Original Article

Dyslipidemia in racially admixtured children with cystic fibrosis

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ABSTRACT

Objectives: There are few studies reporting lipid profile in cystic fibrosis (CF) and most of them are in adult Caucasians. Therefore, the aim of this study was to evaluate the lipid profile of racially admixtured youths with CF. **Materials and Methods:** A cross-sectional survey conducted between August and September 2009 at a reference service for CF, evaluating clinical and laboratory data. **Results:** Forty-six patients aged from 6 years to 16 years and 2 months (median: 9 years and 10 months; 65.2% males) were evaluated. Of these, 26% were Whites, 54.4% Mulattoes and 19.6% Blacks. There were no diabetics, one patient had glucose intolerance and three had insulin resistance. Pancreatic sufficiency was present in 74% and malnutrition in 26% of the patients. The lipid profile revealed hypertriglyceridemia in 56%, hypercholesterolemia in 17.4% and hypocholesterolemia in 46.5%. In 30.4% of the patients, hypertriglyceridemia and hypocholesterolemia was observed. The serum levels of high density lipoprotein (HDL) were low in 56.5% and the low density lipoprotein (LDL) elevated in 15.2% of the patients. **Conclusions:** The lipid profile of this sample of Brazilian racially admixtured patients with CF showed a higher prevalence of hypertriglyceridemia and hypocholesterolemia. There was no association of dyslipidemia with the various racial groups, nutritional status, pancreatic sufficiency or glucose tolerance.

Key words: Cystic fibrosis, dyslipidemia, ethnicity, race

Introduction

Cystic fibrosis (CF) is an autosomal recessive disease caused by mutations that alter the Cystic Fibrosis Transmembrane Regulator (CFTR) protein, leading to dysfunction in the chloride channel, thickening of secretions and progressive obstruction of organs.[1] The ΔF508 mutation is identified in 60–70% of the patients of Caucasian origin,[2,3] but in Brazil, the prevalence of this mutation varies in the different regions of the country due to differences in the ethnic composition of the population.[4]

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The lipid profile of CF patients shows a trend toward a dyslipidemic pattern characterized by hypertriglyceridemia and/or hypocholesterolemia.[5,6] The mechanisms postulated to explain this disturbance are: diet rich in carbohydrates and poor in fats, diabetes, liver disease, elevation of pro-inflammatory cytokines and use of corticosteroids, probably all acting in a combined manner.[5-7] Recently, lung transplantation was described as being associated with hyperlipidemia in CF patients, probably related to cyclosporine use.[8]

Dyslipidemia, especially hypertriglyceridemia, is a risk factor for atherosclerotic disease. Although the prevalence of ischemic heart disease is lower in CF patients compared to the normal population, it is not known, in the long range, with the increased life expectancy of the CF patients, what would be the repercussions of these metabolic abnormalities in their cardiovascular morbidity.

As there are few reports describing the prevalence of dyslipidemia in CF and no study in a racially admixtured

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population such as ours, the aim of this study was to evaluate the lipid profile of racially admixtured young persons with CF, followed at a reference service.

Materials and Methods

This work is a part of a project designed to assess the metabolic aspects of CF. A previous paper, in this cohort, reporting on the carbohydrate aspects of CF was recently published.[7] This cross-sectional study was conducted between August and September 2009. All 46 patients, aged between 6 and 16 years and 2 months , followed at a reference service for CF were selected. Diagnosis of CF was based on clinical criteria and by analyzing twice the concentration of chloride in sweat, in accordance with the technique described by Gibson and Cooke.[9] Search for the ΔF508 mutation was conducted by analyzing the nucleotide sequence as previously described.[10] Patients using corticosteroids and those with acute pulmonary exacerbations in the previous month were excluded from the study.

The nutritional status was assessed by the body mass index (BMI) calculated by the formula [weight (kg)/height (m^2)], using the Must *et al*. curves.[11,12] Nutritional failure was defined by a BMI lower than or equal to 10th centile.[13]

Racial categorization was evaluated by self-declaration in accordance with the criteria of the Brazilian Institute of Geography and Statistics (IBGE).[14]

As the pancreatic enzyme capsules ranged from 4500 to 18,000 IU, the amount of pancreatic enzyme used for each patient was described in units/kg/day of lipase.

Blood was collected at 08:00 hours, after a 12-hour fast. Total cholesterol (TC), triglycerides (TG) and high density lipoprotein (HDL) serum levels were assessed by an enzymatic biochemical method (Dade Behring-Dimension RXL-Dade Behring Inc., Newark, NJ, USA). Low density lipoprotein (LDL) concentrations were calculated by the Friedewald equation [LDL = TC - (HDL - TG/5)], valid for values of TG < 400 mg/dL and very low density lipoprotein (VLDL) was calculated by the equation [TG/5]. The normal values used were those of the National Cholesterol Education Program Expert Panel on Cholesterol Levels in Children.[15]

Glucose tolerance was defined as blood glucose between 141 and 199 mg/dL, 2 hours after an ingestion of a glucose overload (1.75/Grams/Kg, maximum of 75 grams).[10] Insulin resistance was assessed by the Homeostasis Model Assessment (HOMA) calculated as: [blood glucose (mg/dL) × serum insulin μUI/mL/405].[10]

Age was stratified in quartis. Scores were compared through the Spearman's correlation coefficient test (TG × HDL and BMI × lipid values). Results were calculated in percentage.

This study was approved by the Research Ethics Committee of the Medical Faculty in accordance with the Helsinki Declaration of 1975, as revised in 1983, and all of the participants agreed to take part by signing the Term of Free and Pre-informed Consent.

Results

The study was conducted in 46 patients of whom 62.5% were boys. The participants' ages ranged between 6 and 16 years (median: 9 years and 10 months). The study population comprised 26% Whites, 54.4% Mulattoes and 19.6% Blacks. Pubertal staging showed 62.5% prepubertal girls and 60% prepubertal boys. Half of the patients (52%) were under the age of 10 years.

The median duration of disease (checked by the date of diagnosis) was 5.3 years (variation: 0.3–12 years). Four patients were unable to report the time of disease. On diagnosis, the patients' ages ranged from 4 months to 12 years (median: 4 years). In 33 patients (71.7%), the CFTR genotype was analyzed exclusively for the presence of ΔF508. Of these, 6% were heterozygous and the others were negative for this mutation.

Thirty-five patients (76%) were followed up by a nutritionist and instructed to follow a hypercaloric and hyperproteic diet according to their age and nutritional status. Eleven patients (24%) had nutritional failure diagnosed by a BMI ≤10th centile. There were no differences in the lipid profile between nourished and malnourished CF patients.

Mean ingestion of pancreatic enzymes was 4113 units/kg/day of lipase. Twelve patients (26%) did not make use of pancreatic enzymes. The patients who did not use the enzymes presented similar cholesterol levels as those who used them (median 150 mg/dL vs. median 149 mg/dL).

The lipid values for the total number of participants were as follows: TC = 145.8 ± 28.3 mg/dL (median: 149.5 mg/dL, variation: 84–224 mg/dL); TG = 93.5 ± 45.7 mg/dL (median: 84 mg/dL, variation: 37–243 mg/dL); LDL = 82.4 ± 25.8 mg/dL (median: 80.4 mg/dL, variation: 6.4–136 mg/dL); VLDL = 18.8 ± 9.2 mg/dL (median: 17 mg/dL, variation: 7.5–48.6 mg/dL); and HDL = 43.4 ± 10.3 mg/dL (median: 42.5 mg/dL, variation: 18–76 mg/dL). TC was elevated (>170 mg/dL) in 17.4% and TG in 56.5%. LDL was elevated in 15.2%, VLDL was increased in 22.2% and HDL was diminished in 56.5%

Table 1: Lipid values according to racial group

Lipids (mg/dL)	Whites (n = 12) Median (variation)	Mulattoes (n = 25) Median (variation)	Blacks (n = 9) Median (variation)	Median difference (White – Black)
TC	160.5 (84–224)	150 (99–190)	141 (106–172)	19.5
HDL	41.5 (18–52)	46 (25–76)	37 (30–51)	4.5
LDL	87.4 (41.2–136)	79,4 (6.4–121.8)	75.8 (41.2–114)	11.6
VLDL	19.1 (9.8–40)	16 (7.4–48.6)	18.4 (11–34.2)	0.7
TG	95.5 (49–200)	77 (37–243)	92 (55–171)	3.5

HDL: High density lipoprotein, LDL: Low density lipoprotein, VLDL: Very low density lipoprotein, TG: Triglycerides, TC: Total cholesterol

patients. Hypocholesterolemia was diagnosed in 46.5% of the patients.

Table 1 summarizes the results of the lipid values according to the racial group. It is observed that Black children had lower lipid values in all measurements when compared to White children, with the major differences being observed for TC (19.5 mg/mL) and LDL (11.6 mg/mL). Table 2 demonstrates that there were no important differences in the lipid values when they were stratified by quartis of age. Correlation analysis between BMI × lipid values and between HDL × TG demonstrated a weak result in all of them, with 27% being the highest result.

Glycated hemoglobin (HbA1c) was normal in all patients. Only one participant (12 years old) had glucose intolerance. Insulin levels ranged from 1 to 23 μIU/mL (median: 4.5 μIU/mL) at baseline and from 3.2 to 192.1 μIU/mL (median: 11 μIU/mL) after a glucose overload. Insulin resistance evaluated by the HOMA index, stratified by sex and age, was present in three patients.

Table 2: Lipid values according to quartis of age

Lipids (mg/dL)	Quartis of age			
	1 (n = 12)	2 (n = 11)	3 (n = 11)	4 (n = 12)
TC	M: 152.0	M: 127.0	M: 150.0	M: 150.0
	IQR: 33.7	IQR: 48.5	IQR: 31.5	IQR: 29.5
	VC: 22.2	VC: 38.2	VC: 21.0	VC: 19.7
HDL	M: 41.0	M: 43.0	M: 42.0	M: 47.5
	IQR: 6.5	IQR: 10.0	IQR: 12.0	IQR: 15.8
	VC: 15.8	VC: 23.3	VC: 28.6	VC: 33.1
LDL	M: 87.1	M: 63.0	M: 79.4	M: 80.1
	IQR: 32.1	IQR: 45.3	IQR: 44.5	IQR: 21.0
	VC: 36.8	VC: 71.9	VC: 56.0	VC: 26.2
VLDL	M: 14.4	M: 16.6	M: 24.6	M: 16.1
	IQR: 6.4	IQR: 4.4	IQR: 9.8	IQR: 8.8
	VC: 44.4	VC: 26.5	VC: 39.8	CV: 54.9
TG	M: 70.5	M: 83.0	M: 123.0	M: 80.5
	IQR: 27.5	IQR: 22.0	IQR: 49.0	IQR: 44.2
	VC: 39.0	VC: 26.5	VC: 39.8	VC: 54.9

M: Median, VC: Variation coefficient, IQR: Interquartile range, HDL: High density lipoprotein, LDL: Low density lipoprotein, VLDL: Very low density lipoprotein; TG: Triglycerides, TC: Total cholesterol

Discussion

There are few studies in the literature describing the prevalence of dyslipidemia in patients with CF and the majority of these were performed in adult Caucasians.[16]

In the study of Figueroa *et al*.,[5] where the patients aged between 5 and 44 years, 16% had hypertriglyceridemia with a mean TC lower than that of the North American population. In the present study evaluating patients from 6 to 16 years, the lipid profile, stratified by age, showed that 56.5% had hypertriglyceridemia and 46.5% had hypocholesterolemia. Hypertriglyceridemia associated with hypocholesterolemia was observed in 30.4%. Padoa *et al*.[17] observed that in populations of Black ancestry, the mutations responsible for CF differ from those of Caucasian populations. With regard to the prevalence of ΔF508 mutation in Brazil, a study in the State of Minas Gerais showed that its frequency was related to the ethnic ancestry, being more frequent in those of Caucasian origin.[4] In the present study in which the majority of participants were of African origin [Blacks (n = 9, 19.5%) and Mulattoes (n = 25, 54.3%)], only 6% of those evaluated for the ΔF508 mutation were positive and all were heterozygous. Schmitt-Grohe *et al*.,[18] studying homozygous patients for the ΔF508 mutation, presumed that the lipoproteins had a protective effect on the preservation of pulmonary function, with a positive correlation with the serum levels of HDL. In our study, the HDL was diminished in 56.5% of patients.

Worgal,[3] reviewing lipid metabolism in CF, calls attention to the fact that the alteration in the expression of CFTR protein affected cholesterol metabolism, leading to a the dyslipidemic pattern observed in these patients (low LDL and low HDL). Levy *et al*.[19] also observed hypertriglyceridemia and hypocholesterolemia, with low LDL and HDL, drawing attention to the role of tumor necrosis factor (TNF)-α on the causality of hypertriglyceridemia.

Lipid value analysis in the different ethnic groups revealed lower cholesterol levels in Blacks than in Whites. Stratification of lipid values by age was not significant. Slesinski *et al*.,[20] comparing adults with CF and a control group, observed that in spite of consuming a diet rich in fats, the CF patients presented normal to low cholesterol levels. No dietary records were kept in the present study, which limited the evaluation of this factor in association with lipid disturbances. However, the majority (76%) of the

patients were followed up by nutritionists and instructed to keep to a hypercaloric and hyperproteic diet.

Some studies in the literature report that the consumption of a hyperlipidic diet by patients with CF and pancreatic insufficiency did not promote worsening of the lipid profile, in contrast with those with pancreatic sufficiency, in whom the available data suggest to have the same atherogenic risk as in the general population.[6,20] In the present report, hypercholesterolemia was found in 17.4% of the patients (of whom 38% did not present pancreatic insufficiency). Of the patients without pancreatic insufficiency, only three presented hypercholesterolemia (with TC levels ranging between 171 and 179 mg/dL). Contrary to the study by Rhodes *et al*.,[16] we did not demonstrate an association of pancreatic sufficiency and hypercholesterolemia, probably due to the younger age of our patients. The group of patients that did not use enzymes presented a median age older than the group that used enzymes (median: 10 years and 2 months vs. median: 9 years and 3 months).

Uncontrolled diabetes and insulin resistance may be associated with dyslipidemia. In this series, there were no diabetics and the three patients with insulin resistance had a normal lipid profile, the results which are as described in a recent study.[16]

This study suffers from some limitations such as a small sample size, not allowing separation of the independent effects of sex, age, and pubertal status on the concentrations of the lipoproteins, the fact that it did not assess CF mutations other than ΔF508, and that it did not perform a survey to assess the nutritional intake. However, it indicates, for the first time, that the prevalence of dyslipidemia in this young, racially admixtured population is similar to that described for Caucasians, with no association between dyslipidemia, nutritional status, pancreatic sufficiency or glucose tolerance. Since the majority of the data in this subject come from Caucasians, studies reporting racial differences or similarities are important to widen the knowledge of the CF lipid profile in racially admixtured populations. These preliminary data indicate the need for future research with longitudinal studies including a controlled diet and a comparison group to investigate these unanswered questions and if the genotype:phenotype correlation influences the lipid disturbances in these patients.

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