Lack of Agreement Between the Plasma Lipid-Based Criteria and Apoprotein B for the Diagnosis of Familial Combined Hyperlipidemia in Members of Familial Combined Hyperlipidemia Kindreds

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Our objective was to analyze the concordance between abnormally high-cholesterol and triglyceride concentrations and increased apoliprotein B (apoB) concentrations for considering subjects as affected in familial combined hyperlipidemia (FCHL) kindreds. Twenty-two FCHL families (n = 217) were included. There was a lack of agreement in the identification of the abnormal subjects when several cholesterol- and triglyceride-based criteria were compared against various apoprotein B-based criteria. The agreement, measured as κ coefficients, between 14 lipid-based criteria and 8 apoB concentrations is reported. For the most frequently used criterion (≥ 90th percentile for cholesterol or triglyceride concentrations), the agreement was low for all apoB levels (κ, 0.42 to 0.49). A concentration of triglycerides ≥ 150 mg/dL and cholesterol ≥ 200 mg/dL was the only criterion with a κ value above 0.6; the acceptable agreement was found with an apoB concentration ≥ 120 mg/dL (κ = 0.604). In conclusion, the data reported here clearly show that a large degree of diagnostic uncertainty exists in the categorization as normal or abnormal of members of FCHL kindred. Different diagnostic criteria would result in conflicting results. This is a critical issue, depending on the diagnostic criteria used, completely different conclusions could result from the linkage analysis in the FCHL studies.

FAMILIAL COMBINED HYPERLIPIDEMIA (FCHL) is a common and heterogeneous disorder characterized by the presence of multiple lipoprotein phenotypes and high risk for coronary heart disease within kindreds.[1] In fact, FCHL is the cause of 10% to 20% of the coronary artery disease patients under 60 years of age. The frequency of FCHL is approximately 1% in all populations examined.[2,3]

The original description of this disorder was made in 1973 by Goldstein and et al.[4] The diagnostic criteria were the presence of at least 1 relative besides the proband who would be unequivocally hyperlipidemic (ie, whose lipid level was ≥ 99th percentile for adults 20 years of age and older or ≥ 95th percentile for younger individuals). Probands should have a cholesterol or triglyceride greater than the 95th percentile. As a consequence, family studies are required to diagnose FCHL. The lipoprotein phenotypes can be variable, even in the same affected individual. FCHL is characterized by variable expression of both hypertriglyceridemia and hypercholesterolemia. Usually, the lipid abnormalities are moderate, but when a secondary cause of hyperlipidemia coexist, severe hypertriglyceridemia and mixed lipemia have been reported.[5]

In 1987, a workshop attempted to obtain a consensus on the diagnosis of FCHL[1]; however, no clear cut diagnostic criteria were proposed. The investigators stated "an abnormality that appears to be characteristic of FCHL is an increased concentration of apolipoprotein B (apo B) in whole plasma". Research performed in the past few years had proved the complexity and heterogeneity of the disease in which apolipoprotein B (apoB) plays a critical role.[6-10] Overproduction of ApoB-100, the main structural apolipoprotein of very–low-density lipoprotein (VLDL) and low-density lipoprotein (LDL), is the explanation for these lipid abnormalities in the majority of the kindreds.[11-13] However, a FCHL kindred with normal apoB-100 production rates and decreased VLDL- and LDL-apoB elimination rates has been reported.[14] Other cases with normal apoB-100 production rates have been reported.[15,16] The LDL particle distribution is abnormal with a predominance of smaller and denser particles.

Contradictory results have been a common ground in this field. One possible reason is the criteria used for considering the subjects as normal or affected. The absence of a genetic marker has resulted in multiple diagnostic criteria. That first definition is long gone. Some groups had based the classification on the cholesterol, triglycerides, and high-density lipoprotein (HDL) cholesterol concentrations[12,17-30]; others included the apoB levels[13,31-41] based on the critical importance of this apolipoprotein in the pathogenesis and clinical characteristics of the disease.[42] Furthermore, different cut points have been used for the diagnosis of increased concentrations of either plasma cholesterol or triglycerides ranging from the 90th percentile to the National Education Cholesterol Education Program (NCEP) cut points. Also, different apoprotein B concentrations have been selected as cut points. Consequently, it is a critical issue, especially for genetic studies, to define adequate cut points for the categorization of the subjects as possibly affected or normal within a FCHL kindred.

The objective of this study was to analyze the concordance between abnormally high cholesterol and triglyceride concentrations and increased apoB concentrations found in members of FCHL kindreds.

MATERIALS AND METHODS

Subjects

Twenty-two FCHL kindreds were included. FCHL was diagnosed in families with a history of premature coronary heart disease and the

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presence of hypertriglyceridemia (> 200 mg/dL) and/or hypercholesterolemia (> 240 mg/dL) in at least 2 subjects. As many members as possible were sampled. At least 3 members/family were included in the analysis. Of the 380 subjects living members of these kindreds, samples were obtained in 302. Cases having secondary causes of hyperlipidemia, triglycerides above 11.2 mmol/L (1,000 mg/dL) or using lipid-altering drugs were excluded from the analysis (n = 35). Fifty cases were 20 years old or younger; these cases were excluded from the analysis. A total of 217 cases were included.

Methods

The laboratory of the Departamento de Endocrinología y Metabolismo of the Instituto Nacional de Ciencias Médicas y Nutrición in Mexico performed all lipid and clinical laboratory measurements using standardized procedures. This laboratory is certified for standardization of tests by the External Comparative Evaluation of Laboratories Program of the College of American Pathologists. Blood samples were taken after an overnight fast (9 to 12 hours). Patients were carefully instructed about the importance of the required fasting for obtaining the sample. All laboratory analyses were performed with commercially available standardized methods. Glucose was measured using the glucose oxidase method and hemoglobin A_{1c} (HbA_{1c}) using latex immunoagglutination inhibition (Bayer Diagnostics, Tarrytown, NY). Total serum cholesterol and triglycerides were measured using an enzymatic method (SERA-PAK; Bayer Diagnostics) (coefficient of variation [CV], 3.3%). HDL-cholesterol (HDL-C) levels were assessed using phosphotungstic acid and Mg^{2+} (CV, 2.5%). LDL-cholesterol (LDL-C) concentrations were estimated by the Friedewald formula.[42a] ApoB concentration was measured by an immunonephelometric method (CV, 2.5%).

Statistical Analysis

The analysis of agreement of diagnosis was made by κ.[43] The resultant coefficient gives values between -1 and 1. Although negative numbers are theoretically possible, they are not seen in a clinical setting. The nearest value to 1 indicates a perfect agreement. What constitutes an acceptable level of agreement is often hard to say; however, a value less than 0.6 was considered indicative of a nonsignificant agreement between 2 variables. The following classification shows ranges for κ with some corresponding qualitative terms: $\leq$ 0.2, poor; 0.2 to 04, fair; 0.4 to 0.6, moderate; 0.6 to 0.8, acceptable; and $\geq$ 0.81, excellent.[44] The cut points for the lipid parameters were selected based on the recommendations of the NCEP, the American Association of Clinical Endocrinologists and European guidelines, and the most frequently used criteria in FCHL-related papers.[45-47] The results from a national survey performed in 2,227 Mexican adults, aged 20 to 69 years, were used to obtain the values of the cut points based on the percentile distribution of the lipid parameters adjusted for age and gender. The 90th percentile for the apoB concentrations for men and women, age 60 to 69 years, was 116 mg/dL; in subjects younger than age 50, this cut point ranged from 85 to 100 mg/dL.

RESULTS

A total of 217 cases were included. The frequency of several apoB concentrations is shown in Table 1. Assuming that FCHL is a dominant highly penetrant disease,[8] close to 50% of family members should be affected. The apoB concentrations that better fit this assumption were the 115 and 120 mg/dL (54.8 and 49.8%, respectively). A value of 130 mg/dL, used in other populations[5] identifies only 34.1% of our subjects. The frequencies of other lipid abnormalities are shown in Tables 1 and 2. Frequencies close to 50% were found for triglycerides $\geq$ 180 mg/dL, cholesterol $\geq$ 90th percentile, and the combination HDL-C below 35 mg/dL for men and 45 mg/dL for women. The frequencies of several combinations of abnormal lipid concentrations are shown in Table 2. Several were close to 50%. These combinations were triglycerides $\geq$ 150 mg/dL plus cholesterol $\geq$ 200 mg/dL (48.4%) and triglycerides $\geq$ 250 mg/dL or cholesterol $\geq$ 240 mg/dL (53%).

Table 1. Frequencies of Increased apoB and Abnormal Plasma Lipid Concentrations in 22 FCHL Kindreds

Parameter	Frequency (% of the sampled population)
ApoB (mg/dL)	
≥100	70.5
≥105	65.9
≥110	58.5
≥115	54.8
≥120	49.8
≥125	39.2
≥130	34.1
≥90th percentile	73.3
Triglycerides (mg/dL)	
≥90th percentile	15.7
≥150	58.1
≥180	47.9
≥200	41.0
≥250	29.5
Cholesterol (mg/dL)	
≥90th percentile	47.9
≥200	72.4
≥240	41.9
HDL-cholesterol (mg/dL)	
<10th percentile	8.8
<35 mg/dL women or <45 mg/dL males	47.0

There was a lack of agreement in the identification of the abnormal subjects when several cholesterol-and triglyceride-based criteria were compared against various apoprotein B cut points. ApoB concentrations above 130 mg/dL were not included in the analysis based on the low prevalence of these apoB levels found in our FCHL kindreds. The agreement between these 2 sets of parameters (measured as κ coefficients) is shown in Tables 3 and 4.

Two strategies of combinations were used. When the presence of both lipid abnormalities was required, the highest agreement was found with apoB concentrations $\geq$ 120 mg/dL. As expected, better agreement was found when low cut points were used. In this set of combinations, the only 1 with a κ value above 0.6 was found. A concentration of triglycerides $\geq$ 150 mg/dL and cholesterol $\geq$ 200 mg/dL had an acceptable agreement with an apoB concentration $\geq$ 120 mg/dL (κ = 0.604). No other combination in which both abnormalities were required was even close to having an acceptable concordance with any apoB concentration. The second approach was to demand the existence of at least 1 of the abnormalities. As expected, better agreement was found when high cut points were used. With this approach, the highest agreement was found with apoB concentrations below 120 mg/dL. None of these combinations had an acceptable agreement with any of the apoB levels. The addition of the HDL-C had no impact on the results of any of the combinations shown in Tables 3 and 4.

Table 2. Frequencies of Several Combinations of Abnormal Plasma Lipid Concentrations in 22 FCHL Kindreds

Parameter	Frequency (% of the sampled population)
Combinations	
Triglycerides ≥ 90th percentile or cholesterol ≥ 90th percentile	53.5
Triglycerides ≥ 90th percentile and cholesterol ≥ 90th percentile	10.1
Triglycerides ≥ 150 mg/dL or cholesterol ≥ 200 mg/dL	82.0
Triglycerides ≥ 150 mg/dL and cholesterol ≥ 200 mg/dL	48.4
Triglycerides ≥ 180 mg/dL or cholesterol ≥ 200 mg/dL	78.8
Triglycerides ≥ 180 mg/dL and cholesterol ≥ 200 mg/dL	41.5
Triglycerides ≥ 180 mg/dL or cholesterol ≥ 240 mg/dL	61.8
Triglycerides ≥ 180 mg/dL and cholesterol ≥ 240 mg/dL	28.1
Triglycerides ≥ 200 mg/dL or cholesterol ≥ 240 mg/dL	59.9
Triglycerides ≥ 200 mg/dL and cholesterol ≥ 240 mg/dL	23.0
Triglycerides ≥ 250 mg/dL or cholesterol ≥ 240 mg/dL	53.0
Triglycerides ≥ 250 mg/dL and cholesterol ≥ 240 mg/dL	18.4
Triglycerides ≥ 200 mg/dL or cholesterol ≥ 200 mg/dL	77.9
Triglycerides ≥ 200 mg/dL and cholesterol ≥ 200 mg/dL	35.5

The κ value of the most frequently used criterion for considering a subject as having FCHL, the 90th percentile for cholesterol or triglyceride concentrations, was low; the κ values ranged from 0.423 to 0.497. The best agreement was found with an apoB value ≥ 100 mg/dL.

The apoB [3] 90th percentile had no significant agreement with any of the lipid-based diagnostic criteria. The highest κ value (0.477) was found with the combination of triglycerides ≥ 200 mg/dL or cholesterol ≥ 200 mg/dL.

A total of 108 subjects had apoB ≥ 120 mg/dL. As shown in Table 5, this cut point separates 2 different populations. Subjects with apoB ≥ 120 mg/dL had significantly higher cholesterol and triglyceride concentrations and lower HDL-C levels than the cases with lower apoprotein B levels. The magnitude of the lipid abnormalities was moderate, as is usually observed in FCHL.

A strong correlation was found between the cholesterol and the apoprotein B concentrations ($r = .821$, $P < .001$). As expected, an inverse relationship was observed between the HDL-C and the apoprotein B concentrations ($r = -.23$, $P < .001$).

DISCUSSION

Significant heterogeneity exists among the reported cohorts of FCHL kindreds. In Table 6, the mean lipid concentrations of various studies are shown. All of these reports come from investigators who have published more than 1 report related to FCHL or represent multicenter populations. Big differences between the highest and the lowest mean cholesterol (98 mg/dL), triglycerides (310 mg/dL), HDL-C (20 mg/dL), and apoprotein B (47 mg/dL) were found. Some studies[28] had a mean triglyceride concentration 2 times greater than the mean level reported by Goldstein et al[4] in their original description. These observations are proof of the diversity of abnormalities included in the FCHL term.

Some heterogeneity may be caused by the diagnostic criteria. The lack of a genetic marker has been substituted by a diversity of criteria based on either the lipid concentrations or the apoB levels. The main conclusion of this report is the lack of agreement between the lipid-based criteria and the apoprotein B criteria for the diagnosis of abnormality in members of FCHL kindreds. No concordance was found even after trying multiple cut points for cholesterol, triglycerides, and apoB. Only the combination triglycerides ≥ 150 mg/dL and cholesterol ≥ 200 mg/dL had an acceptable agreement with an apoB concentration ≥ 120 mg/dL ($\kappa = 0.604$). No other combination of the plasma lipids abnormalities was even close to having an acceptable concordance with any apoB concentration. The implications of these findings are important. The number of subjects considered as affected will be remarkably different based on

Table 3. Analysis of Agreement, Expressed as κ Values, Between Increased Apoprotein B Concentrations (100, 105, 110, and 115 mg/dL) and Different Abnormalities in the Lipid Profile

Combination	ApoB Concentrations (mg/dL)			
	≥100	≥105	≥110	≥115
Triglycerides ≥ 90th percentile or cholesterol ≥ 90th percentile	0.497	0.482	0.487	0.49
Triglycerides ≥ 90th percentile and cholesterol ≥ 90th percentile	0.09	0.11	0.148	0.136
Triglycerides ≥ 150 mg/dL or cholesterol ≥ 200 mg/dL	0.512	0.479	0.41	0.381
Triglycerides ≥ 150 mg/dL and cholesterol ≥ 200 mg/dL	0.527	0.580	0.597	0.596
Triglycerides ≥ 180 mg/dL or cholesterol ≥ 200 mg/dL	0.541	0.549	0.469	0.434
Triglycerides ≥ 180 mg/dL and cholesterol ≥ 200 mg/dL	0.423	0.467	0.507	0.501
Triglycerides ≥ 180 mg/dL or cholesterol ≥ 240 mg/dL	0.5	0.512	0.549	0.538
Triglycerides ≥ 180 mg/dL and cholesterol ≥ 240 mg/dL	0.281	0.32	0.40	0.416
Triglycerides ≥ 200 mg/dL or cholesterol ≥ 240 mg/dL	0.508	0.518	0.552	0.54
Triglycerides ≥ 200 mg/dL and cholesterol ≥ 240 mg/dL	0.223	0.253	0.316	0.361
Triglycerides ≥ 250 mg/dL or cholesterol ≥ 240 mg/dL	0.433	0.436	0.516	0.499
Triglycerides ≥ 250 mg/dL and cholesterol ≥ 240 mg/dL	0.173	0.194	0.243	0.279
Triglycerides ≥ 200 mg/dL or cholesterol ≥ 200 mg/dL	0.57	0.574	0.491	0.454
Triglycerides ≥ 200 mg/dL and cholesterol ≥ 200 mg/dL	0.341	0.376	0.403	0.426

Table 4. Analysis of Agreement, Expressed as κ Values, Between Increased Apoprotein B Concentrations (120, 125, and 130 mg/dL and 90th percentile) and Different Abnormalities in the Lipid Profile

Combination	ApoB Concentrations (mg/dL)			
	≥120	≥125	≥130	≥90th Percentile
Triglycerides ≥ 90th percentile or cholesterol ≥ 90th percentile	0.466	0.428	0.423	0.438
Triglycerides ≥ 90th percentile and cholesterol ≥ 90th percentile	0.112	0.142	0.136	0.079
Triglycerides ≥ 150 mg/dL or cholesterol ≥ 200 mg/dL	0.357	0.247	0.204	0.462
Triglycerides ≥ 150 mg/dL and cholesterol ≥ 200 mg/dL	0.604	0.499	0.488	0.364
Triglycerides ≥ 180 mg/dL or cholesterol ≥ 200 mg/dL	0.403	0.279	0.229	0.446
Triglycerides ≥ 180 mg/dL and cholesterol ≥ 200 mg/dL	0.502	0.435	0.415	0.274
Triglycerides ≥ 180 mg/dL or cholesterol ≥ 240 mg/dL	0.521	0.43	0.383	0.286
Triglycerides ≥ 180 mg/dL and cholesterol ≥ 240 mg/dL	0.437	0.471	0.454	0.219
Triglycerides ≥ 200 mg/dL or cholesterol ≥ 240 mg/dL	0.54	0.443	0.393	0.299
Triglycerides ≥ 200 mg/dL and cholesterol ≥ 240 mg/dL	0.372	0.384	0.377	0.167
Triglycerides ≥ 250 mg/dL or cholesterol ≥ 240 mg/dL	0.512	0.454	0.43	0.298
Triglycerides ≥ 250 mg/dL and cholesterol ≥ 240 mg/dL	0.279	0.306	0.308	0.124
Triglycerides ≥ 200 mg/dL or cholesterol ≥ 200 mg/dL	0.421	0.293	0.241	0.477
Triglycerides ≥ 200 mg/dL and cholesterol ≥ 200 mg/dL	0.437	0.351	0.340	0.204

the prevalence of the lipid abnormality selected as diagnostic criteria (Tables 1 and 2). It could be as low as 10% or as high as 77.9%. The use of apoB concentrations ≥ 130 mg/dL, as proposed by Bredie et al,[5] will detect only 34.1%. This percentage is not compatible with a dominant penetrant disease as FCHL has been generally considered.[8] Furthermore, the patients considered as affected will not be the same, even when diagnostic criteria with similar prevalence are used. For example, in the population reported here, the most commonly used criteria, the set, triglycerides or cholesterol ≥ 90th percentile, will consider 116 cases as affected. The apoB level of 115 mg/dL will include in this category only 3 patients more. However, both diagnostic criteria will match for considering a subject as affected in only 69 of the 116 (59%) cases. Also, of the nonaffected cases (n = 101), only 43 will be considered in that way by both criteria.

The lack of agreement between the plasma lipid-based criteria and the apoprotein B for the diagnosis of FCHL could be demonstrated in other populations. Wijsman et al[20] showed no association of FCHL with the apolipoprotein AI-CIII-AIV gene complex in 3 large families including 127 subjects. They considered affected 42 subjects because they had lipid levels ≥ the 90th percentile (33% of the population). If they had used an apoB level ≥ 120 mg/dL, 59 cases would be considered as abnormal (46% of the population). Only 29 would be detected by both criteria. The mean triglyceride concentrations would be statistically different in the populations detected by these 2 criteria (276 ± 401 *v* 528 ± 657, $P = .02$). On the other hand, Dallinga-Thie et al[31] found that some haplotypes of the apolipoprotein AI-CIII-AIV gene complex contributes to the appearance of dyslipidemia in FCHL kindreds. These investigators included the apoB concentration (≥ 75th percentile, close to ≥ 120 mg/dL for adults) in the diagnostic criteria. A total of 178 of the 388 subjects were considered as affected (45% of the population). In this report, the triglyceride concentrations of the affected cases were lower than the abnormal subjects reported by Wijsman et al[20] (292 ± 437 *v* 528 ± 657). However, the mean triglyceride value would be very similar if Wijsman et al[20] had included the apoB in the diagnostic criteria (292 ± 437 *v* 276 ± 401 mg/dL). Furthermore, Porkka et al[48] reported that a large percentage of the subjects with increased apoB concentrations (defined by the 90th percentile in the Finnish Multinational Monitoring of Trends and Determinants of Cardiovascular Disease [FINMONICA] study) could be missed by using the lipid concentrations above the 80th to 98th percentile (40% to 90%, respectively).

The observations described above demonstrate that very different populations could be considered as having FCHL depending on the characteristics of the diagnostic criteria. The selected cut points for cholesterol, triglycerides, and apoB may differ between populations, based on the large diversity found in these parameters among ethnic groups. Some of the problems in the categorization of the subjects for genetic studies could be overcome by considering as unknown all the cases not

Table 5. Clinical Characteristics of the Study Subjects Classified by Their Apoprotein B Concentration (≥120 mg/dL or below)

	Apoprotein B Levels		
	≥120 mg/dL	<120 mg/dL	*P*
Age (yr)	47 ± 15	41 ± 16	<.05
Gender (M/F)	45/63	42/67	NS
Fasting plasma glucose (mg/dL)	84 ± 10	78 ± 10	NS
Cholesterol (mg/dL)	260 ± 42	197 ± 31	<.05
Triglycerides (mg/dL)	257 ± 148	159 ± 136	<.05
HDL cholesterol (mg/dL)	39 ± 9	45.6 ± 14	<.05
Apoprotein B (mg/dL)	142 ± 12	92 ± 14	<.05

NOTE. Data expressed as mean ± SD.
Abbreviation: NS, not significant.

Table 6. Mean Lipid Values of Cases Considered as Affected in Several FCHL Cohorts

Author	No.	Cholesterol	Triglycerides	HDL-Cholesterol	Apoprotein B
Goldstein[4]	47	298 ± 52	240 ± 116	42 ± 16	
Porkka[48]	90	257 ± 41	269 ± 134	38 ± 14	139 ± 31.8
Hokanson[35]	13	245 ± 32	373 ± 196	35 ± 8	147 ± 31
Babirak[40]	56	268 ± 70	327 ± 201	36 ± 7	149 ± 39
Ascaso[37]	20	260 ± 37	301 ± 149	34 ± 5	149 ± 18
Meijssen[41]	7	262 ± 28	318 ± 37	27 ± 2	154 ± 19
Aouizerat[33]	253	281 ± 90	243 ± 143		131 ± 30
Pei[27]	137	249 ± 62	269 ± 401	43 ± 14	
Pihlajamäki[24]	27	291 ± 44	213 ± 81	47 ± 11	137 ± 23
Coon[29]	170	242 ± 39	523 ± 48	44 ± 11	
Venkatesan[17]	7	330 ± 45	326 ± 160		
Gehrisch[28]	19	283 ± 94	462 ± 700	39 ± 13	168 ± 42
Cortner[12]	4	232 ± 22	461 ± 49	31 ± 8	178 ± 46
Pajukanta[18]	61	271 ± 43	269 ± 167	44 ± 17	142 ± 36
All studies					
Mean ± SD	911	269 ± 26	332 ± 96	37 ± 6	150 ± 14
Range		232-330	213-523	27-47	131-178
Studies in which the apoB was included in the diagnostic criteria[33,35,37,40,41,46]					
Mean ± SD	439	262 ± 11	305 ± 45	34 ± 4	146 ± 7
Range		245-281	243-373	27-43	131-149
Studies in which the apoB was not included in the diagnostic criteria[4,12,17,18,24,27-29]					
Mean ± SD	472	269 ± 26	332 ± 96	37 ± 6	150 ± 14
Range		232-330	213-523	31-47	137-178

classified as affected, but still, large variations in the number of affected cases will result from the diagnostic criterion. Besides these findings, there are a number of explanations for the nonreplication between reports of linkage of FCHL with several genes or loci, including a false positive result by chance, genetic heterogeneity, and variability in pedigree selection.

Based on these results and because of the lack of a gold standard, it is not possible to identify the best diagnostic criteria. Our objective was to demonstrate the large differences that result from the application of the most frequently used criteria for defining a subject as affected in FCHL kindreds. The diagnosis of FCHL based on the cholesterol and/or triglycerides $\geq$ 90th percentile results in heterogeneous populations with a wide range of apoB and triglyceride concentrations. Meanwhile, until a genetic marker is found, we can have better diagnostic criteria useful for identifying homogenous sets of FCHL patients who are probably affected. As shown in Table 6, the inclusion of the apoB in the diagnostic criteria, regardless the selected cut point, resulted in smaller differences between the mean lipid levels. We[49] and others[50] believe that the apoB concentrations must be selected as the first choice for the categorization of the members of a FCHL kindred based on the pathophysiology of the disease and the recent demonstration[51] that this parameter is 1 of the best markers of increased cardiovascular risk. The measurement of the apoB concentrations also allows identification of hyperapobetalipoproteinemia cases, a variant of FCHL associated with normal LDL-C concentrations.[11] This strategy overcomes the high degree of variability of the lipid levels in FCHL cases due to transient elevations or temporary spontaneous normalization of these parameters commonly found in this disorder. In summary, these observations suggest that the inclusion of the apoB in the diagnosis of FCHL could decrease the heterogeneity of the subjects classified as affected.

Unfortunately, a great variability has existed in the selection of the diagnostic cut points for the apoB. Meanwhile, some studies have included patients with apoB as low as 90 mg/dL,[31] and others have proposed cut points as high as 130 mg/dL.[5] The large degree of variability in the apoB concentrations between ethnic groups is 1 possible explanation for the difficulty in establishing an appropriated cut point. In this report, a concentration $\geq$ 120 mg/dL allows us to identify 2 populations with significant differences in their lipid profile. The lipid abnormalities observed in the high apoprotein B group are in accordance with the FCHL lipid disturbances. This value is above the 90th percentile in all age groups in the Mexican population, and it is close to the 75th in all age groups in the National Health and Nutrition Examination Survey (NHANES) III population.[52]

Thus, the data reported here clearly show that a large degree of diagnostic uncertainty exists in the categorization as normal or abnormal of members of FCHL kindreds. A specific metabolic or genetic marker is urgently needed for the study of FCHL.[53] These results are a demonstration of the difficulties involved in studies concerning FCHL, and it could explain some of the existing discrepancies. This is a critical issue; depending on the diagnostic criteria used, completely different conclusions could result from the linkage analysis in FCHL studies.

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