.58)	0.49 (-28.33, 45.9)	0.63	45.1 (51)	0.78 (-17.62, 39.79)	0.42	57.12 (35.01)	0.07 (-29.65, 27.79)	0.95
Glucose 90 min	122.8 (27.92)	236.5 (41.15)	- (-142.18, -85.22)	<0.001	186.17 (31.58)	- (-85.54, -43.2)	<0.001	165.33 (21.73)	- (-69.26, -15.81)	0.016
Insulin 90 min	52.96 (37.33)	67.4 (89.07)	-8.26 (-68.86, 39.98)	<0.001	55.17 (47.83)	-0.15 (-31.47, 27.05)	0.88	66.88 (36.97)	-0.77 (-51.57, 23.72)	0.45
Glucose 120 min	111.44 (19.23)	229.36 (32.9)	- (-138.57, -97.28)	<0.001	163.22 (15.38)	- (-62.55, -41.02)	<0.001	124.5 (14.22)	- (-31.15, 5.02)	0.12
Insulin 120 min	44.61 (22.34)	72.14 (94.71)	-1.13 (-78.29, 23.23)	0.27	61.63 (35.41)	-1.72 (-37.03, -2.99)	0.09	53.92 (20.84)	-0.89 (-31.26, 12.63)	0.39

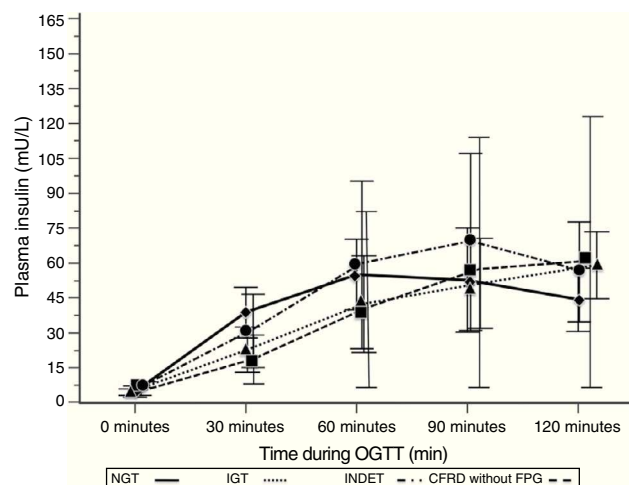


Figure 2 Mean insulin concentration in mU/L after the oral glucose tolerance test in patients with cystic fibrosis and different diagnostic categories of carbohydrate metabolism disorders. NGT vs CFRD without FPG: $p=0.022$ at 30 min; $p<0.001$ at 90 min; $p=NS$ at 60 and 120 min. NGT vs IGT: $p=0.021$ at 30 min; $p<0.001$ at 60, 90, and 120 min. NGT vs INDET: $p=NS$ at 30, 60, 90, and 120 min. CFRD without FPG: cystic fibrosis-related diabetes with no impaired fasting blood glucose; IGT: impaired glucose tolerance; INDET: indeterminate glucose tolerance; NGT: normal glucose tolerance.

($p<0.001$ at each of these points). As regards plasma insulin levels, the differences consisted of lower values at 30 min in patients with CFRD without FPG ($p=0.022$) and higher values at 90 min ($p<0.001$) (Table 2; Fig. 2).

In the comparison of glucose and insulin values in the NGT and IGT groups (Table 2), differences persisted for glucose levels at 60, 90, and 120 min ($p<0.001$ at each of these points), and also at the lowest insulin levels at 30 min in the IGT group ($p=0.021$). In the NGT and INDET groups, differences were also seen in plasma glucose levels at 60 and 90 min ($p<0.001$ and $p=0.016$ respectively).

The time to glucose peak (T_{max} minutes) was significantly shorter in patients with NGT as compared to all other categories (NGT 52.5 min [17.32] vs 71.59 min [24.39], $t=-2.87$, -19.09 [95% CI: -32.4, -5.78], $p=0.005$). Glucose T_{max} of the CFRD without FPG and IGT groups was also significantly delayed as compared to the NGT (Table 3) but not the INDET group. Differences in AUC_{0-120} for glucose were also found between the NGT and all other categories (5344.7 [2037.4] vs 10,178.9 [3050.3], $t=-5.87$, -4834.2 [95% CI: -6484.1, -3184.3], $p<0.001$), and higher values were also reached in each of them as compared to NGT (Table 3).

Plasma insulin T_{max} (minutes) was even more delayed if patients had any carbohydrate metabolism disorder (NGT 73.13 [28.92] vs 109.50 [17.39], $Z=4.37$, $p<0.001$); it was particularly delayed in the IGT and all other categories (IGT 111.92 [18.12] vs 88.00 [28.33]; $Z=3.58$, $p<0.001$). In addition, these differences in T_{max} for insulin persisted when NGT was compared to CFRD without FPG or IGT, but not in the case of INDET.

In AUC_{0-120} for insulin, no significant differences were found when the groups were compared to NGT (Table 4).

Table 3 Categories of carbohydrate disorders and plasma glucose parameters as a function of the area under the curve and time to peak concentration.

	TGN (n = 16)	CFRD without FPG (n = 11)	IGT (n = 27)	INDET (n = 6)
<i>Plasma glucose (mg/dL)</i>				
$T_{\max}$ (min) ^a	52.5 (17.32) 95% CI: 43.27–61.73	76.36 (28.03) ^b 95% CI: 54.54–95.19	73.84 (24.34) ^c 95% CI: 64.01–83.68	60 ^d
AUC _{0–120} ^e	5344.7 (2037.4) 95% CI: 4259.0–6430.4	12,923.2 (3115.1) ^f 95% CI: 10,830.41–15,016.0	9058.9 (2538.0) ^f 95% CI: 8033.7–10,084.0	9352.5 (1209.5) ^f 95% CI: 8083.2–10,621.8

^a *p* Values vs all other categories (global): NGT, *p* = 0.005; CFRD without FPG, *p* = 0.18; IGT, *p* = 0.06; INDET, *p* = 0.42.

^b NGT vs CFRD without FPG for $T_{\max}$: *t* = 2.74, 23.86 (95% CI: 5.93–41.8), *p* = 0.01.

^c NGT vs IGT for $T_{\max}$: *t* = 2.75; 19.72 (95% CI: 5.25–34.2), *p* = 0.008.

^d NGT vs INDET for $T_{\max}$: *t* = 1.04; 7.5 (95% CI: 7.47–22.47), *p* = 0.3.

^e Values of AUC_{0–120}. NGT, CFRD without FPG vs the rest of the series (for each category) *p* < 0.001. INDET, *p* = 0.7; IGT, *p* = 0.35.

^f NGT vs CFRD without FPG for AUC_{0–120}: *t* = 7.67; 7578.5 (95% CI: 5542.0–1932.0), *p* < 0.001. NGT vs IGT for AUC_{0–120}: *t* = 5.12; 4087.26 (95% CI: 2476.1–5698.4); *p* < 0.001; NGT vs INDET for AUC_{0–120}: UMW 6.00, *Z* = 3.1; *p* = 0.002.

Table 4 Categories of carbohydrate disorders and plasma insulin parameters as a function of the area under the curve and time to peak concentration, insulin resistance (HOMA-IR), and pancreatic β -cell function.

	TGN (n = 16)	CFRD without FPG (n = 8)	IGT (n = 27)	INDET (n = 6)
<i>Plasma insulin (mU/L)</i>				
$T_{\max}$ (min) ^a	73.13 (28.92) 95% CI: 57.72–88.53	112.5 (13.89) ^b 95% CI: 100.89–124.11	111.92 (18.12) ^c 95% CI: 104.61–119.24	95 (1225) ^d 95% CI: 82.14–107.85
AUC _{0–120} ^e	4268.5 (4733.9) 95% CI: 3289.9–5538.2	3017.2 (2342.9) ^f 95% CI: 1408.2–6464.7	4055.7 (3799.2) ^f 95% CI: 2521.2–5590.3	4982.1 (4478.3) ^f 95% CI: 2150.6–7814.4

^a *p* Values vs all other categories: NGT, *p* < 0.001; CFRD without FPG, *p* = 0.14; IGT, *p* = 0.001; INDET, *p* = 0.21.

^b NGT vs CFRD without FPG for $T_{\max}$: *t* = 3.62, 39.38 (95% CI: 16.81–61.94); *p* = 0.002.

^c NGT vs IGT for $T_{\max}$: UMW 57; *Z* 4.25; *p* < 0.001.

^d NGT vs INDET for $T_{\max}$: *t* = 1.77, 21.88 (95% CI: –3.87, –47.62); *p* = 0.09.

^e Values of AUC_{0–120} vs the rest of the series (for each category): NGT, *p* = 0.19; CFRD without FPG, *p* = 0.44; IGT, *p* = 0.16; INDET, *p* = 0.23.

^f NGT vs CFRD without FPG (log transformation) for AUC_{0–120}: *t* = –1.23, –0.15 (95% CI: –0.41, –0.1); *p* = 0.23. NGT vs IGT (log transformation); *t* = –1.54, –0.13 (95% CI: –0.3, –0.04), *p* = 0.13. NGT vs INDET: *t* = 0.22, 245.31 (95% CI: –2068.6, –2559.2), *p* = 0.83.

Insulin resistance and β -cell function

No significant differences were found in HOMA-IR values (Table 5) (NGT 1.04 [0.88] vs CFRD without FPG 0.85 [0.58]; *Z* = –0.45, *p* = 0.68; vs IGT 0.96 [0.79], *Z* = –0.1, *p* = 0.93; vs INDET 0.79 [0.42]; *Z* = –0.04, *p* = 0.97).

Statistical differences were however seen in the measurement of β -cell function (Table 5) when patients with NGT were compared to those with CFRD without FPG and IGT (NGT 4.34 [2.2] mU/mmol vs CFRD without FPG 1.6 [1.23] mU/mmol, *t* = 3.24, 2.74 [95% CI: 0.98–4.5], *p* = 0.004; vs IGT 2.2 [2.46] mU/mmol, *t* = 2.78, 2.14 [95% CI: 0.58–3.69], *p* = 0.008), but not in the INDET, which maintained a more preserved insulin secretion (vs INDET

2.65 [1.79] mU/mmol, *t* = 1.66, 1.68 [95% CI: –0.44, –3.81], *p* = 0.11).

Discussion

Pancreatic β -cell dysfunction is one of the main physiopathogenetic factors in the development of CFRD.^{8,24} The first phase of insulin secretion in response to an intravenous glucose overload and to other insulin secretion stimuli is impaired in adults with CF. Such impairment has also been reported after oral glucose overload.^{8,25,26} The time required to reach peak insulin levels is delayed from 30–60 min in healthy subjects to 90–120 min in subjects with CFRD.⁸ This

Table 5 Categories of carbohydrate disorders and insulin resistance parameters (HOMA-IR) and pancreatic β-cell function.

	TGN (n = 16)	CFRD without FPG (n = 8)	IGT (n = 27)	INDET (n = 6)
HOMA-IR	1.04 (0.88)	0.85 (0.58) ^a	0.96 (0.79) ^b	0.79 (0.42) ^c
Function β (mU/mmol)	4.34 (2.2)	1.6 (1.23) ^d	2.2 (2.46) ^e	2.65 (1.79) ^f

^a NGT vs CFRD without FPG, $p = 0.68$.

^b NGT vs IGT, $p = 0.93$.

^c NGT vs INDET, $p = 0.97$.

^d NGT vs CFRD without FPG, $p = 0.004$.

^e NGT vs IGT, $p = 0.008$.

^f NGT vs INDET $p = 0.11$.

loss of the first phase of insulin secretion may occur even in subjects with CF and NGT.^{6,18,25,26}

The results of our series are similar to those reported by Hammed et al.¹⁵ despite the use of methods not fully superimposable. In their study, the authors reported that glucose peak was reached at 60 min in half the cases and at 90 min in 33%; insulin peak was also delayed, occurring at 120 min in 42% and at 90 min in 24%.

It may thus be inferred that blood glucose peak is not reached in most CF patients at the classical time of 120 min, as required for the diagnosis of CFRD. In this regard, further study of the importance of blood glucose values at the intermediate OGTT points is needed. It has been suggested that subjects with CF without CFRD already experience hyperglycemia at 30, 60, and 90 min, but have blood glucose levels similar to healthy controls at baseline and 120 min. Therefore, blood glucose levels at 60 and 90 min could be more sensitive for detecting glucose intolerance in these patients.¹⁴ These results may be clinically relevant, because an association has recently been suggested between impaired lung function and the presence of hyperglycemia at the intermediate OGTT points—specifically with a blood glucose value at 60 min higher than 140 mg/dL—while no correlation was found between lung function and blood glucose values at 120 min.¹⁶ With regard to this, there are several studies using continuous glucose monitoring systems as a method for early diagnosis in these patients, who would have a normal blood glucose profile using the OGTT.^{14,27,28}

Glucose AUC_{0–120} in our series was greater in patients with some carbohydrate metabolism disorder as compared to the NGT group. These results are similar to those reported by other researchers.^{23,29,30}

A comparison of blood glucose data in the OGTT in the year of diagnosis in the NGT group to the other categories found significant differences at the intermediate points, including at 30 min in cases of CFRD. As suggested by Lee et al., the possibility of using a simpler test as a screening method should be studied. Lee et al.³¹ studied the glucose challenge test with 50 g of glucose (1 h-GCT), measuring blood glucose at 60 min. Thirty-one patients with CF were given the 1 h-GCT, and the OGTT 1 week later. Hyperglycemia was detected in 9 patients in both tests, but in 11 patients in the 1 h-GCT only (blood glucose 140 mg/dL), because they normalized blood glucose levels at 2 h of the OGTT. The authors concluded that the 1 h-CGT may be a helpful test for detecting postprandial hypoglycemia, and also for identifying patients with an impaired 2 h-OGTT.

In our series, most patients showed an insulin peak at 90 and 120 min. Several previous studies have shown changes in the first and second phases of insulin secretion using hyperglycemic clamp and the intravenous glucose tolerance test.^{29,32–36} Our results show significant differences in mean time to the insulinemic peak, which was shorter in subjects with NGT, but no differences were found in AUC_{0–120} (i.e. in total insulin secretion). In other words, the characteristic of patients with CF and a carbohydrate metabolism disorder is delayed insulin secretion, rather than the total insulin amount produced. Battezzati et al.³³ found that insulin production during the OGTT reached levels similar to healthy controls, despite β-cell dysfunction and impaired insulin secretion in the early phase in patients with CF, and suggested that the absolute insulin secretion rate (or insulin AUC_{0–120}) is not an accurate measure for describing the effects on β-cell function, and that delayed insulin secretion and total secretion are different factors affecting glucose tolerance. However, other authors found a decrease in total insulin secretion when AUC_{0–120} in CF patients and healthy controls was compared.^{23,37}

In our series, patients with NGT had better β-cell function than patients with CFRD without FPG or IGT. The INDET group had better preserved insulin secretion, and there were no significant differences. Yung et al.²³ studied in their series a subgroup of 30 CF patients with different diagnostic categories of carbohydrate disorders and 16 healthy controls, and noted that β-cell function was decreased in subjects with CF as compared to healthy controls ($p < 0.001$). Patients with CF also had significantly higher blood glucose levels at 90 min as compared to healthy controls, but both groups had similar blood glucose levels at 120 min.

As regards HOMA-IR, values suggesting insulin resistance were not found in any group. This method was first reported by Matthew et al. in 1985,²¹ and has been used to test insulin resistance in patients with type 2 diabetes and non-diabetics, although it has not been defined as an accurate method in insulin deficiency states.³⁸ The results of this index should be interpreted with caution, because both normal and decreased peripheral sensitivity states, increased sensitivity but with decreased hepatic sensitivity, and decreased hepatic sensitivity have been reported in patients with CF.¹⁹

In this regard, Yung et al.²³ studied the implication of insulin resistance in diabetes development in 68 adults with CF without CFRD and 46 healthy controls, and found no significant differences either in mean HOMA-IR values as compared to healthy controls or between the different

diagnostic categories of carbohydrate metabolism disorders. Other authors studied the hyperinsulinemic–euglycemic clamp in patients with CF and found no impaired insulin sensitivity.^{39,40}

Our series had design limitations. A retrospective study was conducted without a control group of healthy patients and with a relatively small patient sample, which may have affected its statistical power and did not allow for adjustment for other values (such as sex or age). In addition, a part of the sample consisted of adolescents, and their unique characteristics may have influenced the analysis of the variables. However, we think that the results obtained were comparable in several aspects to series where higher numbers of patients were analyzed.

Conclusions

As regards OGTT characteristics, blood glucose peak was reached at intermediate points rather than at the classical times of 0 and 120 min in half of the cases. We therefore suggest that intermediate time points of the curve may provide relevant information for assessing metabolic status in these patients. Prospective studies to analyze the relationship of hyperglycemia at these intermediate points to clinical and lung function impairment in CF are needed.

When the homeostasis model HOMA-IR was used, no relevant role of insulin resistance in the clinical stability phase was found in these patients.

Patients with some diagnostic impairment had pancreatic β -cell dysfunction, with a delay occurring in the early phase of insulin secretion with no differences in total insulin production (AUC_{0–120}).

Conflict of interest

The authors state that there are no conflicts of interest that could be perceived as detrimental to the impartiality of the research published.

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