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Original Article

Cystic fibrosis dyslipidaemia: A cross-sectional study

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ABSTRACT

Background: The interest in cystic fibrosis (CF) dyslipidaemia as a potential risk factor for cardiovascular disease is increasing with patients' survival. This study aimed to investigate CF dyslipidaemia, its clinical correlates and links to oxidized low-density lipoprotein (oxLDL), adiponectin, and apolipoprotein E (APOE).
Methods: This cross-sectional study assessed clinical characteristics of CF, as well as the serum lipid profile, oxLDL, adiponectin, and APOE.
Results: In total, 108 CF subjects were enrolled in this study, with a median age of 22 years, BMI of 20.5 kg/m^2, FEV1% of 61%, of which 81% were pancreatic insufficient (PI). Healthy subjects (HS; $n = 51$) were in similar age. Hypocholesterolaemia occurred in 31% of CF subjects and in no HS. Hypertriglyceridaemia concerned 21% of patients (HS: 8%, $p = .04$), and low HDL-C 45% (HS: 6%, $p < .0001$). At least one of these three CF dyslipidaemia disturbances was present in 62% of CF subjects, but there were no significant differences in oxLDL, oxLDL/LDL-C ratio, adiponectin, and APOE between CF and HS groups. PI was independently associated with low total cholesterol, LDL-C, and non-high density lipoprotein cholesterol, with age and sex also modifying lipid levels. In CF ($n = 42$), triglycerides did not correlate with serum tumour necrosis factor α (TNF-α).
Conclusions: CF dyslipidaemia is highly prevalent and heterogenous. The lipid profile weakly associates with the clinical characteristics of CF as well as oxLDL, adiponectin, and APOE. Further research is needed, especially regarding HDL function in CF, the causes of hypertriglyceridaemia, and the value of essential fatty acid supplementation for CF dyslipidaemia.

1. Introduction

The growing life expectancy of cystic fibrosis (CF) patients has focussed attention to potential cardiovascular risk modifiers specifically found in this disease, of which CF dyslipidaemia is a notable example. CF dyslipidaemia most commonly involves hypocholesterolaemia, insufficient high density lipoprotein cholesterol (HDL-C) [1,2], or hypertriglyceridaemia [3]; the two latter abnormalities are independent risk factors of cardiovascular disease.

Whereas reduced cholesterol concentration is ascribed to fat maldigestion and malabsorption, hypertriglyceridaemia was proposed to result from excessive carbohydrate intake and chronic inflammation [4]. Surprisingly, in previous studies cholesterol fractions and triglycerides (TG) were largely independent of diabetes mellitus [1,3], but higher levels of low-density lipoprotein cholesterol (LDL-C) and TG tended to associate with both age and preserved exocrine pancreatic function [5]. Since elevated LDL-C is also a well-established cardiovascular risk marker, questions arise regarding the clinical relevance of these observations, including screening and treatment. The emerging picture of CF dyslipidaemia is complex, but there is insufficient detail to impact patient care. The exact correlates and mechanisms of the CF dyslipidaemia and hypertriglyceridaemia conundrum remain unresolved.

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The CF dyslipidaemia might be linked with inflammation, reduced adipose tissue and diminished lipoprotein scavenging capability [4], so three additional factors: oxLDL, adiponectin, and also total circulating apolipoprotein E (APOE) were considered in the present study. With regard to inflammation, oxLDL levels are a proxy for lipid peroxidation, which is a complex process that, among other factors, relies on the presence of unsaturated fatty acids and low vitamin E concentration [6]. OxLDL is internalised by endothelial cells and macrophages in the vascular wall, thereby contributing to atherosclerosis [7]. Chronic inflammation, altered fatty acid profile [8], and reduced tocopherol absorption have prompted the measurement of oxLDL in CF patients for the first time. Furthermore, adiponectin is a protein hormone of the adipose tissue, which reduces blood TG and increases HDL-C [9,10]. Low adiponectin might be associated with greater vascular oxidative stress, ultimately yielding higher oxLDL levels [11]. Although adiponectin concentrations in CF have been investigated in a series of studies, the results are equivocal [12,13] and were not performed in the context of lipid profile investigation. Apolipoprotein E (APOE) is responsible for the uptake of lipoproteins and APOE polymorphisms have been linked to the risk of cardiovascular disease; its serum concentration does not predict cardiovascular events, but may provide information regarding pathophysiology [14]. To the best of the authors' knowledge, circulating APOE concentrations have not been systematically studied in CF patients despite highly prevalent hypertriglyceridaemia. Although oxLDL, adiponectin and APOE are associated with atherosclerosis, they are not independent risk factors for cardiovascular disease.

It was hypothesised that total serum cholesterol, LDL-C, HDL-C, TG, oxLDL, adiponectin, and APOE concentrations differ between CF patients and healthy subjects (HS). In addition, we attempted to verify whether these factors associate with clinical characteristics of CF, with a particular focus on the pancreatic status.

2. Patients and methods

2.1. Design and setting

This prospective multicentre cross-sectional study was a part of the AtheroCF project [15]. The patients were recruited at the Poznan University of Medical Sciences (Poznan, Poland), in the Institute of Tuberculosis and Lung Diseases (Rabka and Warsaw, Poland), and in CF Outpatients' Clinic (Gdansk, Poland) in 2013–2016. Blood sampling took place after an overnight fast.

2.2. Participants

CF patient inclusion criteria were age ≥ 16 years and CF diagnosis compatible with the CF Foundation guidelines [16]. Patients and HS were excluded if they had: a family history of hypercholesterolaemia/hypertriglyceridaemia/early episodes of coronary artery disease or other cardiovascular diseases before 65 years in women or 55 years in men. Only young adults (18–35 years) were allowed to enter the study as HS so that the two groups do not differ in age. Family history was identified by self-report.

2.3. Variables

Serum total cholesterol was measured with an enzymatic method employing cholesterol esterase, cholesterol oxidase, and the Trinder reaction. LDL-C and HDL-C concentrations were assessed directly using an elimination method with catalase. TG evaluation was based on the glycerol phosphate oxidase Trinder method (Advia 1800 Chemistry, Siemens Healthcare, Erlangen, Germany).

High LDL-C threshold (≥100 mg/dL; ≥2.6 mmol/L) was set according to the recommended value in high cardiovascular risk subjects in the 2016 European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) guidelines [17]. TG cut-off (≥150 mg/dL; ≥1.7 mmol/L) conformed to the ESC definition of at least mild hypertriglyceridaemia. The HDL-C threshold was arbitrarily set (≤45 mg/dL; ≤1.2 mmol/L) between the value recommended for men and women by ESC/EAS. Since the total cholesterol threshold was not proposed in the ESC/EAS document, the older definition (2003) was employed (>190 mg/dL; >4.9 mmol/L). Hypocholesterolaemia was defined based on the local laboratory reference ranges (<115 mg/dL; <3.0 mmol/L).

The following ELISA kits were used: human oxLDL (Shanghai Sunred Biological Technology Co., Shanghai, China), human adiponectin (Mediagnost, Reutlingen, Germany), and AssayMax Human Apolipoprotein E (Assaypro, St. Charles, USA). In a subset of patients for whom sufficient samples were available, serum TNF-α was also assessed (Shanghai Qayee Biotechnology, Shanghai, China).

The CF genotype was considered severe if homozygous or compound heterozygous class I or II mutations were found. The percentage of predicted forced expiratory volume in 1 s (FEV1%) was obtained from medical records not older than 6 months. Exocrine pancreatic status was assessed by determining elastase-1 concentration in stools (ELISA; Schebo Biotech, Giessen, Germany) and faecal fat excretion. Patients were divided into PS and PI. Patients were diagnosed with CF-related liver disease (CFRLD) when: (1) on ultrasound the liver had increased echogenicity or heterogenic structure or both and (2) liver enzymes' activities (alanine or aspartate aminotransferase) were raised in three individual instances in the past, but not before the end of the first year of life [18]. Diabetes was diagnosed by specialist physicians after performing an oral glucose tolerance test. A positive *Pseudomonas aeruginosa* status was defined as including both chronic and intermittent culture-validated colonization [19].

2.4. Study size

Initially, 150 participants were to be recruited, 100 CF patients and 50 healthy adults. A sample size of 141 (94:47) is sufficient to detect a parameter difference of 15% assuming the standard deviation of 30%, α of 5% and β of 20% (2:1 enrollment ratio). If 15% of CF patients are pancreatic-sufficient then a comparison with the remaining 85%, preserving the above assumptions, should still be sensitive enough to detect a difference smaller than the standard deviation.

2.5. Data analyses

Statistical analyses were carried out using Statistica 12 and 13 (StatSoft Inc., Tulsa, USA) and R 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria). The data were checked for normality using the Kolmogorov-Smirov test and are reported as median [1st–3rd quartile] unless otherwise specified. Comparisons were carried out using Mann-Whitney *U* test for continuous variables and Fisher's exact test for binary data (*p* calculated in R if <0.0001). Two-sided *p* values were reported where possible and $p < .05$ was considered to indicate significance. When significant differences were stated for binary variables, unadjusted odds ratios (OR) were calculated. In order to adjust for confounders, forward-stepwise general linear regression models were built and analysis of residuals was conducted to assess the models and identify potential outliers. The violin plot was made with BoxPlotR and Inkscape.

2.6. Bioethical aspects

All participants gave their informed written consent for participation in the study. The study protocol was approved by the Bioethical Committee at Poznan University of Medical Sciences (decision 250/10). The project adhered to the tenets of the revised Declaration of Helsinki.

Table 1
Lipid, oxidized low-density lipoprotein (oxLDL), apolipoprotein E, and adiponectin concentrations in cystic fibrosis (CF) patients and healthy subjects (HS). Medians [1st-3rd quartiles] are presented, along with the significance in comparisons using Mann Whitney *U* test or Fisher's exact test.

Parameter	CF	HS	*p*
N	108	51	
Age, yr	22 [19–31]	24 [22–28]	ns. (0.4)
Sex ratio F/M	61/47 (56%)	31/20 (61%)	ns. (0.7)
Body mass index, kg/m^2	20.5 [18.4–22.2]	21.6 [19.9–23.4]	0.02
Total cholesterol, mg/dL	135 [150–167]	170 [147–185]	<0.0001
mmol/L	3.5 [3.9–4.3]	4.4 [3.8–4.8]	
LDL-C, mg/dL	62 [48–87]	82 [67–108]	<0.0001
mmol/L	1.6 [1.2–2.2]	2.1 [1.7–2.8]	
HDL-C, mg/dL	47 [38–56]	66 [53–76]	<0.0001
mmol/L	1.2 [1.0–1.4]	1.7 [1.4–2.0]	
Non-HDL-C, mg/dL	88 [67–111]	100 [82–123]	0.003
mmol/L	2.3 [1.7–2.9]	2.6 [2.1–3.2]	
TG, mg/dL	94 [71–133]	77 [63–93]	0.006
mmol/L	1.1 [0.8–1.5]	0.9 [0.7–1.1]	
Hypocholesterolaemia < 115 mg/dL, 3.0 mmol/L	31%	0%	<0.0001
Hypercholesterolaemia > 190 mg/dL, 4.9 mmol/L	10%	24%	0.03
High LDL ≥ 100 mg/dL, 2.6 mmol/L	14%	35%	0.003
Low HDL ≤ 45 mg/dL, 1.2 mmol/L	45%	6%	<0.0001
Hypertriglyceridaemia ≥ 150 mg/dL, 1.7 mmol/L	21%	8%	0.04
oxLDL, ng/mL	638 [192–1963]	1780 [261–2632]	ns. (0.05)
oxLDL/LDL-C ratio, ‰	1.0 [0.3–3.0]	2.0 [0.2–3.0]	ns. (0.7)
Apolipoprotein E, μg/mL	73 [62–91]	66 [50–83]	ns. (0.1)
Adiponectin, μg/mL	10.0 [7.2–14.2]	8.5 [6.6–11.4]	ns. (0.07)

CF – cystic fibrosis, F/M – female/male, HDL-C – high density lipoprotein cholesterol, HS – healthy subjects, LDL-C – low density lipoprotein cholesterol, ns. – not significant, TG – triglycerides.

3. Results

3.1. Participants, descriptive and outcome data, main results

One hundred and eight patients with CF and 51 HS were recruited for the study (Table 1). The median FEV1% in the CF group was 61% [1st–3rd quartile: 46–84%]. Class I or II genotypes were identified in 52% of the patients ($n = 56$; Supplemental Table 1). The prevalence of PI was 81% ($n = 88$). Twenty-two percent of the CF subjects had diabetes mellitus ($n = 24$), 39% ($n = 42$) had CFRLD, and 62% ($n = 67$) had chronic or intermittent *P. aeruginosa* colonization.

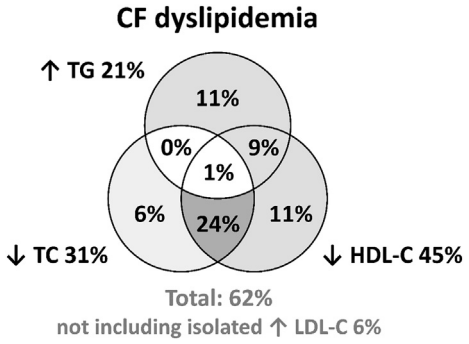

Fig. 2. Venn diagram of cystic fibrosis (CF) dyslipidaemia. Insufficient high-density lipoprotein cholesterol (HDL-C) is the most common abnormality, followed by low total cholesterol (TC) and high triglycerides (TG). Isolated elevation of low-density lipoprotein cholesterol (LDL-C) is, however, non-negligible.

The total cholesterol concentration, LDL-C, HDL-C, and non-HDL-C were all lower in CF patients compared with HS (Fig. 1A), whereas the TG concentration in CF was higher. OxLDL, oxLDL/LDL-C ratio, adiponectin, and APOE levels were similar in both groups. The frequency of lipid disturbances in CF and HS is compared in Table 1. The OR of abnormal results in CF vs. HS were as follows: hypercholesterolaemia 0.37 (95%CI 0.15–0.91), low HDL-C 13.29 (95%CI 3.90–45.30), high LDL-C 0.30 (95%CI 0.13–0.65), hypertriglyceridaemia 3.18 (95%CI 1.04–9.74). There were no cases of hypocholesterolaemia co-occurring with hypertriglyceridaemia (Fig. 2).

In CF, there were no associations between lipids, oxLDL, oxLDL/LDL-C, adiponectin, or APOE (Spearman's rho<0.3 for all). In HS, despite the smaller sample size, there was a weak correlation between oxLDL/LDL-C ratio and total cholesterol (rho = −0.32, $p = .02$), as well as a moderate correlation between adiponectin and HDL-C (rho = 0.49, $p = .0003$), which was not found in CF. Hypertriglyceridemic CF patients had a lower proportion of HDL-C in total cholesterol (not shown; $p < .0001$).

Compared with PS, PI CF subjects had lower cholesterol concentrations (Table 2). Furthermore, hypocholesterolaemia was more frequent in PI compared with PS CF subjects (OR 11.40, 95%CI 1.46–89.15), consequently, high LDL was less prevalent (OR 0.13, 95%CI 0.04–0.42).

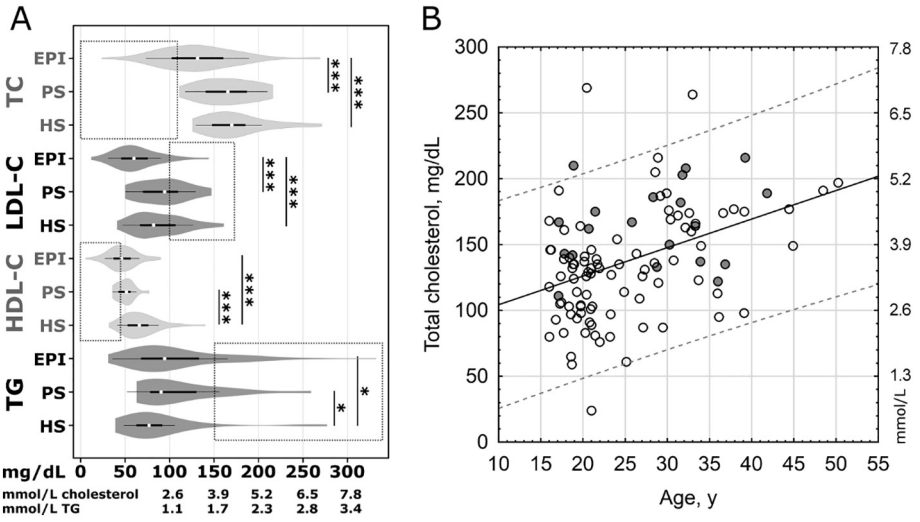

Fig. 1. (A) Violin plot of serum concentrations of total cholesterol (TC), LDL-C, HDL-C, and triglycerides (TG) in pancreatic-insufficient (PI) and pancreatic-sufficient (PS) cystic fibrosis patients, and healthy subjects (HS). Medians, 1st–3rd quartiles (box), and extremes calculated after Tukey's method (whiskers) are shown. Rectangles indicate thresholds for hypocholesterolaemia, high LDL-C, low HDL-C, and hypertriglyceridaemia. Significance: $p < .05$ (*), < 0.01 (**), < 0.001 (***). (B) Scatterplot of total cholesterol vs age of cystic fibrosis (CF) patients. Shaded circles represent pancreatic-sufficient CF subjects. The regression line and 95% confidence intervals for prediction are shown.

Table 2
Lipid, oxidized low-density lipoprotein (oxLDL), apolipoprotein E, and adiponectin concentrations in pancreatic-insufficient (PI) and pancreatic-sufficient (PS) cystic fibrosis (CF) patients. Medians [1st–3rd quartiles] are presented, as is the significance in comparisons using Mann Whitney U test and Fisher's exact test.

Parameter	PI	PS	*p*
N	88	20	
Age, yr	22 [19–30]	29 [20–34]	ns. (0.1)
Sex ratio F/M	48/40 (54%)	13/7 (65%)	ns. (0.5)
Body mass index, kg/m^2	20.2 [17.9–22.1]	21.4 [19.8–23.0]	ns. (0.05)
FEV1%	57% [41–84]	64% [56–79]	ns. (0.2)
Class I or II genotype	64%	0%	<0.0001
Diabetes mellitus	27%	0%	0.006
CFRLD	45%	10%	0.004
Liver cirrhosis	11%	0%	ns. (0.2)
P. aeruginosa colonization	66%	45%	ns. (0.1)
Total cholesterol, mg/dL	131 [102–160]	165 [139–187]	0.0001
mmol/L	3.4 [2.6–4.1]	4.3 [3.6–4.8]	
LDL-C, mg/dL	60 [45–75]	94 [68–110]	<0.0001
mmol/L	1.6 [1.2–1.9]	2.4 [1.8–2.8]	
HDL-C, mg/dL	46 [37–56]	51 [42–56]	ns. (0.3)
mmol/L	1.2 [1.0–1.4]	1.3 [1.1–1.4]	
Non-HDL-C, mg/dL	82 [63–102]	116 [88–135]	0.0002
mmol/L	2.1 [1.6–2.6]	3.0 [2.3–3.5]	
TG, mg/dL	94 [67–133]	90 [77–137]	ns. (0.7)
mmol/L	1.1 [0.8–1.5]	1.0 [0.9–1.5]	
Hypocholesterolaemia < 115 mg/dL, 3.0 mmol/L	37%	5%	0.003
Hypercholesterolaemia > 190 mg/dL, 4.9 mmol/L	8%	20%	ns. (0.1)
High LDL ≥ 100 mg/dL, 2.6 mmol/L	8%	40%	0.001
Low HDL ≤ 45 mg/dL, 1.2 mmol/L	48%	35%	ns. (0.3)
Hypertriglyceridaemia ≥ 150 mg/dL, 1.7 mmol/L	20%	25%	ns. (0.8)
oxLDL, ng/mL	661 [203–1963]	533 [120–1740]	ns. (0.6)
oxLDL/LDL-C ratio, ‰	1.2 [0.3–3.0]	0.6 [0.1–2.0]	ns. (0.07)
Apolipoprotein E, μg/mL	73 [60–91]	73 [64–93]	ns. (1.0)
Adiponectin, μg/mL	9.9 [7.0–14.4]	10.4 [8.1–13.4]	ns. (0.7)
TNF-α, ng/L (n = 33 vs. 9)	9.0 [6.0–17.0]	7.0 [6.0–10.0]	ns. (0.9)

CF – cystic fibrosis, CFRLD – CF-related liver disease, FEV1% – forced expiratory volume in one second (percentage of predicted), F/M – female/male, HDL-C – high density lipoprotein cholesterol, HS – healthy subjects, LDL-C – low density lipoprotein cholesterol, ns. – not significant, TG – triglycerides, TNF-α – tumour necrosis factor α.

Table 3
Predictors of lipid-associated parameters in CF patients. General linear regression forward-stepwise analyses included age, sex, BMI, FEV1%, *CFTR* genotype class (I or II vs. other), pancreatic status, and CF-related liver disease. BMI and age consistently predicted adiponectin levels after residual analysis and exclusion of two outliers.

Predictor	β	β −95%CI	β +95%CI	p
Total cholesterol; $R^2 = 0.22$; $p < .0001$				
Age	0.33	0.15	0.50	0.0003
PI	−0.24	−0.42	−0.07	0.007
Sex (female)	0.19	0.01	0.36	0.03
LDL-C; $R^2 = 0.23$; $p < .0001$				
PI	−0.38	−0.55	−0.21	<0.0001
Age	0.27	0.10	0.44	0.003
HDL-C; $R^2 = 0.14$; $p = .0001$				
Age	0.34	0.16	0.52	<0.0001
Sex (female)	0.18	0	0.36	< 0.05
Non-HDL-C; $R^2 = 0.20$; $p < .0001$				
PI	−0.32	−0.49	−0.14	<0.0001
Age	0.28	0.11	0.46	0.002
Adiponectin; $R^2 = 0.17$; $p < .0001$				
BMI	−0.40	−0.58	−0.22	<0.0001
Age	0.30	0.12	0.49	0.002

APOE – apolipoprotein E, CF – cystic fibrosis, BMI – body mass index, PI – pancreatic insufficiency, FEV1% – forced expiratory volume in one second (percentage of predicted), HDL-C – high density lipoprotein cholesterol, LDL-C – low density lipoprotein cholesterol, oxLDL – oxidized LDL.

PS CF patients had higher TG ($p = .02$) and lower HDL-C ($p = .0001$) than HS. The values of all the other continuous variables shown in Table 2 did not differ between the two groups ($p > .1$). When compared with HS, the OR for low HDL-C in PS CF was 8.6 (95%CI 2.0–38.0; Fisher's exact test $p = .004$), which reflects an almost six-fold difference).

Regression analyses revealed that in CF, PI was independently associated with low total cholesterol, LDL-C, and non-HDL-C (Table 3). Cholesterol and adiponectin concentrations tended to increase with age (Fig. 1B), with women having greater total cholesterol and HDL-C concentrations. TG levels, APOE, oxLDL, and oxLDL/LDL-C ratio could not be predicted by: age, sex, BMI, FEV1%, genotype class (I or II vs. other), pancreatic status, or CFRLD. Two cases were omitted for the regression analyses (no FEV1% measurement).

The median TNF-α in a subgroup of 42 CF patients was 8.5 ng/L [6.0–16.2]. TNF-α did not correlate with total cholesterol, HDL-C, LDL-C, TG, adiponectin, nor apolipoprotein E concentrations. However, it was strongly associated with total oxLDL (rho = 0.81; $p < .0001$; Supplemental Fig. 1) and oxLDL/LDL-C ratio (rho = 0.76; $p < .0001$).

4. Discussion

4.1. Key results

CF dyslipidaemia was heterogenous. Hypocholesterolaemia and hypertriglyceridaemia were highly prevalent, yet they did not co-occur in any CF case. PI determined low LDL-C (and non-HDL-C), but did not associate with insufficient HDL-C. Furthermore, TG were independent of TNF-α and PI. OxLDL/LDL-C ratio, APOE, and adiponectin did not differ between CF and HS and were not predicted by the characteristics of CF. This was the first study to assess oxLDL/LDL-C ratio and circulating APOE in CF.

4.2. Low HDL-C

In our view, the central characteristic of CF dyslipidaemia is low HDL-C, which was most common in this group of patients. Mean HDL-C in CF is known to be low [1,2,5,20] and only in the cohort investigated by Georgiopoulou et al. the levels were, surprisingly, almost normal [3].

Ratios of total cholesterol to HDL-C and TG/HDL-C were also investigated. The former was associated with a higher BMI while the latter seemed to reflect a particularly unfavorable lipid profile. In this study the CF TG/HDL-C ratio was similar to that reported by Woestenenk et al. and also higher than in HS (not shown) [2]. Our findings of a moderate positive correlation between adiponectin and HDL-C in HS and a lack of it in CF patients support the hypothesis that HDL-C metabolism in CF is altered; the involved protein might be lipoprotein lipase. In diabetes, adiponectin is associated with the presence of large HDL particle concentration, which is advantageous, and its influence on HDL-C may be mediated by lipoprotein lipase [21,22]. The similarity between PI and PS patients in HDL-C levels also indicates that fat maldigestion and malabsorption do not explain low HDL-C in CF.

We understand that HDL-C levels in CF are insufficient, but it would be beneficial to determine if HDL is fully functional. Further research on HDL-C deficiency in CF is needed and the pertinent areas of investigation may be: apolipoprotein AI, cholesterol efflux, cholesteryl ester transfer protein, lecithin:cholesterol acyltransferase, and other aspects of HDL formation and turnover [4].

4.3. Hypertriglyceridaemia

TG in this study were at similar levels to those reported by Ishimo et al. and Rhodes et al. [1,20], lower than measured by two other groups [3,5] and higher than in the study by Woestenenk et al. [2].

According to one hypothesis, CF hypertriglyceridaemia results from excessive carbohydrate intake [3]. However, TG could rise as a

consequence of diet including over 60% of total calories from carbohydrates or when fructose consumption is particularly high. An analysis by Woestenenk et al. did not find any association between carbohydrate intake and TG in CF patients, but these results might have been influenced by high fat intake and nearly normal coefficient of fat absorption masking more subtle relationships [2].

It has also been proposed that hypertriglyceridaemia in CF is determined by chronic low-grade inflammation. Lévy et al. reported that TNF-α blocked hepatic lipoprotein lipase in 31 CF patients [4], but this interpretation most probably stemmed from the presence of four outliers. We speculate that hypertriglyceridaemia in CF reflects an intrinsic cellular disorder of lipid metabolism.

High TG were linked to other lipids and clinical characteristics. Ishimo et al. found that hypertriglyceridemic CF patients had a lower proportion of HDL-C in total cholesterol, which we confirmed. They also demonstrated better lung function in CF subjects with elevated TG; it remains unclear whether FEV1% associated with TG concentrations or nutritional status. In a study by Ollero et al. [23], hypertriglyceridaemia correlated with chronic *P. aeruginosa* infection, unlike the present study.

Hypertriglyceridaemia is atherogenic due to proinflammatory and procoagulant effects and is regarded an independent risk factor for cardiovascular disease [24]. If, as Georgiopoulou et al. suggest, CF dyslipidaemia resembles lipid abnormalities encountered in patients infected with human immunodeficiency virus then we could explore the role of treatment of CF hypertriglyceridaemia by the means of eicosapentaenoate and docosahexaenoate supplementation [25].

4.4. Hypocholesterolaemia

The mean total cholesterol level in the present study was almost identical to that described by three other groups [3,5,20], higher than in a pediatric population [2], but lower than in the study by Rhodes et al. [1]. Hypocholesterolaemia in CF cannot be separated from the analysis of pancreatic status, as it occurs already in children, especially PI, even when BMI is normal [26]. Clinically, hypocholesterolaemia may predict poorer survival e.g., of critically ill or haemodialysis patients [27].

It could be proposed that hypocholesterolaemia lowers cardiovascular risk, but such a statement would be too general – more should depend on the lipid profile than total cholesterol. Consequently, one cannot state that PI subjects will have a lower risk of cardiovascular disease, but one could speculate that in PS this risk will be higher. This is difficult to predict since other atherogenic factors are at play, including CF-related chronic inflammation, dysbiosis, and diabetes. Nonetheless, LDL-C is often elevated in older PS patients, which may influence dietary guidelines for such subjects.

4.5. OxLDL, adiponectin, and apolipoprotein E

Lagrange-Puget et al. found a similar lipid peroxide (ROOHs) level in CF and control subjects despite decreased malondialdehyde and reduced glutathione in CF [28]. In our study, total oxLDL and oxLDL/LDL-C did not differ significantly between CF patients and HS. The strong correlation between oxLDL and TNF-α suggests that lipid peroxidation in CF can be driven by inflammation.

Adiponectin is known to be higher in women, reduced in obesity and diabetes, and to increase as a result of caloric restriction, but it does not straightforwardly correlate with BMI. There was insignificantly higher adiponectin in CF than in HS and total adiponectin levels in CF patients and HS were similar to those reported by Ziai et al. [13] and greater than in the control group in the study by Panagopoulou et al. [12].

There were similar concentrations of APOE in CF and HS, with the link between hypertriglyceridaemia and serum APOE in CF being weak. In comparison, it seems probable that even with a greater sample size an analogous effect would not be found in HS. The lack of important associations between APOE and CF characteristics indicates that if there is a role for this protein in mediating CF-related health effects, it likely remains subtle.

4.6. Limitations

This was a cross-sectional study and no causative relationships may be inferred from the data. Although considerable, the CF population was heterogenous and included patients with more severe disease who visited their clinics often. We did not investigate the effects of medication nor obtained dietary data. The employed definition of CFRLD may have given false positives, resulting in overdiagnosis [18]. The cultural background was homogenous due to the setting.

4.7. Generalisability

A high *P. aeruginosa* colonization rate, low FEV1%, and a large burden of CFRLD suggest that the results of the study should be generalized to cases of moderate and severe course of the disease. The study was conducted in Poland and despite the recent rapid development, the care offered two decades ago to our patients differed from many other countries. The number of adult CF patients diagnosed through the newborn screening in Poland has been growing over the last decade. Reimbursement of medicines and nutritional products improved and a considerable patient and staff education effort was undertaken. Whereas multidisciplinary support and transplantation capabilities are growing, lumacaftor/ivacaftor, inhaled levofloxacin and aztreonam are almost inaccessible.

4.8. Conclusions

Despite the growing knowledge of CF dyslipidaemia epidemiology and its clinical context, the underlying molecular mechanisms have not been fully elucidated. The few recent studies on the subject indicate the presence of inherent, CF-related lipid metabolism disturbances [29]. This is clearly of interest for mechanistic investigations into atherosclerosis.

CF dyslipidaemia is highly prevalent and heterogenous, with the lipid profile weakly associating with clinical characteristics of CF as well as oxLDL, adiponectin, and APOE. Further research is needed, especially regarding HDL function in CF, the causes of hypertriglyceridaemia, and the value of essential fatty acid supplementation for CF dyslipidaemia.

Author contributions

JW conceived the study, JKN, MS, IWB, PK, SDC, AN, AP, ES, WS, AL, and JW recruited patients; all authors acquired data; JKN performed analyses; JKN, MS, IWB, EM, AW, PK, SDC, AL, JW interpreted the data; JKN drafted the manuscript; MS, IWB, EM, AW, PK, SDC, AN, AP, ES, WS, AL, and JW revised the manuscript and all authors approved its final version; JW obtained funding and supervised the study.

Conflict of interest statement

Dr. Nowak reports personal fees from Norsa Pharma and non-financial support from Nutricia, outside the submitted work. Dr. Skorupa reports personal fees from Vertex, Valeant, Corbus, Novartis, Fundacja MATIO Warszawski Uniwersytet Medyczny, Termedia, Medius Sp z o.o.; non-financial support from Chiesi, Pari, Roche, GSK, TEVA, outside the submitted work. Prof. Walkowiak reports personal fees and non-financial support from Biocodex, BGP Products, Chiesi, Hipp, Humana, Mead Johnson Nutrition, Merck Sharp & Dohme, Nestle, Norsa Pharma, Nutricia, Roche, Sequoia Pharmaceuticals, and Vitis Pharma, outside the submitted work, and also grants, personal fees and non-financial support from Nutricia Research Foundation Poland,

also outside the submitted work. The authors have no other conflict of interest to declare.

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Appendix A. Supplementary data

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