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PANCREATIC ULTRASONOGRAPHY AS A PREDICTOR OF EXOCRINE ORGAN FUNCTION IN CYSTIC FIBROSIS

ULTRASSONOGRAFIA PANCREÁTICA COMO PREDITORA DA FUNÇÃO EXÓCRINA DE ÓRGÃOS NA FIBROSE CÍSTICA

ECOGRAFÍA PANCREÁTICA COMO PREDICTOR DE LA FUNCIÓN DE LOS ÓRGANOS EXOCRINOS EN LA FIBROSIS QUÍSTICA

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ABSTRACT

Background: Approximately 85% of patients with cystic fibrosis (CF) develop exocrine pancreatic insufficiency (EPI). We aimed to correlate ultrasound (US) echo-intensity of the pancreas with EPI.

Methods: Patients underwent US to measure the echo intensity (histogram) of the pancreatic head in relation to the left lobe of the liver (R ratio). Three cut-off values were defined for R: 1.0, 1.25 and 1.5. Patients were classified into three groups according to these cut-off values and further divided into (a) – with EPI and (b) – without EPI. Data on body mass index, glycaemic status, class I or II genotype, dose of pancreatic enzymes taken per day, presence of EPI (faecal fat ≥ 5 g/day and/or faecal elastase < 200 µg/g) and evidence of pancreatic disease on US (reduced-sized pancreas according to age, “white pancreas” - diffuse increase in echogenicity) were collected. The relationship between variables in the three groups was assessed using the tests of Mann–Whitney, chi-square and Fisher's exact.

Results: We included 49 patients. There was a significant correlation between white pancreas and R ≥ 1.0 (p = 0.0007), and EPI and R ≥ 1.5 (p = 0.0325). The difference between the R values for patients with or without EPI was statistically significant (p < 0,05).

Conclusions: US is a useful method to predict EPI in CF patients. R values above 1.5 could indicate that the patient is changing the status of pancreatic function and has an indication for other confirmatory tests, such as faecal elastase or quantitative faecal fat test.

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Keywords: Cystic Fibrosis. Pancreatic Insufficiency. Ultrasonography.

RESUMO

Contexto: Aproximadamente 85% dos pacientes com fibrose cística (FC) desenvolvem insuficiência pancreática exócrina (IPE). Nosso objetivo foi correlacionar a ecogenicidade do pâncreas avaliada por ultrassonografia (US) com a IPE.

Métodos: Os pacientes foram submetidos a US para medir a ecogenicidade (histograma) da cabeça do pâncreas em relação ao lobo esquerdo do fígado (razão R). Três valores de corte foram definidos para R: 1,0, 1,25 e 1,5. Os pacientes foram classificados em três grupos de acordo com esses valores de corte e subdivididos em (a) – com IPE e (b) – sem IPE. Foram coletados dados sobre índice de massa corporal, estado glicêmico, genótipo de classe I ou II, dose diária de enzimas pancreáticas, presença de insuficiência pancreática exócrina (IPE) (gordura fecal ≥ 5 g/dia e/ou elastase fecal < 200 µg/g) e evidência de doença pancreática na ultrassonografia (pâncreas de tamanho reduzido para a idade, "pâncreas branco" - aumento difuso da ecogenicidade). A relação entre as variáveis nos três grupos foi avaliada utilizando os testes de Mann-Whitney, qui-quadrado e exato de Fisher.

Resultados: Foram incluídos 49 pacientes. Houve correlação significativa entre pâncreas branco e R ≥ 1,0 (p = 0,0007), e entre IPE e R ≥ 1,5 (p = 0,0325). A diferença entre os valores de R para pacientes com ou sem IPE foi estatisticamente significativa (p < 0,05).

Conclusões: A ultrassonografia é um método útil para prever insuficiência pancreática exócrina em pacientes com fibrose cística. Valores de R acima de 1,5 podem indicar que o paciente está apresentando alterações na função pancreática e tem indicação para outros testes confirmatórios, como elastase fecal ou teste quantitativo de gordura fecal.

Palavras-chave: Fibrose Cística. Insuficiência Pancreática. Ultrassonografia.

RESUMEN

Antecedentes: Aproximadamente el 85% de los pacientes con fibrosis quística (FQ) desarrollan insuficiencia pancreática exocrina (IPE). El objetivo de este estudio fue correlacionar la ecogenicidad del páncreas en la ecografía con la IPE.

Métodos: Se realizó una ecografía a los pacientes para medir la ecogenicidad (histograma) de la cabeza del páncreas en relación con el lóbulo izquierdo del hígado (relación R). Se definieron tres valores de corte para R: 1,0, 1,25 y 1,5. Los pacientes se clasificaron en tres grupos según estos valores de corte y se dividieron a su vez en (a) con IPE y (b) sin IPE. Se recopilaron datos sobre el índice de masa corporal, el estado glucémico, el genotipo de clase I o II, la dosis diaria de enzimas pancreáticas, la presencia de insuficiencia pancreática exocrina (IPE) (grasa fecal ≥ 5 g/día o elastasa fecal < 200 µg/g) y evidencia de enfermedad pancreática en la ecografía (páncreas de tamaño reducido para la edad, «páncreas blanco» —aumento difuso de la ecogenicidad—). La relación entre las variables en los tres grupos se evaluó mediante las pruebas de Mann-Whitney, chi-cuadrado y exacta de Fisher.

Resultados: Se incluyeron 49 pacientes. Se observó una correlación significativa entre el páncreas blanco y un valor de R ≥ 1,0 (p = 0,0007), y entre la IPE y un valor de R ≥ 1,5 (p = 0,0325). La diferencia entre los valores de R para los pacientes con y sin IPE fue estadísticamente significativa (p < 0,05).

Conclusiones: La ecografía es un método útil para predecir la insuficiencia pancreática exocrina (IPE) en pacientes con fibrosis quística. Valores de R superiores a 1,5 podrían

indicar cambios en la función pancreática y la necesidad de realizar otras pruebas confirmatorias, como la elastasa fecal o la prueba cuantitativa de grasa fecal.

Palabras clave: Fibrosis Quística. Insuficiencia Pancreática. Ecografía.

1 INTRODUCTION

Cystic fibrosis (CF) is an autosomal recessive genetic disease whose mutations are present in the *cystic fibrosis transmembrane conductance regulator* (CFTR) gene. This gene is responsible for the transcription of the CFTR protein, whose function is to regulate ionic transport in the membrane of epithelial cells. The clinical manifestations of the disease include inflammation and infection of the airways, reduction of pancreatic exocrine secretion, intestinal and glandular duct obstruction, and pancreatic endocrine insufficiency [1].

Regarding pancreatic changes in CF patients, the main histopathological findings are atrophy, fibrosis, and fatty infiltration [2]. Computed tomography and magnetic resonance imaging (MRI) can show a signal intense pancreas with different patterns of fatty infiltration (diffuse or partial) and pancreatic atrophy as a way of evaluating these changes. However, due to its non-invasive nature and low cost, ultrasonography (US) is the recommended routine imaging test for screening for liver disease secondary to CF, which consequently leads to the most frequent evaluation of the pancreas using this method, especially in children [3]. Thus, the characteristics of the pancreas in individuals with CF on abdominal US have already been described in the literature and have a good correlation with MRI images, with similar echo intensity of the organ throughout its extension [4].

Once the exciting potential of US was established, studies began to appear with the aim of relating pancreatic exocrine function with the ultrasound findings of patients with CF. In this context, the histogram is a tool commonly present in US machines that allows the numerical measurement of the echo intensity (EI) of a tissue. For patients with CF, it was observed that after calculating the EI of the pancreas and liver (pancreatic EI/liver EI) and obtaining the R ratio between the numbers, a value capable of indirectly deducing the degree of pancreatic fatty infiltration/fibrosis was obtained – the more echo-intense the pancreas compared to the liver, the greater the tissue involvement [5]. Therefore, a greater R value could reflect indirectly impairment of pancreatic exocrine function. However, few studies have sought to correlate faecal elastase levels with histogram values for the evaluation of pancreatic exocrine function, and this test was the most used test in these studies [5,6]. In addition, the literature records of studies exclusively conducted with the paediatric population are focused on liver evaluation by US, without focusing on the pancreas. In addition, there are no studies exclusively trying to correlate pancreatic endocrine function with US changes in the organs of paediatric patients with CF.

The objective of this study was to evaluate the pancreas of children with CF by means of ultrasound histogram and to correlate the EI of the organ with clinical, laboratorial and imaging data related to the disease in an attempt to predict the exocrine function of the

pancreas, as well as to define the most appropriate cut-off point for CF: the R ratio for objective evaluation of the functional *status* of the organ.

2 MATERIALS AND METHODS

2.1 PATIENTS

Seventy-four children aged between 0 and 21 years with cystic fibrosis underwent abdominal ultrasound to evaluate the echo intensity of the pancreas and liver. Patients with hepatic steatosis were excluded from the study. The criteria for hepatic steatosis were a hyperechoic liver with fine, compact echoes, with posterior beam attenuation, which resulted in a relatively hypoechoic kidney [7]. Patients with incomplete laboratory test data, those in whom the pancreas could not be properly visualized on US due to technical problems with the exam, those who used alcoholic beverages and/or hepatotoxic drugs and those who did not sign the informed consent form were also considered ineligible. We thus present results from 49 CF patients.

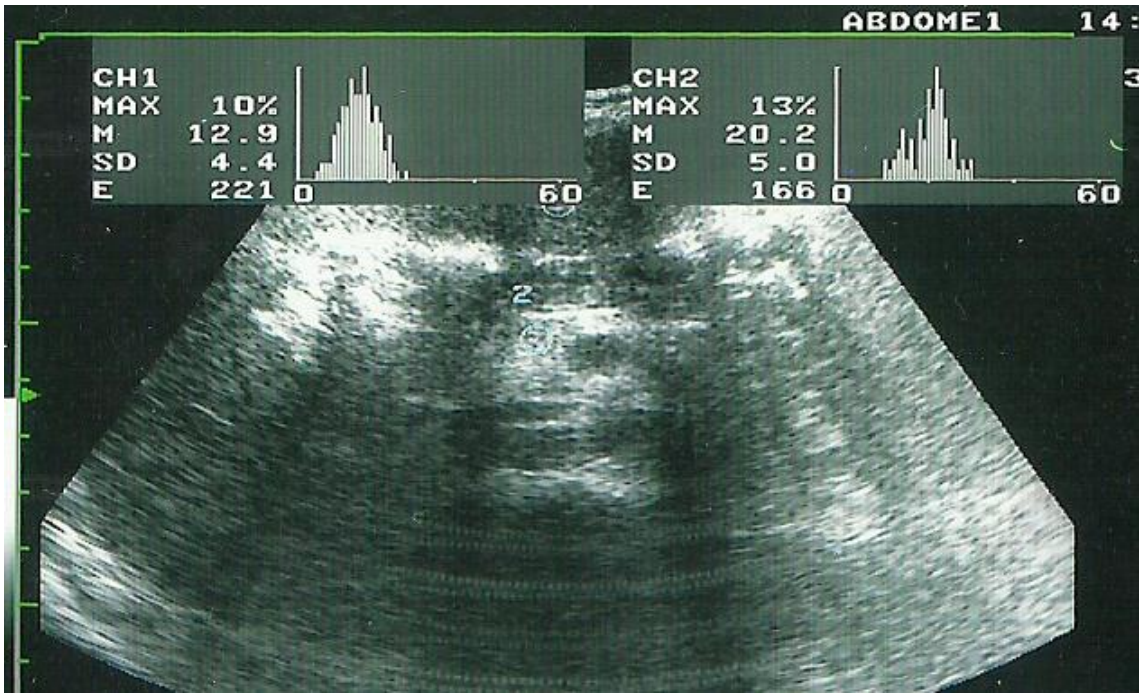
2.2 THE HISTOGRAM

Abdominal ultrasound was performed in patients with at least 6 hours of fasting in a single device, model PowerVision 6000 (manufacturer Toshiba Medical Systems Corporation, Otawara, Tochigi, Japan), using a convex transducer with 3.75 MHz (model PVM - 375AT). We performed a complete ultrasound scanning with the subjects in supine position using a transverse or oblique epigastric probe position.

To obtain the histogram values, the head of the pancreas and the left lobe of the liver were used because they are defined in the literature as anatomical areas with better evaluation of the echo intensity of the organs [5]. Region of interest (ROI) was chosen at approximately the same tissue depths in the measures, avoiding vessels and hyper-echoic areas. Three measures were taken. The median ratio was chosen. Next, the R ratio between the histogram of the pancreas in relation to the histogram of the liver was obtained. The measurement of the pancreas and liver histogram is shown in Figure 1.

Figure 1

Abdominal ultrasound of a patient with cystic fibrosis showing the performance of measurements of liver (CH1) and pancreas (CH2) histograms (M), in addition to the standard deviation (SD)



Patients were evaluated in three ways according to the histogram values and definition of the cut-off point of the R ratio: I) Patients whose R ratio was ≥ 1.0 - suggesting pancreatic fibrosis/steatosis. This group was subdivided into: Ia) R ≥ 1.0; Ib) R < 1.0. II) Patients whose R ratio was ≥ 1.25. This group was subdivided into: IIa) R ≥ 1.25; IIb) R < 1.25.

III) Patients whose R ratio was ≥ 1.5. This group was subdivided into: IIIa) R ≥ 1.5; IIIb) R < 1.5.

To define the cut-off points for the R values, the article by Wilson-Sharp et al. [8] defined the pancreas as normal if the echogenicity was the same as that of the liver parenchyma on US. Thus, the cut-off point for R could be 1.0. In the study by Engjom et al. [5] accuracy data was calculated from receiver operator curves (ROC). Therefore, they performed ROC curves expressing the diagnostic quality of R ratios predicting exocrine pancreatic failure. Sensitivity and specificity were better for predicting pancreatic lipomatosis/fibrosis in adult CF patients when the cut-off point was 1.25 (accuracy = 0.83) and 1.54 (accuracy = 0.90). Thus, in the present study, we decided to study pancreatic echogenicity with the same cut-off points for R of 1.25 and 1.5.

2.3 DATA COLLECTION

The following variables were associated with R values:

- Body mass index (BMI): A Z score of BMI < -2 indicated malnutrition (measured on the day of US).
- CF genetic mutation: the presence of at least one allele of class I or II mutations indicated a severe genotype.
- Age, in years.
- Altered glycaemic status: fasting glucose ≥ 5.5 mmol/L and/or oral glucose tolerance test after 120 minutes ≥ 7.7 mmol/L (performed up to 1 year before US).
- Current dose of orally used pancreatic enzyme, when in use (in IU/kg/day).
- Changes in the US:

- Reduced-sized pancreas: defined according to the age of patient, using the study of Siegel et al. as a reference for normality. To measure the pancreas on US, the largest anteroposterior diameter, in centimetres, of the body, head and tail of the organ was measured. Patients with at least two anatomical structures smaller than the reference value for age were considered to have a reduced pancreas [6].
- "White pancreas": diffuse increase in the echogenicity of the organ, commonly observed in patients with CF.

- Exocrine pancreatic insufficiency: a diagnosis of EPI could be established by either fecal fat or pancreatic elastase.

- Quantitative measurement of faecal fat ≥ 5 g/day [9].
- Quantitative determination of pancreatic elastase in faeces < 200 µg/g [10]. It was performed using the solid phase enzyme-linked immunosorbent assay (ELISA) with the BIOSERV kit [11], and the reading was performed at 450 nm on the GEN5 ELISA reagent plate from the manufacturer Biotek Instruments [12].

2.4 STATISTICAL ANALYSIS

To describe the profile of the sample according to the variables under study, frequency tables were prepared for the categorical variables with absolute values (N) and percentages (%). Descriptive measures were obtained for the continuous variables (mean, standard deviation, minimum, median and maximum), and the R values of the histogram were correlated with the values of age, fasting glucose, 2-hour glucose tolerance test and dose of pancreatic enzyme used by the patient using the Spearman correlation test.

The relationship between patient variables in Groups I, II and III was assessed using the Mann–Whitney test for quantitative variables and the chi-square test or Fisher's exact test for categorical variables [13,14].

For statistical analysis, the computer program “The SAS System for Windows (Statistical Analysis System)”, version 9.4 - SAS Institute Inc, 2002-2012, Cary, NC, USA was used. The significance level adopted for the study was 5%.

2.5 STUDY APPROVAL

The local ethics committee (No. 3,071,435) approved this study. Written informed consent was obtained from all study participants prior to participation.

3 RESULTS

A total of seventy-four patients were studied. However, 25 patients were excluded due to hepatic steatosis, which resulted in a final sample of 49 individuals (57.1% male). Of the sample, eight patients had not measured either faecal elastase or quantitative faecal fat test at the time of the study. Of the remaining forty-one patients, 31 (75.6%) had exocrine pancreatic insufficiency according to the criteria defined in the study. The eight patients without evaluation of exocrine pancreatic function underwent abdominal ultrasound examination and had the other study variables evaluated - BMI, CF genetic mutation, glycaemic status and current dose of orally used pancreatic enzyme, as well as changes in the US.

The distribution of R values was statistically higher in patients with pancreatic insufficiency (PI) than in patients without PI, as shown in the graph in Figure 2 ($p < 0,05$). The values of the means, medians and standard deviations of the clinical and laboratory variables are shown in Table 1.

Table 2 shows the comparative results between the characteristics of patients in groups Ia (R≥1.0) and Ib (R < 1.0). Table 3 shows the same variables for groups IIa (R ≥ 1.25) and IIb (R < 1.25), and Table 4 shows these variables for group IIIa (R ≥ 1.5) compared to group IIIb (R < 1.5).

Regarding the presence of “white pancreas”, there was a significant difference between group Ia in relation to group Ib, between IIa in relation to IIb, and between IIIa in relation to IIIb. For the variable “reduced pancreas”, there was no difference in frequency between groups.

Regarding the presence of EPI, there was a significant difference only between groups IIIa and IIIb. Considering the R≥1.5 threshold for identification of EPI, the following tests were

calculated: sensitivity = 61.3%, specificity = 80.0%, positive predictive value (PPV) = 90.5% and negative predictive value (NPV) = 40.0%.

The correlation between the R values and the quantitative variables (age, fasting glucose, 2-hour glucose tolerance test and dose of pancreatic enzyme used) did not show statistical significance.

Figure 2

Variation in the R ratio values for patients with and without pancreatic insufficiency (PI).

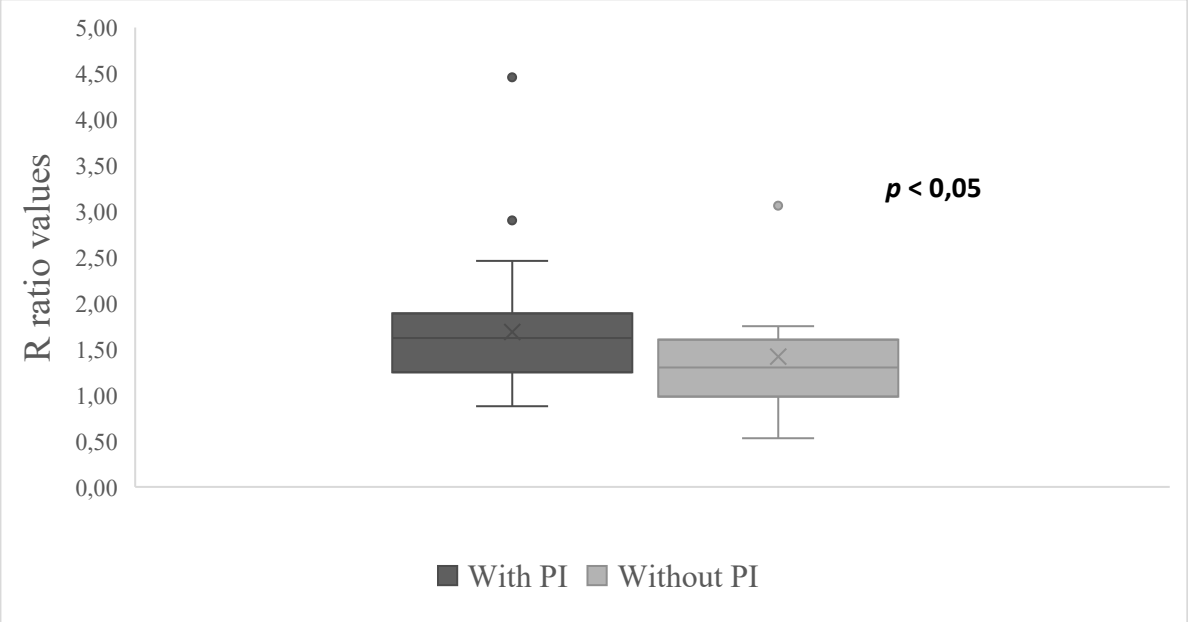


Table 1

Values of mean, median and standard deviation of quantitative laboratorial and clinical variables

Quantitative variable	No.	Mean	Median	SD
Age (years)	49	11.37	10.40	6.13
BMI (kg/m^2)	49	17.52	16.70	3.70
Faecal elastase (µg/g)	33	136.02	29.79	193.40
Dose of pancreatic enzyme (IU/kg/day)	40	6777.78	6857.00	1737.04

Quantitative faecal fat test (g/day)	33	9.60	5.99	10.29
GTT in 2 hours (mmol/L)	28	7.40	7.52	2.51
Fasting glucose (mmol/L)	45	4.67	4.61	0.65
R	49	1.55	1.46	0.67

SD: standard deviation; N: absolute number of patients; BMI: body mass index; GTT: oral glucose tolerance test; R: ratio between pancreatic and liver histogram.

Table 2

Distribution of patients according to clinical, laboratory and ultrasound characteristics in groups Ia (R ≥ 1.0) and Ib (R < 1.0)

Variables	Group Ia N=39	Group Ib N=10	Total N=49	*p*
Age (years)				
mean ± SD	11.6 ± 6.3	10.4 ± 5.8	11.4 ± 6.1	0.6023(*)
median (min–max)	10.4 (1.3-21.9)	10.5 (3.4-19.5)	10.4 (1.3-21.9)	
Exocrine PI				
yes	27 (77.1%)	4 (57.1%)	31 (75.6%)	0.6221(+)
no	8 (22.9%)	2 (33.3%)	10 (24.4%)	
Total	35 (100%)	6 (100%)	41(100%)	
Glycaemic test				
changed	13 (34.2%)	3 (42.9%)	16 (35.6%)	0.6860(+)
normal	25 (65.8%)	4 (57.1%)	29 (64.4%)	
Total	38 (100%)	7 (100%)	45 (100%)	
Genotype				
severe	34 (94.4%)	8 (100%)	42 (95.5%)	---
no	2 (5.6%)	0 (0.0%)	2 (4.5%)	
Total	36 (100%)	8 (100%)	44 (100%)	
BMI Z score <-2				
yes	4 (10.3%)	0 (0.0%)	4 (8.2%)	0.5687(+)
no	35 (89.7%)	10 (100.0%)	45 (91.8%)	
Total	39 (100%)	10 (100%)	49 (100%)	
“White” pancreas				
yes	38 (97.4%)	5 (50.0%)	43 (87.8%)	**0.0007(+)**
no	1 (2.6%)	5 (50.0%)	6 (12.2%)	
Total	39 (100%)	10 (100%)	49 (100%)	

Size of the pancreas				
normal	30 (76.9%)	9 (90.0%)	39 (79.6%)	0.6631(+)
reduced	9 (23.1%)	1 (10.0%)	10 (20.4%)	
Total	39 (100%)	10 (100%)	49 (100%)	

BMI: body mass index; N: absolute number of patients; SD: standard deviation; min: minimum; max: maximum; PI: pancreatic insufficiency; (*): Mann–Whitney test; (+): Fisher's exact test.

Table 3

Distribution of patients according to clinical, laboratory and ultrasound characteristics in groups IIa (R ≥ 1.25) and IIb (R < 1.25)

Variables	Group IIa N=34	Group IIb N=15	Total N=49	*p*
Age (years)				
mean ± SD	11.7 ± 6.4	10.5 ± 5.6	11.4 ± 6.1	0.5292(*)
median (min–max)	10.8 (1.3-21.9)	10.4 (2.4-19.5)	10.4 (1.3-21.9)	
Exocrine PI				
yes	24 (77.4%)	7 (70.0%)	31 (75.6%)	0.6834(#)
no	7 (22.6%)	3 (30.0%)	10 (24.4%)	
Total	31 (100%)	10 (100%)	41 (100%)	
Glycaemic test				
changed	12 (36.4%)	4 (33.3%)	16 (35.6%)	1.0000(#)
normal	21 (63.6%)	8 (66.7%)	29 (64.4%)	
Total	33 (100%)	12 (100%)	45 (100%)	
Genotype				
severe	29 (93.5%)	13 (100%)	42 (95.5%)	---
no	2 (6.5%)	0 (0.0%)	2 (4.5%)	
Total	31 (100%)	13 (100%)	44 (100%)	
BMI Z score <-2				
yes	3 (8.8%)	1 (6.7%)	4 (8.2%)	1.0000(+)
no	31 (91.2%)	14 (93.3%)	45 (91.8%)	
Total	34 (100%)	15 (100%)	49 (100%)	
“White” pancreas				
yes	33 (97.1%)	10 (66.7%)	43 (87.8%)	**0.0077(+)**
no	1 (2.9%)	5 (33.3%)	6 (12.2%)	
Total	34 (100%)	15 (100%)	49 (100%)	
Size of the pancreas				
normal	25 (73.5%)	14 (93.3%)	39 (79.6%)	0.1451(#)
reduced	9 (26.5%)	1 (6.7%)	10 (20.4%)	
Total	34 (100%)	15 (100%)	49 (100%)	

N: absolute number of patients; SD: standard deviation; min: minimum; max: maximum; PI: pancreatic insufficiency; BMI: body mass index; (*): Mann–Whitney test; (#): Chi-square test; (+): Fisher's exact test.

Table 4

Distribution of patients according to clinical, laboratory and ultrasound characteristics in groups IIIa (R ≥ 1.5) and IIIb (R <1.5)

Variables	Group IIIa N=23	Group IIIb N=26	Total N=49	*p*
Age (years)				
mean ± SD	12.1 ± 6.7	10.7 ± 5.6	11.4 ± 6.1	0.4228(*)
median (min–max)	11.3 (1.8-21.9)	10.4 (1.3-19.5)	10.4 (1.3-21.9)	
Exocrine PI				
yes	19 (90.5%)	12 (60.0%)	31 (75.6%)	**0.0325(#)**
no	2 (9.5%)	8 (40.0%)	10 (24.4%)	
Total	21 (100%)	20 (100%)	41 (100%)	
Glycaemic test				
changed	10 (43.5%)	6 (27.3%)	16 (35.6%)	0.2563(#)
normal	13 (56.5%)	16 (72.7%)	29 (64.4%)	
Total	23 (100%)	22 (100%)	45 (100%)	
Genotype				
severe	19 (90.5%)	23 (100%)	42 (95.5%)	---
no	2 (9.5%)	0 (0.0%)	2 (4.5%)	
Total	21 (100%)	23 (100%)	44 (100%)	
BMI Z score <-2				
yes	3 (13.0%)	1 (3.8%)	4 (8.2%)	0.3297(+)
no	20 (87.0%)	25 (96.2%)	45 (91.8%)	
Total	23 (100%)	26 (100%)	49 (100%)	
“White” pancreas				
yes	23 (100.0%)	20 (76.9%)	43 (87.8%)	**0.0237(+)**
no	0 (0.0%)	6 (23.1%)	6 (12.2%)	
Total	23 (100%)	26 (100%)	49 (100%)	
Size of the pancreas				
normal	16 (69.6%)	23 (88.5%)	39 (79.6%)	0.1572(#)
reduced	7 (30.4%)	3 (11.5%)	10 (20.4%)	
Total	23 (100%)	26 (100%)	49 (100%)	

N: absolute number of patients; SD: standard deviation; min: minimum; max: maximum; PI: pancreatic insufficiency; BMI: body mass index; (*): Mann–Whitney test; (#): Chi-square test; (+): Fisher's exact test.

4 DISCUSSION

The present study aimed to evaluate the usefulness of the histogram as an auxiliary tool in the evaluation of the *status* of pancreatic function in patients with CF. Regarding mutations in the CFTR protein, the relationship between loss of exocrine pancreatic function and specific genotypes is well established. According to experts from the *Canadian Consortium for Cystic Fibrosis Genetic Studies*, class I or II mutations are correlated with a high

prevalence of PI in this population [15]. This knowledge explains why in the present study, with a high prevalence of class I or II mutations (85.7%), we observed more than two-thirds of the patients with exocrine PI. Of these, 87.1% had an elevated pancreatic histogram value, but there was no statistical significance when relating R values ≥ 1.0 with a more severe genotype. This result may be because, in the present sample, almost 100% of the patients presented mutations considered severe.

Regarding the nutritional assessment, all patients in the sample with a BMI Z score <-2 had R ≥ 1.0, but we did not find a statistically significant association between BMI Z score <-2 and R ≥ 1.0. This may be explained by the fact that exocrine PI is only one of the factors that phenotypically determines a more severe disease in CF, and other factors, such as loss of lung function, chronic inflammatory *status*, increased energy expenditure associated with the occurrence of airway infections and low caloric intake linked to several biopsychosocial factors, are also important.

Regarding the US findings, we found an association of “white pancreas” in almost the entire sample with R values ≥ 1.0. Considering that “white pancreas” is an ultrasound finding suggestive of fatty infiltration of the organ, the association of R values ≥ 1 with this US finding suggests that the histogram is a good complementary tool for assessing the degree of pancreatic liposubstitution of the pancreatic parenchyma.

Regarding the glycaemic status of the patients, there was no statistical association between higher R values and altered blood glucose, even considering the cut-off value of R ≥ 1.5, showing that, based on the results of the present study, it is not possible to infer pancreatic endocrine function by histogram values. In an attempt to correlate exocrine PI with cystic fibrosis related-diabetes (CFRD), Soave et al. [16] comparatively evaluated the serum immunoreactive trypsin level (biomarker for exocrine PI) in neonates and the evolution of the endocrine pancreatic function of these patients - the trypsin level was inversely proportional to the risk of developing CFRD, suggesting that a more severe PI at an early age predicts the later development of CFRD. This could explain, in part, the fact that we did not find a relationship between R values and altered glycaemic *status* in the present study.

Regarding pancreatic exocrine function, we chose to use faecal elastase and quantitative faecal fat test for the diagnosis of PI. Faecal elastase is currently considered one of the main methods for this purpose, with good accuracy, and its normality value is standardized as above 200 µg/g [10]. The quantitative faecal fat test has the advantage of not presenting sample collection bias, as with the steatocrit, whose faecal fat value may vary according to the patient's diet in the 24 hours prior to collection [17]. Patients with CF and pancreatic sufficiency may evolve, at some point, to a state of pancreatic insufficiency that

will require the use of enzyme replacement therapy. In view of the fact that we found a statistically significant difference between groups with R ≥ and < 1.5 when evaluating exocrine pancreatic insufficiency (p < 0,05), in addition to the fact that the test presented good specificity and PPV, the change in R with a result above 1.5 could therefore indicate that patients who were previously being followed with pancreatic sufficiency could be changing the *status* of pancreatic function and has an indication for other confirmatory tests, such as faecal elastase or quantitative faecal fat test. Thus, we suggest that the histogram can be used as a complementary tool to infer exocrine pancreatic function in CF patients when R is greater than or equal to 1.5. This result is consistent with the fact that clinically manifested PI, with steatorrhea, intestinal malabsorption syndrome and fat-soluble vitamin deficiency, is established only after extensive involvement of the pancreatic tissue, when approximately 90% of pancreatic function has been lost [18]. Many patients with elastase < 200 µg/g had R values close to the cut-off point of 1.0, and there was a considerable number of patients who did not have faecal elastase measurement or quantitative faecal fat test (8 individuals), which may have interfered with the results. Furthermore, all patients in the sample with defined exocrine PI were on enzyme replacement therapy, which could explain why no association was found between the quantitative faecal fat test and lower R values, since the treatment enzyme reduces steatorrhea. These data indicate the need to investigate the histogram in a larger number of children with CF and identify a range of R values to establish a more consistent correlation with PI markers.

Regarding the dose of pancreatic enzymes used, the lack of correlation with R may be because the dose administered has a maximum value (300,000 IU/day), and even if there is an increase in weight and R, this dose is usually not increased. In addition, the need to increase the dosage of enzymes is not always due to worsening of pancreatopathy but is due to problems related to the release of enzymes in the duodenum due to pH changes in this region. Additionally, as the pancreas can maintain residual function even with extensive tissue loss [18], US may show an organ already with signs of fatty infiltration/fibrosis, without the patient having clinically manifested exocrine PI, requiring enzyme replacement therapy.

Regarding the evolution of pancreatopathy in CF, it is known that approximately 15% of CF patients who do not have exocrine PI, despite being clinically asymptomatic, do not have completely normal pancreatic function, which should deteriorate over time, with or without complications of pancreatitis [19]. In this context, although faecal elastase measurement is widely used to assess exocrine PI, its values may fluctuate throughout the course of the disease [20]. In addition, as previously mentioned, a loss of more than 90% of pancreatic tissue is needed for clinically manifested exocrine PI [18]. Therefore, we propose that when

the annual US evaluation is performed in patients with CF, if the US changes are very evident ("white" pancreas and high tissue EI), we suggest not postponing the investigation of exocrine PI by methods of functional evaluation of the organ. Furthermore, if the R ratio of the pancreatic histogram to the liver histogram is > 1.5, we suggest starting pancreatic enzyme replacement if the patient presents any clinical manifestation of intestinal malabsorption and/or low weight gain, in the impossibility of systematically measuring the faecal elastase.

The limitations of the study were the fact US was performed by only one examiner, and it was not possible to calculate an intraclass correlation index; and the sample size, which can later be increased for better confirmation of the study conclusions.

5 CONCLUSION

There was a statistically significant difference when comparing the frequency of exocrine pancreatic insufficiency between groups with R ratio ≥ 1.5 and < 1.5, suggesting that organ echo intensity can predict exocrine pancreatic function in patients with CF [21]. The change in R with a result above 1.5 could therefore indicate that the patient is changing the *status* of pancreatic function and has an indication for other confirmatory tests, such as faecal elastase or quantitative faecal fat test.

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