
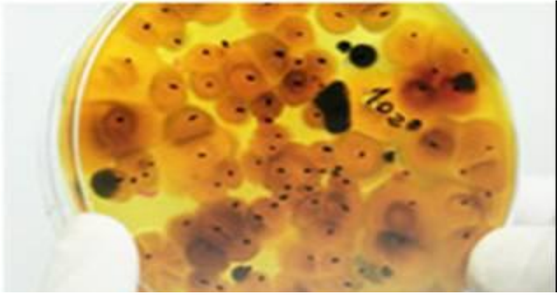

ApoB/ApoA1 ratio improves clinical criteria sensitivity for the identification of FH children

Estudo Português de Hipercolesterolemia Familiar

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on behalf of the investigators of the Portuguese FH Study

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AIM

Familial hypercholesterolemia (FH) is a common autosomal dominant disorder of lipid metabolism. The high levels of plasma cholesterol since birth confers an increased risk of coronary heart disease. Clinical diagnosis of FH is usually done using a set of criteria (MEDPED or Simon Broome Registry (SBR)), however only SBR presents criteria for children. The present work aims to identify useful biomarkers for clinical criteria improvement in clinical settings.

METHODS

A cohort of 237 unrelated children with clinical diagnosis of FH was analysed. Genetic diagnosis of FH was performed by the analysis of *LDLR*, *APOB* and *PCSK9*. ROC curves were performed for lipids and lipoproteins using pre-treatment values of FH and non-FH children to determine novel cut-off values. Different clinical criteria were established using novel cut-off points and compared with genetic diagnosis using cross-tables. Statistical analysis was performed using SPSS v.17 software.

RESULTS

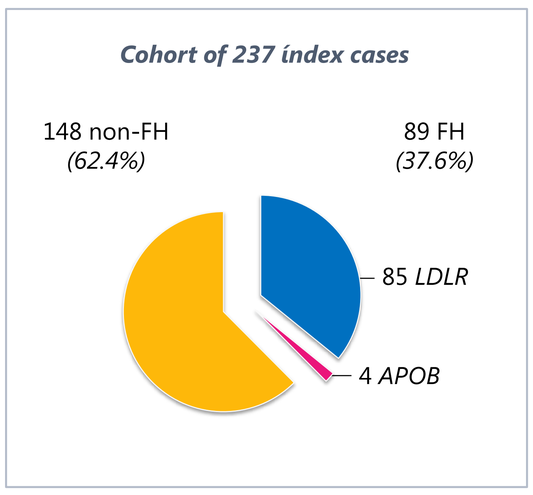

Fig. 1. Genetic diagnosis of the cohort of 237 unrelated children .

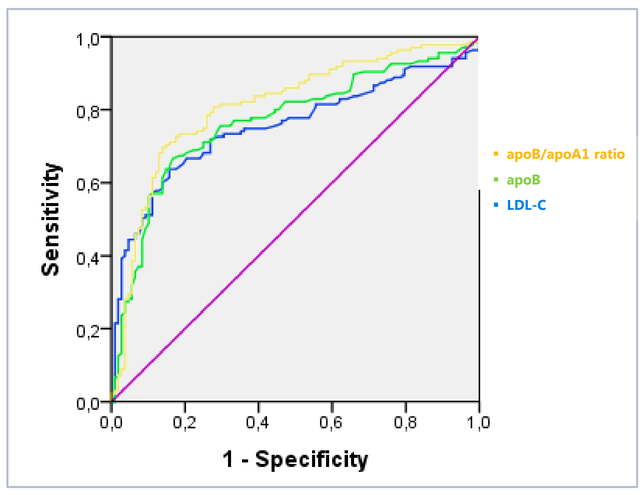

Fig. 2. Receiver operating characteristic (ROC) curves for the three biomarkers that better discriminates between FH and non-FH children: apoB/apoA1 ratio (AUC=0.835); apoB (AUC=0.820); LDL-C (AUC=0.743).

- The cohort was divided according to the genetic diagnosis for further analysis (89 FH children vs 148 non-FH children) (Fig. 1).
- Areas under the curve (AUC) were determined for total cholesterol (0.743), LDL-C (0.743), apoA1 (0.750), apoB (0.820) and apoB/apoA1 ratio (0.835) (Fig. 2).
- Optimal cut-off points were obtained for LDL-C ≥190mg/dL (sensitivity: 72.5%; specificity: 70.3%) and apoB/apoA1 ratio ≥0.68 (sensitivity: 80.0%; specificity: 76.9%) (Table 1).
- SBR criteria revealed a reasonable balance between sensitivity (SS) and specificity (SP) in the identification of index cases (SS: 76.0%; SP: 68.6%) but revealed a low sensitivity in the identification of relatives with FH (SS: 36.0%; SP: 100.0%) (Table 2).
- A combination of SBR criteria with TC>260mg/dL and/or LDL-C ≥190mg/dL and/or apoB/apoA1 ratio ≥0.68 was found to represent the optimal balance between sensitivity and specificity for the identification of index cases (SS: 86.0%; SP: 68.6%), relatives (SS: 84.0%; SP: 75.0%) and both (SS: 85.0%;SP: 70.8%) (Table 2).

Table 1. Cut-off points determined for the six best biomarkers and their discriminative ability (sensitivity and specificity) to distinguish between FH and non-FH children; comparison between novel cut-off points and Simon Broome. Bold indicates the cut-off points used in the proposed criteria*.

					Simon Broome		
Biomarker	**AUC**	**Cut-off point**	**Sensitivity**	**Specificity**	**Cut-off point**	**Sensitivity**	**Specificity**
TC	0.743	257.48 mg/dL	72.6%	68.5%	260 mg/dL	70.7%	71.9%
LDL-C	0.743	**189.93 mg/dL**	72.5%	70.3%	155 mg/dL	87.7%	23.4%
apoB/apoA1 ratio	0.835	**0.6848**	80.0%	76.9%			
non-HDL-C/HDL-C ratio	0.736	3.708	71.7%	67.4%			
apoA1	0.750	137.5 mg/dL	73.1%	67.4%			
apoB	0.820	96.95 mg/dL	77.9%	76.0%			

Table 2. Simon Broome (SBR) criteria and proposed criteria* for the clinical diagnosis of FH using novel cut-off points. Results obtained for sensitivity, specificity and kappa statistic to evaluate the inter-diagnostic agreement are also presented. Criteria were determined using pretreatment values (n=155). Bold indicates the best criteria representing optimal balance between sensitivity and specificity.

	Sensitivity	**Specificity**	**Kappa statistic**
A. Index cases			
#1 (SBR Criteria)	76.0%	68.6%	0.402
#2	70.0%	76.2%	0.439
#3	88.0%	55.2%	0.356
#4	82.9%	66.0%	0.486
#5	**86.0%**	**68.6%**	**0.480**
B. Relatives			
#1 (SBR Criteria)	36.0%	100.0%	0.373
#2	82.0%	75.0%	0.567
#3	86.0%	75.0%	0.605
#4	28.0%	100.0%	0.291
#5	**84.0%**	**75.0%**	**0.586**
C. Index cases + Relatives			
#1 (SBR Criteria)	56.0%	79.5%	0.363
#2	76.0%	75.8%	0.503
#3	87.0%	62.1%	0.450
#4	47.0%	88.8%	0.384
#5	**85.0%**	**70.8%**	**0.526**

* Proposed Criteria for Clinical diagnosis of FH

#1	(TC ≥260 mg/dL OR LDL-C ≥155 mg/dL)	AND (family history of pCVD OR family history of hypercholesterolemia)	
#2	apoB/apoA1 ratio ≥0.68		
#3	[(TC ≥260 mg/dL OR LDL-C ≥155 mg/dL)	AND (family history of pCVD OR family history of hypercholesterolemia)]	OR apoB/apoA1 ratio ≥0.68
#4	(TC ≥260 mg/dL OR LDL-C ≥190 mg/dL)	AND (family history of pCVD OR family history of hypercholesterolemia)	
#5	[(TC ≥260 mg/dL OR LDL-C ≥190 mg/dL)	AND (family history of pCVD OR family history of hypercholesterolemia)]	OR apoB/apoA1 ratio ≥0.68

CONCLUSIONS

Our results suggest that determination of apoB/apoA1 ratio could be a useful biomarker to help distinguish FH children from other dyslipidemic children in clinical settings. The inclusion in clinical criteria of a higher cut-off point for LDL-C and an apoB/apoA1 ratio ≥0.68 optimized the criteria sensitivity and specificity. The correct identification and stratification, at an early age, of all children at-risk is of great importance so specific interventions can be implemented.

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