Influence of Pancreatic Status and Sex on Polyunsaturated Fatty Acid Profiles in Cystic Fibrosis

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BACKGROUND: Some but not all studies have reported abnormal polyunsaturated fatty acid composition in cystic fibrosis (CF) patients. We investigated the influence of pancreatic status and sex on the fatty acid profile in plasma and erythrocyte membranes in patients with CF.

METHODS: After a 1-step transesterification with acetyl chloride on plasma and washed erythrocyte membranes, we quantified fatty acid methyl esters by use of GC-MS in 124 CF patients and 80 age-matched healthy controls. In the CF group, mean (SD) age was 17.5 (11.3) years, and 51.6% were male. Pancreatic insufficiency was diagnosed in 78% of the CF population.

RESULTS: A decrease in docosahexaenoic acid concentrations was observed in CF patients independently of pancreatic status. Pancreatic insufficient CF patients displayed lower concentrations of linoleic acid and arachidonic acid and higher concentrations of dihomo-γ-linolenic acid and eicosatrienoic acid (mead acid) in plasma and erythrocyte membranes compared with healthy controls and pancreatic sufficient CF patients. Male CF patients had significantly lower docosahexaenoic acid and higher eicosatrienoic acid in plasma and erythrocyte membranes compared with female CF patients.

CONCLUSIONS: These results support the concept that multiple abnormalities of polyunsaturated fatty acid composition participate in the CF disease phenotype and that pancreatic status plays a major role in such abnormalities. Moreover, patient sex influences the polyunsaturated fatty acid spectrum in CF, with more marked abnormalities in males.

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Cystic fibrosis (CF)4 is the most prevalent autosomal recessive inherited disease in white populations. Mutations affecting a single gene, located on the long arm of chromosome 7 and encoding for the CF transmembrane conductance regulator (CFTR) protein, are responsible for the clinical manifestations of the disease (1). CFTR is expressed in the apical membrane of various epithelial cells and functions as a phosphorylation-regulated chloride channel and as a regulator of other ion channels (2). The most common CF mutation, a deletion of a single phenylalanine residue at position 508 (ΔF508), causes defective synthesis and folding of the mutant protein that fails to reach the apical membrane of many epithelial cell types (3).

Despite impressive advances in understanding the molecular basis of CF, life expectancy is still limited. Pulmonary disease accounts for most of the morbidity and mortality (4). The majority of CF patients have pancreatic exocrine insufficiency, even in early infancy, which, if untreated, leads to fat malabsorption and malnutrition (5). Pancreatic insufficiency can be alleviated by oral supplementation of pancreatic enzymes; however, many patients continue to experience a degree of steatorrhea, with fat absorption ranging from 80% to 90% of their dietary fat intake (6). Genotype-phenotype correlation in CF is highly variable (7), with modifier genes and environmental factors playing a part in determining severity of the disease.

The prognosis of CF has improved steadily over the past 5 decades, mainly because of aggressive treat-
ment before the onset of irreversible pulmonary changes. Long-term survival is significantly better in patients without pancreatic insufficiency. Increased survival rates of patients with CF have revealed the development of related metabolic alterations. Among these, abnormal blood polyunsaturated fatty acid (PUFA) concentrations have been reported (8). These alterations were first reported to be related to essential fatty acid deficiency (EFAD) (9) or defective essential fatty acid metabolism (10). More recently, an imbalance between arachidonic acid (AA) and docosahexaenoic acid (DHA), rather than a deficiency in PUFAs, was described in an animal model of CF (11) and in patients (12). However, it emerges from previous studies that PUFA status is quite variable in CF and discrepancies can result from a variety of factors such as small population sample sizes, inappropriate age-matching controls, different blood compartments, and analytical techniques (8). To our knowledge, only one work from a Swedish group has reported plasma phospholipid fatty acid composition in a CF population larger than 100 patients (13). As these Swedish CF patients regularly benefit from intralipid treatment (intravenous essential fatty acids course), data obtained from this study may not be representative of a nontreated CF patient population.

This study was designed to test the hypothesis that pancreatic status and sex influence the composition of PUFAs in plasma and erythrocyte membranes in patients with CF.

Materials and Methods

STUDY PARTICIPANTS

Clinical data were collected from 124 CF patients meeting the consensus-statement requirement for the diagnosis of this disease (14) and regularly attending our CF reference center in Brussels. Pancreatic status was determined by fat or elastase contents in stool samples: patients currently not treated by pancreatic enzyme replacement with fecal fat <7% (wt/wt) of the amount of dietary fat or with fecal elastase >200 µg/g were defined as pancreatic sufficient (15, 16), the others as pancreatic insufficient. Respiratory involvement was assessed by lung function testing. Forced expiratory volume in 1 s (FEV₁) was expressed as percentage of the predicted value for age, sex, and height (17). Patients with persistent positive cultures of *Pseudomonas aeruginosa* from on average 2 sputum collections over at least 6 consecutive months were classified as chronically infected. Nutritional status was simply assessed by body mass index [BMI, ratio of body weight (kg) to height (m²)], and BMI z score was calculated on the basis of BMI curves from a reference population (18).

CF-related diabetes was defined by requirement for insulin therapy. Among the patients, 61 were homozygous for the ΔF508 mutation, 51 were heterozygous for the ΔF508 mutation, and 12 had no ΔF508-mutated allele. Eighty age-matched healthy controls were enrolled. Our Institutional Research Ethics Committee approved the study, and all study participants signed informed consent forms before being enrolled.

CHEMICALS

Fatty acid methyl esters were of the highest available grade from either Sigma Chemical or Nu-Chek Prep. Solvents were purchased from Merck. Other chemicals and organic products were purchased from Sigma Chemical.

BLOOD SAMPLE PREPARATION

Blood samples (5 mL on EDTA), collected after fasting, were centrifuged at 1000g for 15 min at 4 °C. The plasma was collected and stored at −80 °C for subsequent analysis. Erythrocyte pellet was lysed with 40 mL Tris buffer (11 mmol/L, pH 7.4), centrifuged at 40 000g for 30 min at 4 °C (Sorvall RC-5B centrifuge, rotor SS-34; Sorvall Heraeus, Kendro Laboratory Products), and the supernatant fraction was discarded. Erythrocytes were washed 3 times with 40 mL ice-cold Tris buffer, and the final erythrocyte membrane pellet was stored at −80 °C for further fatty acid analysis.

FATTY ACID COMPOSITION DETERMINATION

We used the transesterification method developed by Lepage and Roy (19) and adapted by Masood et al. (20) with minor modifications. Briefly, in glass tubes containing 100 µL plasma, we added 20 µL of the internal standard solution (providing 50 mg C19:0/L) and 2 mL of a methanol/toluene (4/1, vol/vol) mixture. Samples were vortex-mixed for 30 s, and we carefully added 200 µL acetyl chloride dropwise while swirling the tubes. Tubes were capped under nitrogen and transferred to a heating oven at 103 °C for 90 min. After cooling, the tubes were uncapped, and samples were treated by addition of 5 mL 6% K₂CO₃ and of 3 mL hexane. Re-capped tubes were vortex-mixed for 1 min and centrifuged for 7 min at 500g. We collected the two upper organic phases and repeated the extraction procedure on the lower phase by adding 1 mL hexane. The two upper combined phases were washed with 1 mL distilled water, followed by a new centrifugation. The final organic phase was collected and evaporated under nitrogen to dryness at 40 °C. The dry residue was then redissolved in 200 µL hexane and transferred to capped vials for further analysis.

Fatty acid methyl esters were separated by use of a gas chromatograph (HP6890; Hewlett-Packard-Agilent) equipped with a capillary column (DB-FFAP).
interassay CVs were monitored and identified fatty acid methyl esters both by their respective retention times and by comparison with spectra of pure reference substances. Intra- and interassay CVs were <3% and <5.7%, respectively (except for γ-linolenate methyl ester, with 9.3%).

STATISTICAL ANALYSIS
Results are expressed as mean ± SD or median (interquartile range). Statistical data were analyzed by non-parametric Kruskal-Wallis test, and between-groups comparisons were evaluated by Mann-Whitney U test. We performed statistical analyses by use of Statview software (Abacus Concepts). Null hypothesis was rejected at \( P < 0.05 \).

Results

POPULATION CHARACTERISTICS
Table 1 summarizes clinical characteristics of CF patients, whose mean age (SD) at time of sampling was 17.5 (11.3) years. Age and male sex distribution were not statistically different between CF and control groups. Moreover, the CF cohort displays an equal sex distribution (64 males, 60 females; \( P > 0.99 \)). Homozygosity for the ΔF508 mutation was present in almost half of the CF cohort, and pancreatic insufficiency was diagnosed in approximately 80% of the CF population (\( n = 97 \)). Lung function was assessed in 101 of 124 patients. FEV\(_1\) averaged 81.7% (25.5%) of predicted. Approximately 20% of patients displayed chronic P. aeruginosa colonization (\( n = 25 \)).

PLASMA FATTY ACID COMPOSITION
Plasma fatty acid composition significantly differed in CF patients compared with healthy controls (Table 2). Overall, mean values of saturated fatty acid (SFA) and monounsaturated fatty acid (MUFA) concentrations were found to be increased, whereas PUFAs were globally decreased in CF compared with healthy controls. Among PUFAs, mean concentrations of linoleic acid (LA, C18:2 n-6), AA (C20:4 n-6), and DHA (C22:6 n-3) were decreased, whereas those of γ-linolenic acid (GLA, C18:3 n-6), dihomo-γ-linolenic acid (DGLA, C20:3 n-6), docosatetraenoic acid (DTA, C22:4 n-6), docosapentaenoic acid n-6 (DPA6, C22:5 n-6), EPA (eicosapentaenoic acid, C20:5 n-3), DPA3 (C22:5 n-3), and ETA (eicosatrienoic acid, C20:3 n-9), the latter considered a good marker of EFAD, were found to be increased in CF patients compared with healthy controls.

ERYTHROCYTE MEMBRANE FATTY ACID COMPOSITION
As observed with the plasma fatty acid profile, CF patients presented disturbances of fatty acid composition of the erythrocyte membranes (Table 3). Accordingly, MUFA concentrations were increased and PUFA concentrations were globally decreased in CF patients compared with healthy controls. LA and DHA concentrations were decreased in membrane preparations from erythrocytes, as they were in plasma samples. There was also a decreasing trend in AA concentrations (\( P = 0.051 \)). As observed in plasma, DGLA, DPA6, EPA, DPA3, and ETA concentrations were increased in CF patients compared with healthy controls.

INFLUENCE OF PANCREATIC STATUS ON PUFA PROFILES
As illustrated in Tables 2 and 3, pancreatic status was shown to exert distinct effects on the fatty acid profile in CF, with pancreatic insufficiency usually accentuating disturbances. Indeed, concentrations of PUFA, LA, and AA were decreased in both plasma and erythrocyte membranes in pancreatic insufficient patients compared with pancreatic sufficient patients. Moreover, GLA, DGLA, DPA6, and EPA concentrations in plasma as well as DGLA, DPA6, and EPA concentrations in erythrocyte membranes were increased in pancreatic insufficient patients. Interestingly, ETA concentrations, which were globally increased in the whole CF population compared with the control group, were found to be higher in the presence of pancreatic insufficiency. Conversely, DHA and DPA3 concentrations, which were respectively reduced and increased in CF compared with healthy controls, did not appear to be affected by pancreatic status.
We next assessed the influence of sex on the fatty acid composition of plasma and erythrocyte membranes in CF patients. It is important to note that none of the monitored clinical characteristics, such as age, prevalence of ΔF508 homozygosity, chronic *P. aeruginosa* colonization, pancreatic insufficiency, degree of lung function, or nutritional status, differed between male and female CF patients (data not shown). However, some influences of sex on the fatty acid profile, diverging from those revealed for pancreatic status, were detected in the CF group but not observed in the control group. Indeed, DHA concentrations [medians (interquartiles)], which were shown to be reduced in the whole CF group, appeared to be much more reduced in the subgroup of male patients compared with female patients in both plasma [1.28 (0.58) vs 1.64 (0.69) g/100 g of total FA, respectively; *P = 0.002*] and erythrocytes [3.51 (1.24) vs 4.06 (1.30) g/100 g of total FA, respectively; *P = 0.005*]. Interestingly, plasma α-linolenic acid (ALA) concentrations, which were not different between the whole CF population and the healthy control group, were found to be significantly reduced in male compared with female CF patients [0.46 (0.36) vs 0.57 (0.43) g/100 g of total FA, respectively; *P = 0.009*]. Moreover, plasma ETA concentrations, which were found to be almost 3-fold higher in the whole CF group compared with healthy controls (Tables 2 and 3), were much more increased in male than in female CF patients, suggesting male-dependent EFAD in CF [0.51 (0.57) vs 0.32 (0.44) g/100 g of total FA, respectively; *P = 0.005*].

### LAxDHA PRODUCT

The LAxDHA product (arbitrary units) was decreased in both plasma and erythrocyte membranes from CF patients compared with healthy controls. This decrease was more prominent in the presence of pancreatic insufficiency (Tables 2 and 3 and Fig. 1). Moreover, male CF patients displayed a lower LAxDHA product in plasma [28.98 (13.61) vs 36.84 (18.52), respectively; *P = 0.002*] and erythrocyte membranes [27.40 (12.70) vs 31.71 (11.89), respectively; *P = 0.013*] than female CF patients.
The AA/DGLA ratio (arbitrary units) was decreased in both plasma and erythrocyte membranes from CF patients compared with healthy controls. Interestingly, values similar to those detected in the control group were found in pancreatic sufficient patients, whereas pancreatic insufficient (PI) patients showed significantly lower values compared with healthy controls. Differences between groups were determined by Mann-Whitney test.

Table 3. Median (interquartile range) erythrocyte membrane fatty acid profile in healthy controls and CF patients according to pancreatic status (g/100 g total FA).

<table>
<thead>
<tr>
<th>Fatty acid</th>
<th>Controls</th>
<th>CF pancreatic sufficient</th>
<th>CF pancreatic insufficient</th>
<th>All CF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=80</td>
<td>27</td>
<td>97</td>
<td>124</td>
</tr>
<tr>
<td>Total SFAs&lt;sup&gt;a&lt;/sup&gt;</td>
<td>44.23 (1.58)</td>
<td>44.49 (1.10)</td>
<td>44.37 (2.25)</td>
<td>44.40 (1.85)</td>
</tr>
<tr>
<td>Total MUFAs&lt;sup&gt;b&lt;/sup&gt;</td>
<td>17.92 (1.51)</td>
<td>18.15 (1.22)</td>
<td>18.98 (1.98)&lt;sup&gt;4&lt;/sup&gt;</td>
<td>18.77 (1.68)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>C18:2 n-6 (LA)</td>
<td>8.66 (1.32)</td>
<td>8.42 (1.20)</td>
<td>7.09 (1.72)&lt;sup&gt;4&lt;/sup&gt;</td>
<td>7.52 (1.78)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>C20:3 n-6 (DGLA)</td>
<td>1.50 (0.53)</td>
<td>1.53 (0.52)</td>
<td>1.81 (0.55)&lt;sup&gt;4&lt;/sup&gt;</td>
<td>1.75 (0.57)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>C20:4 n-6 (AA)</td>
<td>16.26 (1.65)</td>
<td>16.44 (1.01)</td>
<td>15.66 (1.72)&lt;sup&gt;4&lt;/sup&gt;</td>
<td>15.91 (1.51)</td>
</tr>
<tr>
<td>C22:5 n-6 (DPA)</td>
<td>3.17 (0.85)</td>
<td>3.23 (0.81)</td>
<td>2.99 (0.84)</td>
<td>3.08 (0.87)</td>
</tr>
<tr>
<td>C22:5 n-3 (EPA)</td>
<td>0.67 (0.22)</td>
<td>0.66 (0.18)</td>
<td>0.78 (0.37)&lt;sup&gt;4&lt;/sup&gt;</td>
<td>0.76 (0.36)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>C20:5 n-3 (EPA)</td>
<td>0.53 (0.27)</td>
<td>0.55 (0.22)</td>
<td>0.61 (0.27)&lt;sup&gt;4&lt;/sup&gt;</td>
<td>0.59 (0.27)&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>C22:6 n-3 (DHA)</td>
<td>4.43 (1.49)</td>
<td>3.95 (0.91)&lt;sup&gt;4&lt;/sup&gt;</td>
<td>3.77 (1.35)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3.85 (1.32)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>C20:3 n-9 (ETA)</td>
<td>0.01 (0.00)</td>
<td>0.01 (0.09)&lt;sup&gt;4&lt;/sup&gt;</td>
<td>0.17 (0.24)&lt;sup&gt;4&lt;/sup&gt;</td>
<td>0.14 (0.24)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Total PUFAs&lt;sup&gt;c&lt;/sup&gt;</td>
<td>37.84 (1.73)</td>
<td>37.41 (1.26)</td>
<td>36.71 (1.93)&lt;sup&gt;4&lt;/sup&gt;</td>
<td>36.97 (1.60)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>AA/DGLA</td>
<td>10.80 (3.70)</td>
<td>11.08 (3.65)</td>
<td>8.48 (2.92)&lt;sup&gt;4&lt;/sup&gt;</td>
<td>8.75 (2.21)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>LAxDHA</td>
<td>37.88 (12.87)</td>
<td>34.12 (9.88)&lt;sup&gt;4&lt;/sup&gt;</td>
<td>28.47 (11.68)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>29.21 (12.43)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> C12:0 + C14:0 + C16:0 + C18:0 + C20:0 + C22:0 + C24:0.
<sup>b</sup> C14:1 n-7 + C16:1 n-7 + C18:1 n-9 + C18:1 n-7 + C20:1 n-9 + C24:1 n-9.
<sup>c</sup> C18:2 n-6 + C18:3 n-6 + C18:3 n-3 + C20:3 n-9 + C20:3 n-6 + C20:4 n-6 + C20:5 n-3 + C22:4 n-6 + C22:5 n-6 + C22:5 n-3 + C22:6 n-3.
<sup>d</sup> P < 0.0001, <sup>e</sup> P < 0.001, <sup>f</sup> P < 0.01, <sup>g</sup> P < 0.03 significantly different from healthy controls.
<sup>h</sup> P < 0.0001, <sup>i</sup> P < 0.001, <sup>j</sup> P < 0.03 significantly different from CF pancreatic sufficient patients.

**Fig. 1.** Distribution of LAxDHA product values (arbitrary units) expressed as median ± interquartile range (in box) and 10th and 90th percentiles (bars) in plasma (P) and erythrocyte membranes (RBC) in healthy controls (n = 80) and CF patients according to pancreatic status.

CF pancreatic sufficient (PS) patients (n = 27) are significantly different from healthy controls, P < 0.03. CF pancreatic insufficient (PI) patients (n = 97) are significantly different from both healthy controls, P < 0.0001, and CF PS patients, P < 0.03. Differences between groups were determined by Mann-Whitney test.
pancreatic insufficient patients displayed significantly lower values for this ratio (Tables 2 and 3 and Fig. 2). We observed no significant influence of sex on the AA/DGLA ratio.

**Discussion**

Disturbed plasma and tissue fatty acid compositions have been well described in CF patients (8). However, some major discrepancies in PUFA variations have been observed in the blood compartments analyzed in some studies (8). With the use of GC-MS, which provides improved characterization and sensitivity, and the inclusion in our study of a large cohort of CF patients, we have demonstrated characteristic and profound alterations in both plasma and erythrocyte membranes and the influence of pancreatic status and sex on these alterations.

As in the literature background results (8), we observed some significant changes in the plasma PUFA composition of our CF population. Although changes were statistically significant, physiological repercussions could not be established during this study. Reduced concentrations of LA in plasma and tissues have been found in CF patients (8, 12, 13) as well as in our CF population. Concentrations of AA have proved more variable in different studies, including values that were significantly decreased (21, 22) or not different (12, 22–25) compared with controls. Our CF patients presented a slight but significant decrease in plasma AA concentrations. Concerning DHA concentrations, we noted a significant decrease, as previously described in some studies (12, 21) but not in others (22, 23). The discrepancies in AA and DHA plasma concentrations, from the previous studies, can be explained in part by the low number of CF patients enrolled (8). Because of the size of our cohort of CF patients, we were able to find significant decreases in AA and DHA concentrations in plasma as often observed when these PUFAs were analyzed from plasma phospholipids instead of total plasma lipids (8, 26). However, the low DHA concentrations seem not to depend on pancreatic status. The presence of pancreatic insufficiency impaired the n-6 fatty acid concentrations, LA and AA, whereas the negative effect of CF on DHA concentrations was independent of pancreatic status.

Tissues from mammals seem to have a highly regulated specific membrane lipid composition (27, 28). The observed decrease for CF patients in the bioavailability of PUFAs, and notably AA and DHA, induces important changes in membrane fatty acid composition to the detriment of cell functionality. These lasting alterations can be involved, in part, in the progression in the physiopathology of specific tissues altered by CF.

On the assumption that the fatty acid composition of erythrocyte cell membrane may be similar to that of other organs and tissues (29), erythrocyte seems to be a reliable surrogate of the accretion of PUFAs and particularly n-3 fatty acids from exogenous dietary sources as well as endogenous synthesis (30). In studies in which fatty acid composition was monitored in erythrocyte membranes (8, 23, 24, 31–33), no abnormality was detected in AA and DHA concentrations, whereas the most consistent alterations seemed to be detected in LA content. When specific membrane fractions, such as phosphatidylethanolamines and phosphatidyl-
In regard to DHA concentrations, we found a significant decrease in DHA concentrations. The AA/DGLA ratio is usually described as an index of Δ5 desaturase activity, the enzyme that converts DGLA to AA in the essential fatty acid metabolism (8, 34). Thus, a decrease in this ratio can be related to a decrease or inhibition of Δ5 desaturase activity. However, in CF patients, a decrease in this ratio could also reflect enhanced Δ5 desaturase activity, with increased catabolism of AA due to its transformation into proinflammatory metabolites such as eicosanoids (36). In our CF patients, the AA/DGLA ratio was decreased only in pancreatic insufficient CF patients, so this ratio allows differentiation of CF patients according to pancreatic status. Accordingly, the AA/DGLA ratio may be a useful predictive marker for the presence of pancreatic insufficiency in CF patients, and it seems to be more discriminatory than the LAxDHA product. Indeed, the area under the curve (AUC), calculated from comparative ROC curves, was found to be larger in plasma and erythrocyte membranes for the AA/DGLA ratio than for the LAxDHA product (not shown).

In conclusion, we analyzed plasma and erythrocyte membrane fatty acid compositions from a large cohort of CF patients to address some questions arising from observed discrepancies in fatty acid profiles in the literature. The similar changes observed in both plasma and erythrocyte membranes indicate that plasma would be a logistically simpler sample for laboratory determination of fatty acid composition in CF patients. Our data clearly demonstrate that pancreatic status plays a cardinal role in the observed decreases in LA, AA, and DHA concentrations in blood lipids. However, the decrease of DHA concentrations seems to be independent of pancreatic status, since pancreatic sufficient CF patients also had this feature. We demonstrate that the LAxDHA product cannot be a diagnostic marker for pancreatic sufficient CF patients and that...
the AA/DGLA ratio can be a useful predictive marker for pancreatic insufficiency. Finally, the observed decrease of DHA concentrations in male CF patients compared with female CF patients requires further investigation.

Grant/funding Support: T.C.C. is a postdoctoral fellow of FSR (Fonds Spéciaux de Recherche) from the Université Catholique de Louvain. This work was supported by grants from the FSR, the Belgian CF Association, and the French CF Association, Vaincre la Mucoviscidose.

Financial Disclosures: None declared.

Acknowledgments: Critical reading of the manuscript by Pr. Jean Lebacq is gratefully acknowledged. The authors thank Françoise Wustefeld and Véronique Hubaux for their help. The authors also thank all the healthy controls and the CF patients of this study.

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10. Riordan JR, Grinstein S. Conformational maturation of DHA concentrations in male CF patients for pancreatic insufficiency. Finally, the observed decrease of DHA concentrations in male CF patients compared with female CF patients requires further investigation.