Apolipoprotein B and A-I Distribution in Mexican Urban Adults: Results of a Nationwide Survey

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The apolipoprotein (apo) B and A-I distribution found in a survey performed in 417 Mexican cities is described. Information was obtained from 15,607 subjects aged 20 to 69 years. In this report, only samples obtained after a 9- to 12-hour fast were included (1,674 cases, 652 men and 1,022 women). The population is representative of the Mexican urban adults. Mean lipid concentrations were: cholesterol,182.7 mg/dL; triglycerides, 213 mg/dL; high-density lipoprotein (HDL) cholesterol, 38.3 mg/dL; and low-density lipoprotein (LDL) cholesterol, 116 mg/dL. The mean concentration of apo B was 77.8 ± 25.9 mg/dL and 71 ± 22.8 in men and women, respectively. A continuous increase of apo B was observed as subjects got older. A tendency to decrease after age 60 was observed in men, but not in women. The body mass index (BMI) is a major determinant for the apo B concentrations. The 90th percentile of the apo B concentration identifies a similar proportion of abnormal subjects than the LDL cholesterol concentration of 160 mg/dL. The 120 mg/dL concentration, upper normal limit level used in other populations, identified as abnormal only 3.8% of the cases. Regardless of the lipid abnormality, an apo B above the 90th percentile was associated with higher levels of glucose, cholesterol, triglycerides, and non-HDL cholesterol, despite a similar age and BMI. The overall mean concentration of apo A-I was 122.3 ± 31 mg/dL and 129 ± 34 in men and women, respectively. In conclusion, our data show that the apo B and apo A-I concentrations in Mexican urban adults are lower compared with the levels reported in other ethnic groups. Previously used reference ranges are not useful in the population report herein. These observations strengthen the need for obtaining data in population-based studies worldwide.

ASSESSMENT OF CARDIOVASCULAR risk attributable to lipoprotein abnormalities is a controversial issue.[1,2] For this purpose, several parameters, cut points, and conditions have been used.[3-5] The evaluation could be as simple as a random cholesterol measurement[6] or as complex as a fasting complete lipid profile. It has been postulated that apolipoproteins (apo) could be part of the evaluation based on various reports supporting its usefulness as predictors for coronary events. Apo B is the main protein component of the lipoproteins with the higher atherogenic potential (low-density lipoprotein [LDL] and intermediate-density [IDL] particles)[7,8]; it was a better index of risk than total cholesterol or LDL cholesterol in the Quebec[9] and the European Atherosclerosis Research Study (EARS)[10] studies. Abnormalities in the function or amount of the apo A-I cause premature atherosclerosis and severely decreased HDL cholesterol concentrations.[11] In spite of its potential utility, the routine measurement of the apo B and A-I concentrations have been limited mainly to research studies. The lack of standardization until the early 90s and the absence of suitable reference data has hampered its use in clinical medicine.

In 1991, the International Federation of Clinical Chemistry (IFCC) Committee on Apolipoproteins produced reference materials for apo A-I and B[12]; its use made possible valid comparisons of the results even if different methods were used in different laboratories. In the past few years, the distribution of the apo A-I and apo B values were reported in several large populations.[13-16] The results from the Framingham Offspring study were the first attempt to establish reference ranges.[13] Similar approaches were applied in Phase 1 of the Third National Health and Nutrition Examination Survey (NHANES III) and in Finnish and Swedish cohorts.[14-16] No similar data had been published in a non-Caucasian population.

During the period 1992 to 1993, the Ministry of Health of México conducted the National Survey of Chronic Diseases to estimate the prevalence of obesity, type 2 diabetes, renal pathology, hypertension, and dyslipidemia. The objective of this report was to provide the reference intervals, by age and gender, of the apo B and apo A-I concentrations in urban Mexican adults.

MATERIALS AND METHODS

Population Sample

This is a comparative, cross-sectional study that includes individuals from cities with more than 2,500 people. The sampling procedure and characteristics of the population have been described in detail in a previous report.[17] Briefly, a multistage sampling procedure was used. The country was divided into 3 regions (northern, central, and southern) of 10 states each, and the metropolitan area of Mexico City (including the remaining 2 states) compose the fourth region. A random sample of Basic Geographical Statistical Units was obtained in each state from a database recently generated by the Instituto Nacional de Geografía y Estadística and after the general sampling frame was constructed by the Health Ministry. Neighborhood blocks were randomly selected, and all adults (20 to 69 years) in all households of the selected blocks were surveyed with the exception of those living in military, religious, health, and other institutions. A total of 417 cities were studied. The sample was representative of the Mexican urban population, which in 1990, constituted 71% of the total population. A target of 4,731 individuals and 2,030 households/region was estimated using the household as the sampling unit and using the average of 2.33 adults/household (according the 1990 National Census). The sample size was considered capable of detecting risk factors at the regional

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level, which have at least a prevalence of 4% with a relative error of estimation of 0.289 and a nonresponse rate of 30%. Information was obtained from 15,607 subjects; the response rate was 82.5% The study was performed in accordance with the Helsinki Declaration of Human Studies.

Personal Interview

A general structured interview was conducted. A previously standardized questionnaire was used to obtain information on demographic and socioeconomic aspects, family health history, personal medical history, and lifestyle factors such as smoking. In the same visit, anthropometric and blood pressure measurements were obtained. Systolic (1st-phase) and diastolic (5th-phase) blood pressures were measured to the nearest even digit with a sphygmomanometer with the subject in the supine position after a 5-minute rest. Blood pressure was measured twice in every case in which the initial measurement was ≥ 120/80 mm Hg. The second measurement was performed after a 5-minute resting period in the sitting position. The mean value of those measurements was included in the database. The blood pressure was measured only once in the remaining cases.

Participants removed their shoes and upper garments. Height was measured to the nearest 0.5 cm. Body weight was measured on a daily calibrated balance and recorded to the nearest 0.1 kg. Body mass index (BMI) was calculated as weight (kg) divided by height (m^2) and was used as an index of overall adiposity. The equipment was regularly calibrated using reference samples provided by the manufacturer.

Methods

Blood samples were obtained in 77.6% of the population (n = 14,682). This report includes the results of 1,674 subjects who had a 9- to 12-hour fasting period, required for a complete lipid profile (10.72% of the population). These cases were randomly distributed between the population; no bias was detected for region or socioeconomic status in this subset of cases. All analytical measurements were performed at the Departamento de Endocrinología and Metabolismo of the Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán". The sampling procedure was standardized during a 28-week training course. The subjects were sampled at their homes; they remained seated for 5 minutes before the blood was drawn.

Apo A-1 and apo B were measured by an immunoturbidimetric method[18] on a Hitachi 705 (Hitachi Science Systems Ltd, Hitachinaka, Japan); the assays were performed according to the manufacturer's instructions with manufacturer-provided calibrators and antisera. The manufacturer claimed that the values of the calibrator were assigned on the basis of the World Health Organization (WHO)-IFCC International Reference Materials for apo A-1 and apo B. All reagents used for this study were provided from a single source and from the same batch. All samples were kept frozen at -80°C until they were analyzed; the maximum time of storage was 12 months. The external quality control for apo A-I and apo B was based on lyophilized samples for apo A-I and a liquid stabilized serum for apo B at 3 different concentrations of the analytes with values assigned against the WHO-IFCC materials. This strategy is in accordance with the standardization procedures of the WHO and the IFCC Committee on apolipoproteins.

Glucose was analyzed by the glucose-oxidase method (Boehringer Mannheim, Mannheim, Germany). Serum concentrations of total cholesterol and triglycerides were determined by enzymatic methods (Boehringer Mannheim). HDL cholesterol was measured after precipitation of very–low-density lipoprotein (VLDL) and LDL by the phosphotungstate method (Boehringer Mannheim), LDL cholesterol was measured by ultracentrifugation. Intra-assay coefficient of variation (CV) values for total cholesterol, triglycerides, and HDL cholesterol were 3%, 5%, and 5%, respectively. Insulin was analyzed by enzyme-linked immunosorbent assay (ELISA) in the ES-33 system (Boehringer Mannheim). The cross-reactivity with proinsulin for this assay was 40%. Our laboratory followed standardization procedures according to the WHO recommendations, including the use of external control sera.

Definitions

Overweight was defined as BMI 25 to 30 kg/m^2 for males and females. Obesity was defined as BMI ≥ 30 kg/m^2. Individuals were diagnosed as diabetics if they had a previous diagnosis of diabetes or had a fasting blood glucose value ≥ 7 mmol/L (126 mg/dL) and no previous history of diabetes. Hypertension was diagnosed when the systolic pressure was ≥ 140 mm Hg and/or diastolic pressure was ≥ 90 mm Hg and/or current use of antihypertensive medications. Ischemic heart disease was considered if there was a history of myocardial infarction. Smoking was defined as any tobacco consumption during the previous month prior to the sampling.

Statistical Analysis

The data were codified and captured under ASCII fixed format. The database was validated through recognition of missing values, outliers, and inconsistencies between variables. Descriptive analysis included the estimation of mean values and standard deviation (SD) for continuous variables. These values were rounded at the nearest integrer or first decimal. Prevalence and frequencies are expressed as percentages. Mean, SD, and 10th to 90th percentiles described the distribution of the continuous variables. Significance of the differences between the subgroups of the population were tested by 1-way analysis of variance (ANOVA) using Scheffé's multiple comparison method. Categorical variables were compared by the χ^2 statistic with Yates' correction or the exact Fisher test when appropriate. Correlation coefficients were calculated for measuring the association between continuous variables. Analysis of covariance (ANCOVA) was used for gender adjustment of the variables. Sensitivity and specificity were estimated using formulas proposed by Daly and Bourke.[19] All statistical analyses were conducted using the SAS statistical package (SAS Institute, Cary, NC).

RESULTS

A total of 1,674 subjects (652 men and 1,022 women) was included in the study. Mainly subjects younger than 40 years composed the population; the age and gender distribution are representative of the Mexican adults (Tables 1 and 2). Mean lipid concentrations were cholesterol, 182.7 ± 40 mg/dL; triglycerides, 213.4 ± 158 mg/dL; HDL cholesterol, 38.3 ± 9.5 mg/dL; and LDL cholesterol, 116.4 ± 36 mg/dL. The BMI was 27.09 ± 5.6 kg/m^2. As previously described,[17] several cardiovascular risk factors were common in this population. Diabetes, high blood pressure, and obesity were found in 8.5%, 21.88%, and 20% of the subjects, respectively. Smoking was reported in 28% of the population. Almost half (46%) of the population had a primary education or less.

The most frequent abnormality was HDL cholesterol less than 35 mg/dL (46.2% for men, 28.7% for women, and 36% for both genders). The second abnormality in frequency was triglycerides greater than 200 mg/dL (31.9% for men, 18.8% for women, and 24.3% for both genders). Increased LDL cholesterol (≥ 160 mg/dL) concentrations were observed in 12.7% of men, 10.3% of women, and 11.2% of both genders.

Mixed hyperlipidemia, isolated hypoalphalipoproteinemia, and the combination high triglycerides/low HDL cholesterol were the most prevalent abnormal lipid patterns (12.6%, 12.9%, and 18.6%, respectively). These disturbances were even

Table 1. Distribution of the Apo B Concentration

	Men, Age (yr)						Women, Age (yr)					
	20-29	30-39	40-49	50-59	60-69	Total	20-29	30-39	40-49	50-59	60-69	Total
No.	261	173	89	80	50	653	406	278	131	129	80	1,024
Mean	73.6	80.6	85.2	82.0	70.5	77.8	64.5	70.9	75.0	81.9	80.7	71.0
Median	70.0	79.0	81.0	81.5	66.5	75.0	61.0	68.0	72.0	80.0	77.0	67.3
Mode	74.0	70.0	65.0	52.0	63.0	74.0	60.0	57.0	67.0	64.0	72.0	60.0
SD	25.1	25.1	29.5	26.6	18.9	25.9	19.8	23.8	23.4	23.8	19.9	22.8
Variance	630.0	632.2	871.2	709.6	358.6	671.5	393.7	568.8	547.4	566.3	394.9	522.0
Skewness	2.2	0.9	1.3	1.0	0.2	1.5	1.3	2.3	1.3	0.7	0.6	1.4
Kurtosis	11.3	2.1	3.1	2.6	−0.9	5.4	3.2	11.5	3.3	1.3	0.0	5.0
Percentiles												
10	48.0	51.0	53.0	50.1	45.1	50.0	44.0	47.0	49.0	52.0	57.1	47.0
20	55.0	58.5	61.0	56.2	53.4	56.0	49.0	53.0	55.4	62.0	62.2	53.0
30	61.0	65.2	68.0	70.0	58.6	63.0	53.0	58.0	61.6	67.0	69.3	58.0
40	65.9	72.6	76.0	76.0	62.4	69.0	58.0	62.0	67.0	75.0	74.0	62.0
50	70.0	79.0	81.0	81.5	66.5	75.0	61.0	68.0	72.0	80.0	77.0	67.3
60	75.0	85.0	87.0	86.7	74.0	80.9	65.2	73.0	76.4	85.0	82.3	73.0
70	80.4	92.0	96.0	92.0	81.6	88.2	71.0	78.2	83.0	92.0	90.7	79.0
80	90.0	98.2	105.0	97.0	92.2	95.0	78.0	87.0	93.1	100.0	97.1	88.0
90	98.0	112.2	118.0	118.9	97.0	108.0	91.0	97.0	101.8	109.0	108.8	98.7

more common in patients with type 2 diabetes. The distributions of apo A-1 and apo B are given in Tables 1 and 2, respectively.

Apo B

The overall mean concentration of apo B was 77.8 ± 25.9 and 71 ± 22.8 mg/dL in men and women, respectively. These levels are significantly lower compared with those reported in European groups and in the US.[13-16] However, differences between genders and age groups were observed as expected. The apo B concentrations were higher in every age group below 50 years in men compared with women. A continuous increase of apo B was observed as subjects got older. A plateau was reached in those age 40 to 59 in men and 50 to 69 in women. Both male and female apo B concentrations ultimately reached about the same concentrations (≈80 mg/dL), but in males, this occurred 10 years earlier. A tendency to decrease after age 60 was observed in men, but not in women. These results remained virtually the same after excluding subjects with diabetes or high blood pressure. These cases were mainly found in the higher percentiles of the apo B levels; their exclusion resulted in only a 3 mg/dL difference at the most in the highest percentile groups. The BMI was a major determinant for the apo B concentration. As shown in Fig 1, the mean apo B concentration increased in direct relationship to the BMI. After adjusting for age and gender, apo B levels were 20 mg/dL lower in lean individuals (BMI, 20 kg/m^2) compared with obese subjects (BMI, 30 kg/m^2).

Table 2. Distribution of the Apo A-I Concentrations

	Men, Age (yr)						Women, Age (yr)					
	20-29	30-39	40-49	50-59	60-69	Total	20-29	30-39	40-49	50-59	60-69	Total
No.	260	173	89	80	50	652	407	279	130	126	80	1,022
Mean	119.9	123.3	126.9	123.7	120.8	122.3	125.7	127.0	129.0	138.4	140.5	129.2
Median	115.0	118.0	123.0	120.5	121.5	118.0	119.0	121.0	125.0	133.0	133.0	123.0
Mode	105.0	94.0	126.0	137.0	116.0	136.0	114.0	120.0	105.0	151.0	93.0	122.0
SD	29.4	35.7	31.4	31.0	21.7	31.2	32.6	32.6	32.6	37.4	36.5	33.9
Variance	864.4	1275.0	985.2	963.7	469.9	972.1	1059.6	1063.1	1065.6	1396.3	1334.2	1146.2
Skewness	0.8	1.1	1.2	0.9	1.0	1.0	1.0	1.1	0.7	0.6	1.0	0.9
Kurtosis	1.7	1.5	2.4	2.0	1.7	2.0	1.5	2.7	1.8	0.4	1.4	1.6
Percentiles												
10	87.1	87.4	97.0	86.4	97.2	89.2	91.8	93.0	92.1	92.8	103.0	93.0
20	97.0	94.0	105.0	100.0	101.7	98.0	101.0	104.0	105.0	107.4	109.8	104.0
30	102.4	99.4	110.0	108.3	107.4	105.0	107.0	112.0	111.4	118.0	117.3	110.9
40	109.0	112.2	117.0	114.0	113.4	112.6	114.0	116.0	119.4	126.6	123.8	117.0
50	115.0	118.0	123.0	120.5	121.5	118.0	119.0	121.0	125.0	133.0	133.0	123.0
60	123.6	124.0	127.0	129.0	125.4	125.0	126.0	128.0	132.6	146.0	143.6	131.0
70	132.0	134.0	136.0	136.7	129.2	133.1	138.0	135.0	142.6	151.9	150.8	141.0
80	141.0	148.2	142.0	141.8	134.0	142.0	148.0	149.0	153.0	164.0	172.9	152.0
90	158.7	165.4	164.0	168.2	139.9	162.0	167.2	164.0	172.9	194.6	196.2	173.7

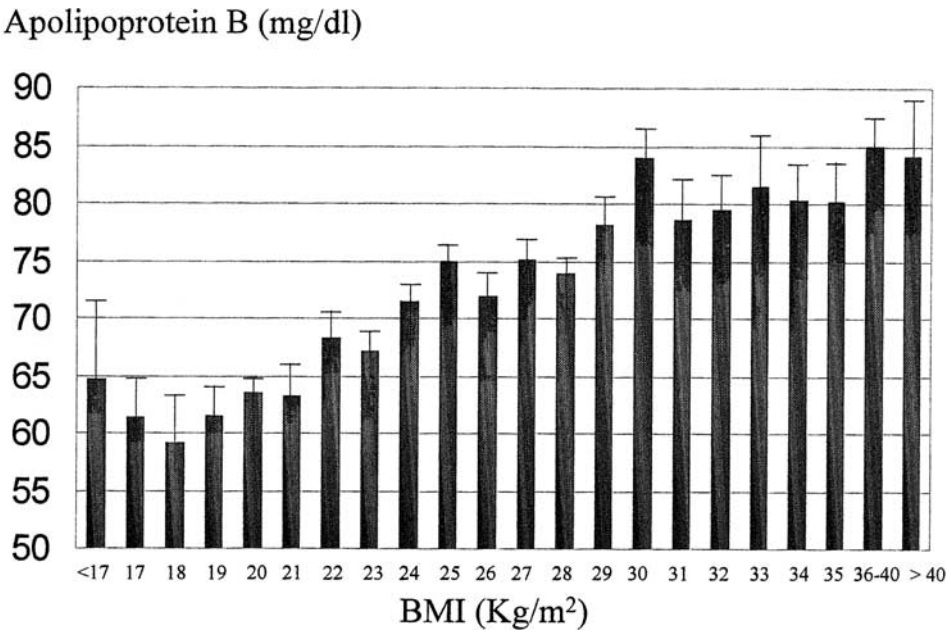

Fig 1. Effect of BMI on the apo B concentration. Data are presented as mean ± SE. Data were adjusted for age and gender.

Previously used reference ranges were not useful in this population. The 120 mg/dL cut point, used in the Framingham study, identified as abnormal only a small number of cases (3.8% of population). The profile of men and women with different apo B concentrations is shown in Table 3. In this analysis, the 50th, 75th, and 90th percentile, as well as other cut points used in previous reports, were included. In the Framingham study, the 120 mg/dL cut point was selected because it identifies the same number of abnormal subjects than the LDL cholesterol concentration ≥ 160 mg/dL. In this report, this characteristic was found for the 90th percentile (10.3% of the population). The 75th percentile had a similar prevalence than the LDL cholesterol concentration of 130 mg/dL (26% *v* 30%, respectively).

A strong trend for higher prevalence of cardiovascular risk factors was observed as the apo B concentrations increased (Table 3). The differences between the apo B concentrations strata remained statistically significant even after adjusting for age, the presence of diabetes, and BMI. Subjects with an apo B concentration above the 90th percentile had a profile for high

Table 3. Profile of Subjects With Different Apo B and LDL Cholesterol Concentrations

	Apo B							LDL Cholesterol	
	0-50th Percentile	51-75th Percentile	76-90th Percentile	>90th Percentile	≥ 120 mg/dL	≥130 mg/dL	*P*	≥130 mg/dL	≥160 mg/dL
No. (%)	845 (50.3)	402 (23.9)	256 (15.27)	174 (10.3)	64 (3.8)	43 (2.5)		505 (30.2)	175 (10.4)
Age (yr)	33 ± 12	38 ± 13	39 ± 13	40 ± 12	40 ± 13	40 ± 13	<.001	40 ± 13	42 ± 13
Glucose (mg/dL)	101 ± 44	109 ± 58	114 ± 60	126 ± 73	135 ± 85	138 ± 88	<.001	116 ± 67	127 ± 81
BMI (kg/m^2)	25.8 ± 5.9	27.3 ± 4.8	27.9 ± 5.2	29.1 ± 5	28.6 ± 4.4	28.1 ± 4.3	<.001	28.2 ± 5.4	28.7 ± 4.5
Systolic BP (mm Hg)	123 ± 16	125 ± 16	128 ± 16	129 ± 18	130 ± 21	126 ± 17	<.001	127 ± 17	129 ± 16
Diastolic BP (mm Hg)	80 ± 11	82 ± 11	83 ± 11	85 ± 14	85 ± 17	82 ± 12	<.001	84 ± 12	86 ± 13
Cholesterol (mg/dL)	165 ± 32	189 ± 27	207 ± 30	228 ± 45	238 ± 57	245 ± 63	<.001	224 ± 32	254 ± 32
Non-HDL cholesterol (mg/dL)	125.5 ± 31	152 ± 24	169 ± 28	193 ± 44	202 ± 55	209 ± 61	<.001	186 ± 31	215 ± 32
LDL cholesterol (mg/dL)	101 ± 27	121 ± 26	132 ± 31	155 ± 42	161 ± 51	167 ± 57	<.001	157 ± 27	186 ± 26
Triglycerides (mg/dL)	175 ± 114	212 ± 111	274 ± 163	395 ± 295	476 ± 46	536 ± 472	<.001	279 ± 198	347 ± 258
HDL cholesterol (mg/dL)	40.9 ± 11	37.8 ± 10	37.8 ± 10	35.2 ± 10	35.1 ± 10	35.3 ± 10	<.001	37.9 ± 10	35.1 ± 10
Apo B (mg/dL)	55.7 ± 9	77 ± 4	93 ± 4	122 ± 24	145 ± 27	156 ± 28	<.001	88 ± 26	99 ± 32
Diabetes (%)	4.2	7.7	12.8	13.2	18.7	20.9	<.001	10.1	12.5
Hypertension (%)	16.6	20.8	30.1	32.3	34.9	30.2	<.001	29.6	34.1
Dyslipidemias (%)*	45.6	72.8	87.1	94.2	93.7	90.7	<.001	91.2	100
Microalbuminuria (%)	1.9	3.4	3.06	3.27	3.6	2.7	<.001	3.3	2.56

NOTE. Data were adjusted for gender distribution. Differences between the groups remained significant even after removing the subjects with diabetes.

*Defined as cholesterol > 200 mg/dL or triglycerides > 200 mg/dL or HDL cholesterol < 35 mg/dL.

Table 4. Apo B Concentrations in Various Lipid Disturbances

	Triglycerides >200 (n = 684)		Triglycerides > 200 Cholesterol >200 (n = 335)		Triglycerides > 200 Cholesterol < 200 (n = 349)		Triglycerides<200 Cholesterol <200 (n = 805)	
	Apo B < 90th Percentile	Apo B ≥ 90th Percentile	Apo B < 90th Percentile	Apo B ≥ 90th Percentile	Apo B < 90th Percentile	Apo B ≥ 90th Percentile	Apo B < 90th Percentile	Apo B ≥90th Percentile
No. (%)	549 (80.2)	135 (19.7)	228 (68.1)	107 (31.9)	321 (91.9)	28 (8.02)	787 (97.7)	18 (2.2)
Age (yr)	39.9 ± 13*	40.4 ± 12	43.3 ± 13	40.7 ± 12	37.4 ± 13	38.4 ± 13	32.4 ± 11	41 ± 4
Apo B (mg/dL)	74.8 ± 16.6	123.2 ± 26	78.9 ± 18	122 ± 24	71.5 ± 14	127 ± 30	61 ± 14	122 ± 19
Glucose (mg/dL)	121 ± 67	132 ± 81	127 ± 77	134 ± 88	117 ± 61	121 ± 46	96 ± 35	106 ± 24
BMI (kg/m^2)	28.6 ± 6	29.3 ± 4.9	29.1 ± 5.7	29 ± 4.5	28.3 ± 6.2	27.5 ± 6	25.5 ± 5.1*	29 ± 6.6
Systolic BP (mm Hg)	128 ± 17	130 ± 18	130 ± 16	130 ± 18	126 ± 17	128 ± 18	121 ± 15	121 ± 14
Diastolic BP (mm Hg)	83 ± 12	85 ± 6	85 ± 11	87 ± 14	82 ± 12	80 ± 13	78 ± 10	78 ± 10
Cholesterol (mg/dL)	194 ± 35*	232 ± 42	225 ± 24*	246 ± 35	170 ± 21*	180 ± 16	160 ± 22*	171 ± 16
Non-HDL cholesterol* (mg/dL)	157 ± 33*	197 ± 40	185 ± 24*	210 ± 34	137 ± 21*	150 ± 16	119 ± 22*	135 ± 17
LDL cholesterol (mg/dL)	120 ± 32*	155 ± 39	145 ± 29*	167 ± 35	103 ± 20*	112 ± 18	98 ± 20*	114 ± 16
Triglycerides (mg/dL)	322 ± 137*	462 ± 300	345 ± 166*	478 ± 317	299 ± 108*	415 ± 216	121 ± 41*	141 ± 26
Diabetes (%)	13.4	14.0	15.3	14.9	12.1	10.7	2.6*	11.1
Hypertension (%)	30.3	32.8	36.5	34.9	25.5	25	13.4	22.2

NOTE. Data were adjusted for gender distribution. Differences between the groups remained significant even after removing the subjects with diabetes.

*Versus the corresponding group with apo B ≥ 90th percentile.

cardiovascular risk. Their mean concentrations of almost every evaluated parameter were abnormal; the prevalence of diabetes was 3 times higher in this group compared with the subjects with an apo B level below the 50th percentile. The magnitude of these abnormalities was very similar to that observed in subjects with LDL cholesterol ≥ 160 mg/dL, except for lower cholesterol and LDL cholesterol. Almost every case with an apo B above the 90th percentile had some form of dyslipidemia (94.2%). These data suggest that the 120 mg/dL cut point, used in other ethnic groups, is not useful in urban Mexican adults. Instead, the 90th percentile is a specific marker for increased cardiovascular risk in this population.

Although an apo B value above the 90th percentile and a LDL cholesterol greater than 160 mg/dL identifies a similar number of cases, the subjects were not the same. The 90th percentile criterion of apo B had a specificity and sensitivity of 93% and 44%, respectively, for detecting an LDL cholesterol ≥ 160 mg/dL. In other words, a large proportion of cases that had an apo B ≥ 90th percentile also had an LDL cholesterol level ≥ 160 mg/dL. However, a significant proportion of the subjects with a high LDL cholesterol were not detected by the apo B criterion. An apo B value above the 75th percentile had a better sensitivity (68%), but some specificity was lost (79%). These data confirm previous observation[16] suggesting that apo B and LDL cholesterol concentrations do not have good agreement for the identification of the high-risk cases.

The prevalence of increased apo B concentrations in cases with different lipid patterns is shown in Table 4. An apo B value above the 90th percentile was detected in 19.7% of the hypertriglyceridemic patients and in 31.9% of the mixed hyperlipidemic subjects. This abnormality was found in only 2.2% of the normolipidemic individuals. The coexistence of high apo B with high triglycerides identifies a subset of cases with significantly higher cardiovascular risk compared with cases with high triglycerides/"normal" apo B. The same phenomenon was observed in every lipid profile shown in Table 4. Regardless of the lipid abnormality, increased apo B levels were associated with higher levels of glucose, cholesterol, triglycerides, and non-HDL cholesterol despite a similar age and BMI.

Spearman correlations for apo B with other lipid and clinical parameters were estimated. Apo B was significantly correlated with age ($r = .19$, $P > .001$), cholesterol ($r = .55$, $P < .001$), non-HDL cholesterol ($r = .609$, $P < .001$), LDL cholesterol ($r = .52$, $P < .001$), BMI ($r = .16$, $P < .001$), triglycerides ($r = .44$, $P < .001$), glucose ($r = .14$, $P < .001$), and insulin ($r = .34$, $P < .001$). An inverse relationship was found with the HDL cholesterol ($r = -.17$, $P < .001$). The association between apo B and non-HDL cholesterol was observed even in patients with fasting triglycerides above 200 mg/dL ($r = .47$, $P < .001$); the significance of the relationship between LDL cholesterol and apo B was lower in this subset of subjects ($r = .38$, $P < .001$).

Apo A-I Distribution

The overall mean concentration of apo A-I was 122.3 ± 31 mg/dL and 129 ± 34 in men and women, respectively. The apo A-I concentrations were higher in every age group in women compared with men. Mean apo A-I concentrations in males remained constant with age and ranged from 120 to 127 mg/dL. This pattern of the apo A-I concentrations in females differed from that in males because the mean apo A-I values tended to increase with age and reached a plateau in the groups age ≥ 50 years. Mean apo A-I concentrations in females ranged from 125 to 140 mg/dL. The apo A-I concentrations were not significantly affected by the BMI; the cumulative percent distribution curve was remarkably similar in subjects with BMI above or below 30 kg/m^2.

Table 5. Apo A-I Concentrations in Various Lipid Disturbances

		HDL Cholesterol < 35	HDL Cholesterol < 35	Apo A-I				
	HDL Cholesterol < 35	Triglycerides < 200	Triglycerides > 200	≥ 50th Percentile	25-50th Percentile	<25th Percentile	<120 mg/dL	*P*
No. (%)	552	238	314	851 (51.1)	410 (24.6)	404 (24.2)	791 (47.1)	
Age (yr)	36.6 ± 13	32.8 ± 11*	39.5 ± 13	37 ± 15	35 ± 12	34 ± 12	34.7 ± 12.5	<.05
Glucose (mg/dL)	109 ± 52	90 ± 29*	122 ± 62	112 ± 61	101 ± 38	103 ± 44	102 ± 42	<.05
BMI (kg/m^2)	28 ± 5.7	26.2 ± 4.8*	29.4 ± 6	27.2 ± 5.7	26.7 ± 4.8	27.2 ± 6.1	27 ± 5.5	NS
Systolic BP (mm Hg)	126 ± 16	122 ± 14*	129 ± 16	125 ± 17	123 ± 16	124 ± 15	124 ± 16	NS
Diastolic BP (mm Hg)	82 ± 11	80 ± 10.2*	84 ± 12	81 ± 11	81 ± 11	81 ± 11	81 ± 12	NS
Cholesterol (mg/dL)	180 ± 38	163 ± 33*	192 ± 37	191 ± 39	179 ± 35	174 ± 38	177 ± 36	<.05
Non-HDL cholesterol (mg/dL)	152 ± 38	135 ± 33*	165 ± 36	150 ± 39	143 ± 35	141 ± 39	142 ± 37	<.05
LDL cholesterol (mg/dL)	117 ± 34	108 ± 31*	123 ± 35	120 ± 35	114 ± 32	112 ± 35	112 ± 34	<.05
HDL cholesterol (mg/dL)	27.8 ± 3.6	28.5 ± 3.2*	27.2 ± 3.9	42.2 ± 11	38 ± 9	33.5 ± 9	35.2 ± 9.4	<.05
Triglycerides (mg/dL)	272 ± 192	137 ± 40*	375 ± 196	244 ± 191	205 ± 137	200 ± 129	202 ± 128	<.05
Apo B (mg/dL)	78 ± 27	68 ± 19*	87 ± 11	79 ± 26	67 ± 17	66 ± 20	67 ± 19	<.05
Apo A-I	115 ± 30	111 ± 28	119 ± 7	150 ± 27	112 ± 4.6	90.5 ± 12	101 ± 14	<.05
Diabetes (%)	9.1	2.5*	14.0	9.4	4.3	5.4	4.9	<.05

NOTE. Data were adjusted for gender distribution.

Abbreviation: NS, not significant.

*$P < .05$ between HDL cholesterol < 35+TG < 200 *v* HDL cholesterol < 35+TG > 200.

The profile of subjects with different apo A-I concentrations is shown in Table 5. The 25th percentile of the apo A-I concentration identifies 226 of the 552 cases with HDL cholesterol concentrations of ≤ 35 mg/dL (sensitivity, 40%; specificity, 84%). The apo A-I concentration less than 120 mg/dL identifies 127 cases more, but this criteria was less specific (sensitivity, 63%; specificity, 60%).

Spearman correlations for apoA -I with other lipid and clinical parameters were estimated. Apo A-I was correlated with cholesterol ($r = .207$, $P < .001$), non-HDL cholesterol ($r = .11$, $P < .001$), LDL cholesterol ($r = .108$, $P < .001$), apo B ($r = .34$, $P < .001$), triglycerides ($r = .14$, $P < .001$), glucose ($r = .083$, $P < .001$), and insulin ($r = .14$, $P < .001$). The strongest relationship was found with HDL cholesterol ($r = .33$, $P < .001$). In contrast to the correlations found for apo A-I, the HDL cholesterol was inversely correlated with non-HDL cholesterol ($r = -.132$, $P < .001$), BMI ($r = -.117$, $P < .001$), triglycerides ($r = -.23$, $P < .001$), insulin ($r = -.122$, $P < .001$), and apo B ($r = -.17$, $P < .001$).

DISCUSSION

The best way to assess the lipoprotein-related cardiovascular risk is still under debate. The US-recommended diagnostic and therapeutic algorithms are based on LDL cholesterol.[3] Technical problems on its estimation and the partial information obtained from LDL cholesterol are major weakness of this approach.[20] The LDL cholesterol is calculated, using the Friedewald formula,[21] based on cholesterol, triglycerides, and HDL cholesterol concentrations. Each one of these parameters has its own variability and errors in their measurement. Significant inaccuracy on the LDL cholesterol estimation is a major problem in hypertriglyceridemic sera. This problem is particularly relevant in populations with a high prevalence of hypertriglyceridemia, like the Mexican urban adults.[17] Apo B has been proposed as a possible alternative to overcome the LDL cholesterol limitations.[22] The apo B value gives an accurate estimation of the number of potentially atherogenic plasma lipoproteins. More than 90% of its concentration is explained by the amount of the 2 particles with the highest atherogenic potential (VLDL and LDL).[23] This assumption is even true in hypertriglyceridemic subjects.[24] This parameter is useful in random samples.[25,26] An additional advantage is that the LDL heterogeneity and the presence of small dense LDLs do not affect the risk estimation.[27] These data sustain the value of the apo B levels as marker for increased cardiovascular risk. Additional support for this conclusion is found in the lower apo B levels observed in the older male individuals in the population reported here. This trend suggests a survival effect; the ones who survived had lower apo B levels and those with higher levels could already be dead. This evidence is in accordance with the results from a prospective study,[9] in which apo B was one of the most useful predictors for cardiovascular mortality.

The introduction of suitable reference materials approved by the WHO and the IFCC has allowed comparability between methods and laboratories. However, the interpretation of the data may be difficult for the clinician, because limited information is available regarding the distribution of the apo concentrations worldwide (Table 6). The reference limits based on standardized assays have been published only in 4 nationwide populations. Those reports included subjects of ethnic groups distant from our population; the majority of them had cholesterol concentrations significantly higher than the levels reported in Mexican adults.[28] On the other hand, the prevalence of hypertriglyceridemia, low HDL cholesterol, mixed hyperlipidemias, and type 2 diabetes are remarkably higher in our population[17] compared with those reported in Caucasian groups. These characteristics make it unlikely that the reference limits used in Caucasian groups could be applied to the Mexican population. Our data clearly show that the Mexican urban adults have significantly lower apo B concentrations compared with US, Finnish, and Swedish groups.[13-16] The mean apo B level is 30 to 50 mg/dL lower compared with Swedish and US,

Table 6. Apo B and A-I Concentrations in Several Ethnic Groups

		Percentile		
	Mean ± SD	10	50	90
Apo B (mg/dL)				
Males				
Swedish	131 ± 35	89	127	181
Finnish	121 ± 32	79	120	159
Framingham Study	103 ± 24	74	103	133
USA	107 ± 25	74	106	138
Mexican	77 ± 25	50	75	108
Females				
Swedish	122 ± 36	80	117	170
Finnish	109 ± 32	71	105	155
Framingham Study	96 ± 24	67	93	130
USA	107 ± 25	71	99	140
Mexican	71 ± 22	47	67	98
Apo A-I (mg/dL)				
Males				
Swedish	136 ± 22	110	135	165
Finnish	138 ± 24	109	134	169
Framingham Study	134 ± 23	107	132	163
USA	136 ± 22	111	133	164
Mexican	122 ± 31	89	118	162
Females				
Swedish	151 ± 24	122	149	183
Finnish	158 ± 29	125	155	196
Framingham Study	154 ± 28	122	151	192
USA	154 ± 28	122	147	186
Mexican	129 ± 34	93	123	173

NOTE. The data from Framingham, Sweden, Finland, and USA (NHANES III) come from references 13-16, respectively.

respectively.[14,16] Also, the 90th percentile was 30 to 80 mg/dL lower compared with the same groups. These data included subjects with diabetes or high blood pressure, who frequently had higher apo B levels. After excluding cases with these disorders from the analysis, the conclusion remained unchanged; the 70th to 90th percentiles were even lower (≈ 2 mg/dL). Low apo B concentrations were also reported in Italians in a nonpopulation-based sample.[29] These data suggest that the variability in apo B levels is remarkable between ethnic groups, as it is clearly shown in Table 6. This characteristic makes it difficult to extrapolate reference ranges between populations. Multiple investigators have proposed explanations for these differences, and this matter is out of the context of this report.[30-31] Genetic and environmental factors explain the large differences observed between Mexican and Caucasian adults.[32-34]

The most frequently used upper limit of the apo B concentrations was derived from the Framingham study (120 mg/dL); this value identifies a very small number of individuals in our population, leaving undetected a large number of subjects with an abnormal lipid profile. This cut point was selected because it identifies a similar number of abnormal cases as the LDL cholesterol concentration of 160 mg/dL. Surprisingly, this cut point was useful in populations with significantly different apo B concentrations.[29] However, Bachorik et al[16] clearly showed that although the number identified was the same, no agreement exists between the 2 diagnostic criteria. In our population, the 90th percentile of apo B identifies the same number of abnormal cases as the LDL cholesterol level of 160 mg/dL. This cut point is close to 110 and 100 mg/dL in men and women, respectively, regardless of their age. The corresponding apo B level for LDL cholesterol of 130 mg/dL was in the 75th percentile. The clinical characteristics of the cases with an apo B concentration above either the 90th percentile or 120 mg/dL are those of a high cardiovascular risk. However, the 90th percentile identifies 110 dyslipidemic cases more than the 120 mg/dL cut point. These observations clearly demonstrate that the upper normal limit concentration of 120 mg/dL leaves undetected a large number of cases at risk for cardiovascular complications. Lowering the limit to the 90th percentile in this population seems correct, because this marker is more sensitive and still highly specific.

Hypertriglyceridemia could be caused by either atherogenic or nonatherogenic disorders. Several investigators have proposed that measurement of apo B in hypertriglyceridemic patients is a useful diagnostic tool to distinguish between these 2 groups.[35] A high apo B distinguishs a subset of hypertriglyceridemic patients with increased cardiovascular risk. According to Sniderman et al,[36] close to 30% of the patients with increased triglyceride concentrations had an apo B above the 90th percentile of the population. In this report, close to 20% of cases with fasting triglycerides above 200 mg/dL had an apo B above the 90th percentile. Significant differences in the clinical characteristics were found between the hypertriglyceridemic patients with or without increased apo B concentrations. Those with high apo B had significantly higher cholesterol, non-HDL cholesterol, triglycerides, and lower HDL cholesterol concentrations compared with their peers with "normal" apo B concentrations. The former group had a similar cardiovascular risk profile than the mixed hyperlipidemia cases, a subset of patients with an increased cardiovascular risk.[37] A total of 79% of the high triglycerides/high apo B group had a mixed hyperlipidemia, suggesting that cholesterol above 200 mg/dL may also be a useful substitute for apo B for detecting subjects at risk among the hypertriglyceridemic patients. These cases had the worst profile of all the groups shown in Table 4. However, the agreement between abnormal cholesterol and apo B was poor in the mixed hyperlipidemic group; 68% of the mixed hyperlipidemic cases had a "normal" apo B concentration. The risk profile of the high triglycerides/high cholesterol/normal apo B subjects was remarkably worse than the normolipidemic subjects with normal apo B. Similar abnormalities were found in cases with high triglycerides/high apo B/normal cholesterol. These data suggest that the apo B and cholesterol concentrations give complementary information for assessing the cardiovascular risk of a hypertriglyceridemic patient. The analysis of prospective data is required for confirming these observations.

The measurement of apo B allows the identification of other sets of individuals with increased cardiovascular risk. Cases with a normal lipid profile with an increased apo B concentration (condition called hyperapobetalipoproteinemia) had at least 2 times the prevalence of coronary events compared with the reference group reported in the Quebec Study.[9] One percent of our population had this lipid profile (apo B above the 90th percentile). Those cases were older, heavier, and had higher lipid concentrations compared with the normolipidemic cases

with normal apo B concentrations. The increased atherogenicity of the hyperapobetalipoproteinemia is due to the increased number of atherogenic particles found in these cases.[38] The smaller and denser LDL particles are the predominant subclass among the LDLs in this condition.[39] This characteristic explains the normal lipid concentrations based on the low cholesterol concentration/particle of these LDLs.[40]

The apo A-I concentrations were lower in the population reported here compared with previous reports. As shown in Tables 2 and 6, lower apo A-I levels were found in both men (≈ 15 mg/dL) and women (≈ 20 mg/dL) compared with those in the US and Finland. The most frequently used lower limit of the apo A-I concentrations was derived from the Framingham study (120 mg/dL).[41] This cut point was selected because it identifies a similar number of abnormal cases as the HDL cholesterol concentration less than 35 mg/dL. In our population, this criterion had a low specificity (60.6%); by its use, 237 more cases were classified at risk than the number of subjects with HDL cholesterol below 35 mg/dL. In the population reported here, none of the apo A-I concentrations had good agreement with the concentrations of HDL cholesterol below 35 mg/dL. The same phenomenon has been reported in other populations.[16] The 25th percentile had an acceptable specificity (84%), but a low sensitivity (40%); this criterion identifies 143 less patients than the HDL cholesterol less than 35 mg/dL. These observations clearly demonstrate that the lower normal limit concentration of 120 mg/dL is not useful in Mexican urban adults. Since it is not clear that measurement of apo A-I is superior to HDL cholesterol as a measure of atherogenic risk,[18] it may not be useful to substitute or even complement the information provided by the HDL cholesterol with the >apo A-I assay.[8]

In conclusion, our data show that the apo B and apo A-I concentrations in Mexican urban adults are lower compared with the levels reported in other ethnic groups. Previously used reference ranges are not useful in the population reported here. Lowering the limit to the 90th percentile in this population seems correct, because this marker is more sensitive and still highly specific for detecting patients with an abnormal lipid profile and increased cardiovascular risk. Our observations also show that increased apo B levels give valuable information for assessing the risk profile in hypertriglyceridemic patients. These data strengthen the need for obtaining data in population-based studies worldwide. Further studies are needed to evaluate prospectively the usefulness of the apo B values not only as a predictor for cardiovascular mortality in several ethnic groups; it could also be used as an efficacy parameter during hypolipidemic therapy. The diagnostic profile of apo B for detecting an increased cardiovascular risk shown in this and other studies makes this parameter a simple and logical choice for extending its use as an intermediate goal for the preventive efforts to reduce the likelihood of suffering a coronary event.

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