# Lipid profile reference intervals in individuals from Maracaibo, Venezuela: an insight from the Maracaibo City Metabolic Syndrome prevalence study

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## Abstract

**Objectives**: Cardiovascular diseases are the main cause of death in adults worldwide. Dyslipidemias are an important risk factor, which is why committees like the ATP III have established cut-off points for lipid profiles dichotomizing the diagnosis instead of setting normal intervals. Currently, there is no general consensus about the reference intervals in our population, so the purpose of this paper is to establish lipid profile reference ranges in Maracaibo City, Venezuela.

**Materials and Methods:** A cross-sectional study was made, enrolling 2,043 randomly selected individuals from both genders over 18 years old, for the Maracaibo City Metabolic Syndrome Prevalence Study (MMSPS). To determine the reference population, the patients with pathologic history and medication intake that could modify the lipid profile were taken out. Extreme values were calculated mathematically for each lipid variable and then excluded. The results were expressed in absolute and relative frequencies, medians and 25th-75th percentiles for the general and gender classified population.

**Results**: The medians and percentiles for the reference population (n=434) were indicated respectively for women (n=221; 50.9%) and men (n=213; 49.1%). For HDL-C (mg/dL): 48.00 (42.00-56.00) and 43.00 (37.00-50.00); Triglycerides (mg/dL): 70.98 (50.35-102.53) and 78.50 (57.00-126.63); VLDL-C (mg/dL): 14.20 (10.07-20.48) and 15.70 (11.40-25.33). Were raised general reference values for Total Cholesterol (mg/dL): 176.00 (149.50-201.50); LDL-C (mg/dL): 110.23 (86.25-132.80) and Lp(a) (mg/dL): 25.20 (18.40-33.85).

**Key Words**: Reference Intervals, Lipid Profile, Cardiovascular Disease, Dyslipidemia.

## Introducción

Cardiovascular diseases are the primary cause of death worldwide[1], and Venezuela is no exception to this reality as this pathology stands as the first of the 25 leading causes of death in both men and woman and among individuals 65 -74 years in the country[2]. However, the fact that a high proportion of vulnerableindividuals areyoung adults helps to understand the importance of defining the population at risk of suffering from cardiovascular disease in a timely manner[3].

Dyslipidemia constitutes thefundamental factor for atherogenesisand is considered one of the most important cardiovascular risk factors[4-6], beingdirectly related to modifiable factors such as diet or lifestyle habits, as well as non-modifiable factors from each individual like genetic predisposition[7-9]. For this reason, various committees including the Adult Treatment Panel III (ATP III) have defined and established reference values for plasma lipids[8] in order to reduce the risk of developing cardiovascular disease[10]. Taking into accountthatlifestyle, genetics, and environmental conditions vary in each population, countries such as China, Spain and Turkey have conducted studies to determine their own cut-off values[11-13] for objectively establishing abnormal lipid profiles that could be considereda cardiovascular risk for their population.Given these variations in lipid determination and the diversity of factors that influence the behavior of dyslipidemia in each population, it is necessary to determine lipid profile reference intervals in order to amplify the spectrum of evaluation that provides the dichotomization of a specific diag-

nosis. Proposals such as this have also been designed in countries like India, Mexico and Colombia[14-19].

Therefore, taking into consideration that mortality rate fromcardiovascular events in the Zulia population is among the highest in Venezuela, the lack of epidemiological analyzing resident lipid behavior, and whether or not the valuesassigned by the ATP III committee are useful to assess the risk in the local population, it´sof extreme importance to evaluate the presence of dyslipidemia in the Maracaibo Municipality, Zulia State, and determine new and appropriate local reference intervals for plasma lipids.

**Ethical considerations**

Individuals were included in the study after signing awritten consent form prior to obtaining a history and physical examination. The study design was approved by the Ethics Committee of The Metabolic and Endocrine Diseases Research Center "Dr. Félix Gómez".

**Selection of Individuals**

The sample method was already published in the MMSPS cross-sectional proposal (20), yet the main features will be mentioned. Using population estimations for the population of Maracaibo (1,428,043 for 2007 according to the National Institute of Statistics), the sample size estimate was calculated to be 1,986 individuals with or above 18 years of age. Moreover, taking into account that in a previous pilot study approximately 10% of the subjects rejected being part of the study (unpublished data), an oversampling number was calculated (200 individuals); the overall number of individuals was 2,230 (with 244 subjects– 12.0% – added because of the oversampling method) were randomly selected between July 2008 and July 2011[20]. The only inclusion criterion was to have ≥18 years of age. Thecity of Maracaibo isdividedintoparishes and each of thesewasproportionallysampled: Antonio Borjas Romero, Bolívar, Cacique Mara, Caracciolo Parra Pérez, Cecilio Acosta, Cristo de Aranza, Coquivacoa, Chiquinquirá, Francisco Eugenio Bustamante, Idelfonso Vásquez, Juana de Ávila, Luis Hurtado Higuera, Manuel Dagnino, Olegario Villalobos, Raúl Leoni, Santa Lucía, San Isidro, and Venancio Pulgar. The sampling process was undertaken using a 2-phase method: During the first phase, the sorting was random and stratified —where each stratus was represented by sectors from each of the 18 parishes— choosing 4 from each parish. The second sampling was stratified to represent a city block, in which they were selected using a random number generation tool. Once the houses were selected, every adult in the family unit from the selected city blocks was invited to participate in the study and were interviewed on prior written consent, and subjected to a routine medical examination using the clinical chart provided by the Health and Social Development Ministry of Venezuela as data collecting tool. The sample used in this research was of 2,043 individuals that gathered all the required biochemical parameters for the study.

**Anthropometric assessment**

Body Mass Index (BMI): Weight was determined using a digital scale (Tanita, TBF-310 Body Composition Analyzer GS, Tokyo - Japan), while height was obtained using a vertical strip calibrated in centimeters and millimeters. The patients were barefooted and in light clothing at the time of the measurements. BMI was calculated by the mathematical formula: Weight (kg) / Height$^2$ (m$^2$).

**Laboratory tests**

Prior 8 to 12 hours of fasting, 5 cm$^3$ of blood was extracted from each individual by venipuncture of the antecubitalvein, being placed afterwards in test tubes and centrifuged at 4000 rpm for 10 minutes; serum was extracted and placed in polypropylene test tubes for subsequent freezing at -70 ° C. The time between sample collection and processing did not exceed three months.Total Cholesterol was estimated by enzymatic colorimetric methods (Wiener Lab SAIC). Triglycerides (TAG) and High Density Lipoprotein (HDL-C) were evaluated using an enzyme-colorimetric commercial kit (Human GesellschoftBiochemica and DiagnosticaMBH) following the manufacturer instruction.Low Density Lipoprotein (LDL-C) was estimated using the Friedewald formula[21] in subjects with triglycerides below 400 mg/dl[15]. Those who obtained TAG> 400 mg/dl, underwent measurement of their concentration by electrophoresis techniques. Very Low Density Lipoproteinwas calculated indirectly from the mathematical expression [TAG/5].Lipoprotein (a) [Lp (a)] was estimated through the latex turbidimetricmethod ,HumanGesellschaftfürBiochemica und DiagnosticambH, Germany. In this method, the presence of Lp(a) in the sample causes agglutination of latex particles coated with antibodies against Lp(a). The agglutination is proportional to the Lp(a) concentration in the sample and can be measured by turbidimetry (22).For glucose determination a colorimetric enzymatic glucose oxidase kit (Sigma, USA) was used, using both standard and 0.02 ml of sample, then adding 2 ml of the enzyme reagent. Incubated for 10 minutes at 20-25 °C or 5 minutes at 37 °C, then absorption was measured at 500nm against a target reagent.Basal Insulin plasma levels were quantified through the international DRG insulin kit. Inc. USA. New Jersey. A solid phase immunoassay of two sites that uses two monoclonal antibodies directed to two antigenic determinants on different sites in the insulin molecule which are detected by reaction with 3,3', 5,5'-tetramethylbenzidine and the addition of an acid to stop the reaction and provide a colorimetric endpoint read by spectrophotomer. Detection limit <1 mU/l.Calculation of insulin resistance was conducted applying the HOMA-Calculator, Homa-IR2, which is an update and adaptation by Jonathan Levy et al.[23].

### Exclusion Criteria

For the determination of reference intervals in biological variables such as lipid profile is necessary to establish a reference population[25-28], for which exclusion criteria listed in Table 1 was used.

**Table 1: Exclusion criteria based on clinical history and laboratory tests to define the reference individuals.**

| Exclusion Criteria | |
|---|---|
| Obesity as BMI (≥30 kg/m²) | Personal history of Hypertension |
| Glycemia ≥ 126 md/dL | Personal history of Diabetes Mellitus |
| HOMA-IR ≥ 2 | Personal history of Thyroid and/or Hepatic disease |
| Acanthosis Nigricans | Personal history of Polycystic Ovary Syndrome |
| Alcohol Consumption | Personal history of Acute Myocardial Infarction |
| Consumption of medications that modify lipid profile and/or Alcohol | Personal history of Angina. Arrythmia and/or Cerebrovascular disease |

### Calculation of Extreme Values

Once the reference population was established, we proceeded to calculate the extreme values for each lipid variable to avoid any bias that might have an influence on the reference intervals distribution[24,29,30]. This was performed using the mathematical expression:

$$[\text{Upper limit: } Q_3 + 1{,}5\ (Q_3\text{-}Q_1)]$$
$$[\text{Lower limit: } Q_1 - 1{,}5\ (Q_3\text{-}Q_1)]$$

Where:

$Q_1$ = firstquartile (25th percentile)

$Q_3$ = thirdquartile (75th percentile)

Therefore any result above the upper limit or below the lower limit, is an extreme value[30] and was removed from the study[24,29].

### Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences for Windows, version 19.0 (SPSS Inc.) and the R-project program, version 2.11.0. The qualitative variables (Gender and Age group) were expressed as absolute and relative frequencies. The quantitative variables: Total Cholesterol, Triglycerides, VLDL-C, LDL-C, HDL-C and Lp(a), were tested by goodness of fit (normality and homoscedasticity). To check the normality of the variables the Geary test was used. We applied the Levene test to evaluate the homoscedasticity. For those who showed a normal distribution results were expressed as mean ± SD (standard deviation) with their respective confidence intervals at 95% (CI 95%). The differences between these were established using the Student's Ttest or one-way ANOVA with the Tukey post-hoc test depending on the case, considering p <0.05 as statistically significant. The results ofabnormally distributed variables were expressed as medians and percentiles p2, 5, p5, p10, p25, p50, p75, p90, p95, p97, 5. After statistical processing of the variables, the reference values for the lipid profile were determined using p25 as lower value and p75 as upper value. The differences between these were calculated using the Mann-Whitney U test or ANOVA with Bonferroni correction when indicated.

## Results

### General Characteristics of the Population

The Maracaibo City Metabolic Syndrome Prevalence Study (MMSPS) has an overall sample of 2,043 individuals of both genders, male: n=952 (46.6%), female: n=1,091 (53.4%). The mean population age was 39.78 ± 15.45 (CI 95%: 39.78 to 40.45) years. By stratifying the age variable there was a predominance of the age group 20-29 years with 24.6% (Table 2), the group of 40 to 49, 21.1%; the group of 30 to 39 years with 17.7%, so it was observed that about 63.4% of the population was aged between 20 and 49 years. The population behavior for each of the lipid profile variables by gender are shown in Table 3.

**Table 2: Distribution of general population by age group and gender. Maracaibo Municipality, Zulia State, 2011**

| Age Group (Years) | Female | | Male | | Total | |
|---|---|---|---|---|---|---|
| | n | ( % ) | n | ( % ) | n | ( % ) |
| 18 – 19 | 96 | (8.8%) | 71 | (7.5%) | 167 | (8.2%) |
| 20 – 29 | 233 | (21.4%) | 270 | (28.4%) | 503 | (24.6%) |
| 30 – 39 | 183 | (16.8%) | 178 | (18.7%) | 361 | (17.7%) |
| 40 – 49 | 247 | (22.6%) | 184 | (19.3%) | 431 | (21.1%) |
| 50 – 59 | 189 | (17.3%) | 160 | (16.8%) | 349 | (17.1%) |
| ≥ 60 | 143 | (13.1%) | 89 | (9.3%) | 232 | (11.4%) |
| Total | 1091 | (100%) | 952 | (100%) | 2043 | (100%) |

**Table 3: Percentiles and measures of central tendency and dispersion of the lipid profile in the general population of the Maracaibo Municipality, Zulia State, 2011.**

| Lipid Profile (mg/dL) | Gender | | | Percentiles | | |
|---|---|---|---|---|---|---|
| | | Mean | SD | P25 | P50 | P75 |
| HDL-C | Female | 47.07 | 11.89 | 39.00 | 46.00 | 54.00 |
| | Male | 41.07 | 11.58 | 34.00 | 39.00 | 46.00 |
| | Total | 44.27 | 12.12 | 36.00 | 43.00 | 51.00 |
| TAG | Female | 116.90 | 85.30 | 64.00 | 96.00 | 143.00 |
| | Male | 146.08 | 117.37 | 76.00 | 117.00 | 174.00 |
| | Total | 130.50 | 102.53 | 68.82 | 105.00 | 159.40 |
| VLDL | Female | 23.38 | 17.06 | 12.80 | 19.20 | 28.60 |
| | Male | 29.22 | 23.47 | 15.20 | 23.40 | 34.80 |
| | Total | 26.10 | 20.50 | 13.76 | 21.00 | 31.88 |
| Total Cholesterol | Female | 194.25 | 44.67 | 162.00 | 190.00 | 220.00 |
| | Male | 189.33 | 47.36 | 159.00 | 184.00 | 214.00 |
| | Total | 191.96 | 46.00 | 161.00 | 187.00 | 217.00 |
| LDL | Female | 123.85 | 38.11 | 96.58 | 120.94 | 146.15 |
| | Male | 120.03 | 38.65 | 93.40 | 116.80 | 144.00 |
| | Total | 122.10 | 38.40 | 95.45 | 119.27 | 145.66 |
| Lp(a) | Female | 28.54 | 14.07 | 19.60 | 26.60 | 35.70 |
| | Male | 27.33 | 14.11 | 18.20 | 25.25 | 35.40 |
| | Total | 28.01 | 14.10 | 19.05 | 26.10 | 35.60 |

*SD: Standard deviation*

After applying the exclusion criteria, a population consisting of 434 healthy individuals, of whom 50.9% (n=221) were female and 49.1% (n= 213) were male was obtained. The meanaverage age of this group was 33.26 ± 14.10 years (CI 95% 31.93 to 34.59 years).In order to evaluate the lipid profile in the reference population, extreme values were calculated to exclude them from the analysis, obtaining reference samples for each lipid variable (Table 4). Based on these reference samples, results obtained from analysis of each lipid profile variable are expressed in Table 5.

**Table 4: Reference samples for lipid profile study grouped by gender and age group. Maracaibo Municipality, Zulia State, 2011.**

| Lipid Profile (mg/dL) | Gender | Age group (Years) 18-19 n (%) | 20-29 n (%) | 30-39 n (%) | 40-49 n (%) | 50-59 n (%) | ≥ 60 n (%) | Total n (%) |
|---|---|---|---|---|---|---|---|---|
| HDL-C | Female | 35 (16.3%) | 66 (30.7%) | 45 (20.9%) | 43 (20.0%) | 16 (7.4%) | 10 (4.7%) | 215 (100%) |
| | Male | 33 (15.9%) | 82 (39.6%) | 38 (18.4%) | 15 (7.2%) | 23 (11.1%) | 16 (7.7%) | 207 (100%) |
| | Total | 68 (16.1%) | 148 (35.1%) | 83 (19.7%) | 58 (13.7%) | 39 (9.2%) | 26 (6.2%) | 422 (100%) |
| Triglycerides VLDL-C | Female | 34 (16.0%) | 63 (29.7%) | 46 (21.7%) | 43 (20.3%) | 17 (8.0&) | 9 (4.2%) | 212 (100%) |
| | Male | 32 (15.8%) | 84 (41.6%) | 38 (18.8%) | 15 (7.4%) | 18 (8.9%) | 15 (7.4%) | 202 (100%) |
| | Total | 68 (15.9%) | 147 (35.5%) | 84 (20.3%) | 58 (14.0%) | 35 (8.5%) | 24 (5.8%) | 414 (100%) |
| LDL-C | Female | 36 (17.1%) | 63 (29.9%) | 46 (21.8%) | 43 (20.4%) | 14 (6.6%) | 9 (4.3%) | 211 (100%) |
| | Male | 33 (15.6%) | 85 (40.3%) | 37 (17.9%) | 17 (8.1%) | 23 (10.9%) | 16 (7.6%) | 211 (100%) |
| | Total | 69 (16.4%) | 148 (36.1%) | 83 (19.7%) | 60 (14.2%) | 37 (8.8%) | 25 (5.9%) | 422 (100%) |
| Total Cholesterol | Female | 36 (16.7%) | 65 (30.2%) | 46 (21.4%) | 43 (20.0%) | 15 (7.0%) | 10 (4.7%) | 215 (100%) |
| | Male | 33 (15.7%) | 85 (40.5%) | 37 (17.6%) | 17 (8.1%) | 22 (10.5%) | 16 (7.6%) | 210 (100%) |
| | Total | 69 (16.2%) | 150 (35.3%) | 83 (19.5%) | 60 (14.1%) | 37 (8.7%) | 26 (6.1%) | 425 (100%) |
| Lp (a) | Female | 28 (15.6%) | 53 (29.4%) | 40 (22.2%) | 38 (21.1%) | 13 (7.2%) | 8 (4.4%) | 180 (100%) |
| | Male | 29 (19.5%) | 52 (34.9%) | 23 (15.4%) | 13 (8.7%) | 16 (10.7%) | 16 (10.7%) | 149 (100%) |
| | Total | 57 (17.3%) | 105 (31.9%) | 63 (19.1%) | 51 (15.5%) | 29 (8.8%) | 24 (7.3%) | 329 (100%) |

**Table 5: Lipid profile percentiles in the reference sample distributed by gender. Maracaibo Municipality, Zulia State, 2011.**

| | Female | | | | | | Male | | | | | | Total | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Percentiles | Total Cholesterol (mg/dL) | TAG (mg/dL) | VLDL-C (mg/dL) | LDL-C (mg/dL) | HDL-C (mg/dL) | Lp(a) (mg/dL) | Total Cholesterol (mg/dL) | TAG (mg/dL) | VLDL-C (mg/dL) | LDL-C (mg/dL) | HDL-C (mg/dL) | Lp(a) (mg/dL) | Total Cholesterol (mg/dL) | TAG (mg/dL) | VLDL-C (mg/dL) | LDL-C (mg/dL) | HDL-C (mg/dL) | Lp(a) (mg/dL) |
| p2.5 | 121.40 | 31.00 | 6.20 | 56.6 | 30.40 | 2.70 | 107.55 | 33.00 | 6.6 | 45.16 | 30.00 | 1.66 | 114.95 | 31.38 | 6.28 | 53.64 | 30.00 | 2.06 |
| p5 | 126.80 | 34.47 | 6.89 | 62.72 | 33.80 | 8.80 | 117.55 | 38.15 | 7.63 | 57.44 | 31.00 | 3.39 | 122.30 | 36.00 | 7.20 | 61.66 | 32.00 | 6.18 |
| p10 | 133.60 | 40.30 | 6.06 | 71.64 | 36.00 | 12.71 | 127.10 | 45.16 | 9.03 | 68.68 | 33.00 | 9.80 | 130.60 | 42.00 | 8.40 | 70.40 | 35.00 | 12.60 |
| p25 | 151.00 | 50.35 | 10.07 | 87.20 | 42.00 | 18.63 | 147.00 | 57.00 | 11.40 | 85.60 | 37.00 | 18.25 | 149.50 | 53.75 | 10.75 | 86.25 | 39.00 | 18.40 |
| p50 | 176.00 | 70.98 | 14.20 | 109.60 | 48.00 | 25.35 | 175.00 | 78.50 | 15.70 | 110.80 | 43.00 | 24.90 | 176.00 | 74.69 | 14.94 | 110.23 | 45.00 | 25.20 |
| p75 | 202.00 | 102.53 | 20.48 | 130.20 | 56.00 | 34.30 | 200.25 | 126.63 | 25.33 | 134.60 | 50.00 | 33.65 | 201.50 | 109.93 | 21.99 | 132.80 | 53.00 | 33.85 |
| p90 | 231.40 | 133.16 | 26.63 | 150.85 | 63.40 | 40.67 | 234.60 | 173.70 | 34.74 | 159.52 | 61.00 | 41.80 | 231.40 | 154.90 | 30.98 | 157.54 | 62.00 | 41.10 |
| p95 | 248.40 | 154.37 | 30.87 | 162.20 | 70.20 | 46.56 | 251.90 | 199.00 | 39.80 | 178.72 | 67.20 | 48.65 | 249.70 | 181.00 | 36.20 | 173.01 | 68.00 | 46.85 |
| p97.5 | 271.00 | 170.75 | 34.15 | 176.14 | 75.60 | 50.84 | 269.73 | 207.93 | 41.59 | 195.82 | 76.40 | 51.93 | 270.00 | 199.00 | 39.80 | 185.41 | 75.43 | 50.98 |

**HDL-C**

The reference sample for the calculation of HDL-C was 422 individuals (Table 4) with anaverage age of 33.18 ± 14.15 years (CI 95% 31.83 to 34.53 years).In the overall sample a median of 45.00 (39.00 to 53.00) mg/dL was obtained. When divided by gender it showed that female individuals

had a median of 48.00 (42.00 to 56.00) mg/dL, while men obtained a value of 42.00 (37.00 to 50.00) mg/dL. In the analysis of both groups statistically significant differences were appreciated ($p=1.437x10^{-6}$); (Figure 1, panel A). The median concentrations of HDL-C obtained by gathering age groupby gender are given in Table 6 where statistically significant differences between men and women in age groups between 18-19; 30-39; 40-49and in the 60 and over group are shown (Figure 3). No statistically significant differences were observed in different age groups when studying HDL-C concentrations by gender while gathering them by age group.

**Figure 1: Comparison of median values of HDL-C, VLDL-C and Lp(a) in a reference sample by gender. Maracaibo Municipality, Zulia State, 2011.**

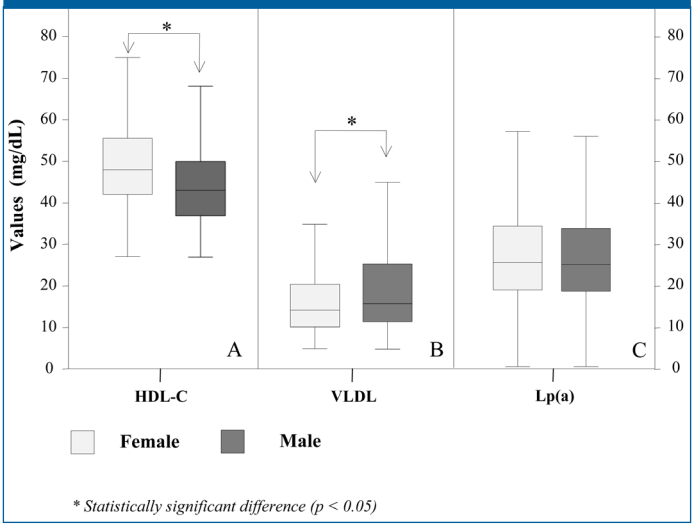



**Figure 3: Comparison of medians of concentration of HDL-C in a reference sample by age group. Maracaibo Municipality, Zulia State, 2011.**

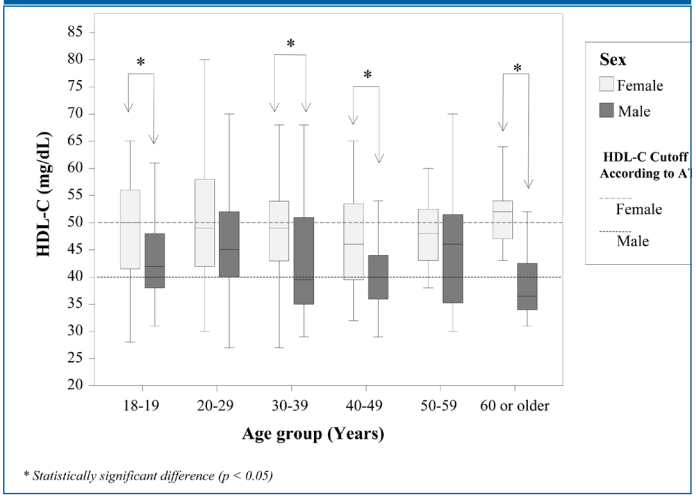



**Table 6: Comparison of reference intervals of Lipid profile distributed by gender and age group. Maracaibo Municipality, Zulia State, 2011.**

| Age Group (Years) | | HDL-C (mg/dL) | | | TAG (mg/dL) | | | VLDL-C (mg/dL) | | | Total Cholesterol (mg/dL) | | | LDL-C (mg/dL) | | | Lp(a) (mg/dL) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | P25 | P50 | P75 | P25 | P50 | P75 | P25 | P50 | P75 | P25 | P50 | P75 | P25 | P50 | P75 | P25 | P50 | P75 |
| 18 – 19 | Female | 41.00 | 50.00 | 56.00 | 44.57 | 58.50 | 93.00 | 8.91 | 11.70 | 18.60 | 143.00 | 156.50 | 176.00 | 79.35 | 92.18 | 108.57 | 13.07 | 21.87 | 34.62 |
| | Male | 38.00 | 42.00 | 48.00 | 44.25 | 68.00 | 100.33 | 8.85 | 13.60 | 20.06 | 124.00 | 146.00 | 166.00 | 70.90 | 85.00 | 106.82 | 11.70 | 18.30 | 26.15 |
| | *P* [a] | | *0.033** | | | *0.534* | | | *0.534* | | | *0.036** | | | *0.175* | | | *0.196* | |
| 20 – 29 | Female | 41.75 | 49.00 | 58.25 | 49.00 | 65.00 | 82.00 | 9.80 | 13.00 | 16.40 | 136.00 | 167.00 | 189.00 | 77.40 | 100.50 | 120.40 | 18.10 | 22.80 | 31.90 |
| | Male | 40.00 | 45.00 | 52.00 | 51.00 | 67.01 | 106.75 | 10.20 | 13.40 | 21.35 | 144.50 | 172.00 | 193.00 | 79.70 | 107.60 | 126.50 | 18.40 | 23.95 | 32.72 |
| | *P* [a] | | *0.103* | | | *0.142* | | | *0.142* | | | *0.420* | | | *0.170* | | | *0.980* | |
| 30 – 39 | Female | 43.00 | 49.00 | 54.00 | 47.00 | 64.00 | 102.17 | 9.40 | 12.80 | 20.42 | 149.75 | 171.50 | 206.25 | 91.82 | 111.00 | 134.99 | 20.52 | 26.10 | 30.92 |
| | Male | 35.00 | 39.50 | 51.00 | 75.25 | 114.50 | 168.50 | 15.05 | 22.90 | 33.70 | 162.50 | 187.00 | 210.50 | 98.00 | 120.20 | 147.30 | 19.70 | 24.80 | 31.70 |
| | *P* [a] | | *0.006** | | | *$6.59x10^{-5}$** | | | *$6.59x10^{-5}$** | | | *0.146* | | | *0.223* | | | *0.836* | |
| 40 – 49 | Female | 39.00 | 46.00 | 54.00 | 55.00 | 82.09 | 115.00 | 11.00 | 16.41 | 23.00 | 167.00 | 189.00 | 207.00 | 105.00 | 124.80 | 140.20 | 20.25 | 28.30 | 36.00 |
| | Male | 35.00 | 40.00 | 44.00 | 63.83 | 76.00 | 119.40 | 12.76 | 15.20 | 23.88 | 147.00 | 192.00 | 205.00 | 80.80 | 124.80 | 136.70 | 25.55 | 34.00 | 37.00 |
| | *P* [a] | | *0.028** | | | *0.852* | | | *0.852* | | | *0.571* | | | *0.486* | | | *0.331* | |
| 50 – 59 | Female | 42.00 | 48.00 | 52.75 | 71.44 | 90.00 | 138.00 | 14.28 | 18.00 | 27.60 | 186.00 | 226.00 | 264.00 | 122.15 | 151.21 | 173.15 | 21.05 | 27.60 | 38.15 |
| | Male | 35.00 | 46.00 | 54.00 | 73.50 | 105.00 | 148.67 | 14.67 | 21.00 | 29.73 | 168.00 | 211.50 | 236.25 | 104.20 | 145.74 | 173.40 | 19.75 | 28.90 | 39.80 |
| | *P* [a] | | *0.288* | | | *0.613* | | | *0.613* | | | *0.152* | | | *0.344* | | | *0.714* | |
| ≥ 60 | Female | 46.00 | 52.00 | 55.00 | 72.35 | 102.00 | 164.00 | 14.47 | 20.40 | 32.80 | 179.15 | 207.00 | 265.50 | 114.23 | 130.20 | 155.19 | 24.56 | 31.00 | 39.25 |
| | Male | 33.50 | 36.50 | 43.75 | 69.00 | 88.00 | 159.00 | 13.80 | 17.60 | 31.80 | 177.25 | 193.00 | 231.50 | 119.70 | 132.20 | 159.45 | 22.52 | 32.30 | 40.77 |
| | *P* [a] | | *0.001** | | | *0.682* | | | *0.682* | | | *0.363* | | | *0.487* | | | *0.881* | |

F = Female; M = Male

a U de Mann – Whitney

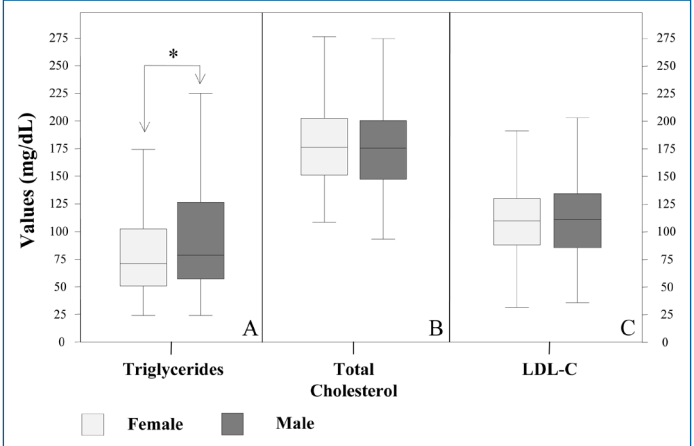
* Statistically significant difference ($p < 0.05$)

## Triglycerides

The reference sample for the calculation of TAG was 414 individuals (Table 4), showing a mean age of 32.90 ± 13.90 (CI 95% 31.56 to 34.24) years.In the study of the general reference sample a median of 74.69 (53.75 to 109.93) mg/dL was gained, with a median of 79.22 (50.35 to 102.53) mg/dL in females and 94.67 (57.00 to 126.63) mg/dL in males, observing statistically significant differences (p=0.004) between both individuals. The percentiles of this variable are shown in Table 5, and the results

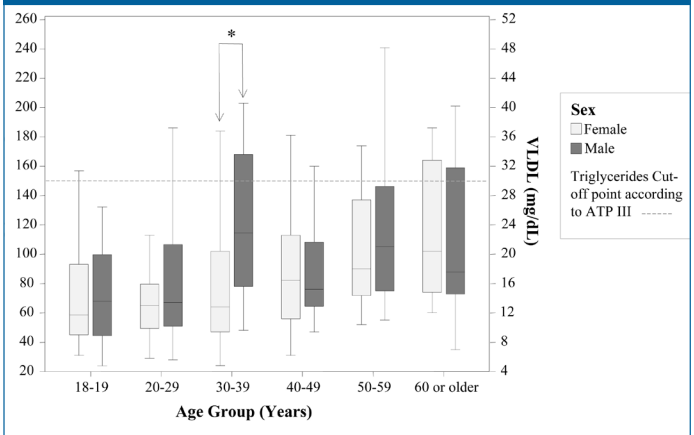
of the comparisons are seen in Figure 2, panel A.When stratifying both individuals by age group to compare concentrations of triglycerides among them, significant differences in the group of 30 to 39 years were appreciated (Table 6 and Figure 4).By studying the behavior of TAG in the different age groups by gender, significant differences were observed in female individuals between groups 18-19 years and 20-29 years with the group 60 years or older (p=0.006 and p=0.002 respectively). In males, these differences were observed between the group 18-19 years with the 30-39 years group (p=0.003).

**Figure 2: Comparison of median values of Triglycerides, Total Cholesterol and LDL-C in a sample reference by gender. Maracaibo Municipality, Zulia State, 2011.**




** Statistically significant difference (p < 0.05)*

**Figure 4: Comparison of TAG and VLDL median concentrations in a reference sample by age group. Maracaibo Municipality, Zulia State, 2011.**




** Statistically significant difference (p < 0.05)*

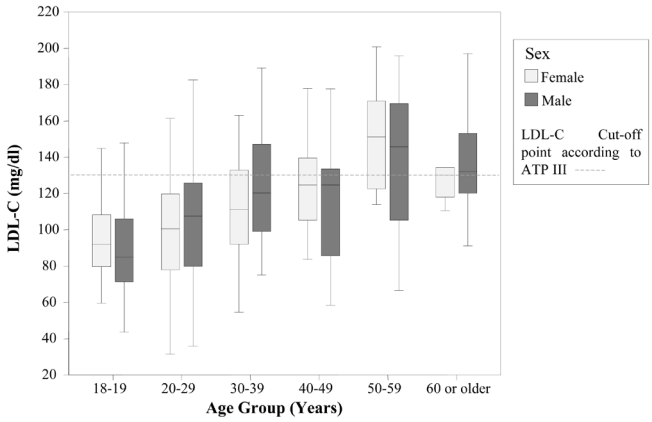
## VLDL-C

For the VLDL-C study of a total of 414 individuals of both genderswere the reference sample (Table 4) with a mean age of 32.90 ± 13.90 years (CI 95% 31.56 to 34.24 years). Inthe general reference sample a median of 14.92 (10.75 to 21.98) mg/dL was obtained. When divided by gender, female individuals obtained a median of 14.19 (10.07 to 20.48) mg/dL while in the male group a median of 15.70 (11.40 to 25.33) mg/dL was obtained, with a statistically significant difference p=0.004 (Figure 1, panel B). Percentiles for the VLDL-C concentration are given in Table 5.By stratifying according to gender and age group statistical results obtained from the VLDL concentrations analysis were the same as for the variable of triglycerides (Table 6 and Figure 4) due to the direct relationship between both lipid variables.

## LDL-C

A reference sample of 422 individuals with a mean age of 33.00 ± 14.00 years (CI 95% 31.66 to 34.34 years) was used to calculate LDL concentrations(Table 4). The overall reference sample median was 110.20 (86.25 to 132.80) mg/dL.The value of the median in the female group was 109.60 (87.20 to 130.20) mg/dL;for the male group a median of 110.80 (85.60 to 134.60) mg/dL was obtained. No significant statistical difference was observed between both groups (p=0.673) (Figure 2, panel C). Similarly, the percentiles to determine the reference intervals for this variable by gender are expressed in Table 5.LDL-C concentration median grouped by gender and age groupwas obtained and shown in Table 6.No significant statistical differences were observed. The distribution of this lipid variable according to age group and gender is shown in Figure 5.When grouped by gender and age group,medians of LDL-C concentrations expressed in Table 6 were obtained, were no statistical significant differences were observedaccording to gender for each age group. The distribution of this lipid variable according to age group and gender is shown in Figure 5. Table 7exhibitsp values, according to different age groups for each gender.

**Figure 5: Comparison of LDL-C medians of concentration in a reference sample by age groups. Maracaibo Municipality, Zulia State, 2011.**




** Statistically significant difference (p < 0.05)*

## Total cholesterol

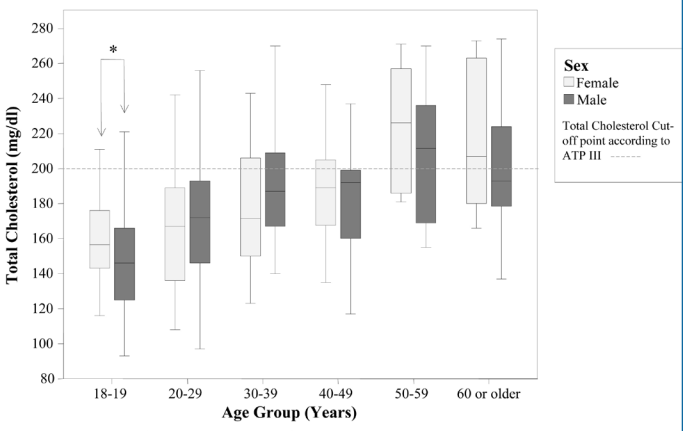
The reference sample for calculation of Total Cholesterol was 421 individuals (Table 4) with a mean age of 33.06 ± 14.08 years (CI 95% 31.71 to 34.40 years). In the overall sample a median of 176.00 (149.50 to 201.50) mg/dL was obtained. Grouped according to gender, female individuals had a median of 176.00 (151.00 to 202.00) mg/dL while men showed a median of 175,00 (147.00-200.25) mg/dL.

We found no significant differences in the analysis of both entities (p=0.721) (Figure 2, panel B). Reference intervals for total cholesterol according to gender are presented in Table 5.After classifying individuals according to gender and grouped by age, significant differences were observed only in the youngest group, 18-19 years, with p=0.036 (Figure 6).Table 8 shows p values, according to the different age groups for each gender.While analyzing each gender separately, statistically significant differences were observed between age groups located in extreme ages. In the case of females, differences were found between the age group 18 to 19 years with all groups over 40 years. As for the behavior between groups of 20 -29 years and 30-39 years a difference was shown with other groups starting from the age of 50 (Figure 6).When evaluating male individuals significant differences were observed between the younger group (18-19 years) with all individuals in each subsequent age group. In addition, individuals belonging to the 20-29 years group had more differencewith other groups starting from 50 years of age. The p values when comparing different age groups belonging to each gender are shown in Table 8, panel A and B.

### Lipoprotein(a)

To calculate the concentrations of Lp(a), a reference sample of 329 individuals was used (Table 4) with a mean age of 33.81 ± 59 years (CI 95% 32.23 to 35.39).The overall reference sample median was 25.20 (18.40 to 33.85) mg/Dl; with a median of 25.35 (18.16 to 34.30) mg/dL for females and 24.90 (18.25 to 33.65) mg/dL for males. No significant statistical difference was shown between both groups (p=0.571) (Figure 1, panel C). Similarly, the percentiles to determine the reference intervals for this variable by gender are expressed in Table 5.When grouped by gender and age median concentrations of Lp(a) were obtained and expressed in Table 6 where statistically significant differences weren't observed between male and female individualsin each age group. The distribution of this lipid variable according to age group and gender is shown in Figure 7.By measuring the behavior of Lp(a) according to age groupfor each gender separately, there were no significant differences between different age groups for female subjects, however when assessing behavior in male individuals differences were found between the group of 18-19 years and 40-49 years group and the group of 18-19 years with the group 60 and over (p=0.044 and p=0.019 respectively).

**Figure 6: Comparison of Total Cholesterol medians of concentration in a reference sample by age group. Maracaibo Municipality, Zulia State, 2011.**




** Statistically significant difference (p < 0.05)*

**Table 7: P values from comparison of LDL-C concentration in individuals by gender and age group. Maracaibo Municipality, Zulia State, 2011.**

| Age Group (Years) | 18-19 | 20-29 | 30-39 | 40-49 | 50-59 | ≥60 |
|---|---|---|---|---|---|---|
| **18-19** | - | 1.000 | 0.045 | $8.06x10^{-5}$* | $3.75x10^{-9}$* | 0.003* |
| **20-29** | 1.000 | - | 0.073 | $5.81x10^{-5}$* | $2.92x10^{-9}$* | 0.006* |
| **30-39** | 0.045 | 0.073 | - | 1.000 | $7.84x10^{-5}$* | 0.705 |
| **40-49** | $8.06x10^{-5}$* | $5.81x10^{-5}$* | 1.000 | - | 0.013 | 1.000 |
| **50-59** | $3.75x10^{-9}$* | $2.92x10^{-9}$* | $7.84x10^{-5}$* | 0.013 | - | 1.000 |
| **≥60** | 0.003* | 0.006* | 0.705 | 1.000 | 1.000 | - |

**Panel B:** Male

| Age Group (Years) | 18-19 | 20-29 | 30-39 | 40-49 | 50-59 | ≥60 |
|---|---|---|---|---|---|---|
| **18-19** | - | 0.086 | $2.43x10^{-4}$* | 0.061 | $6.95x10^{-7}$* | $6.57x10^{-7}$* |
| **20-29** | 0.086 | - | 0.220 | 1.000 | 0.001 | 0.004 |
| **30-39** | $2.43x10^{-4}$* | 0.220 | - | 1.000 | 1.000 | 1.000 |
| **40-49** | 0.061 | 1.000 | 1.000 | - | 0.543 | 0.591 |
| **50-59** | $6.95x10^{-7}$* | 0.001 | 1.000 | 0.543 | - | 1.000 |
| **≥60** | $6.57x10^{-6}$* | 0.004 | 1.000 | 0.591 | 1.000 | - |

** Statistically significant difference (p < 0.0083)*

**Table 8: p-values from comparison of Total Cholesterol concentration in individuals by gender and age group. Maracaibo Municipality, Zulia State, 2011.**

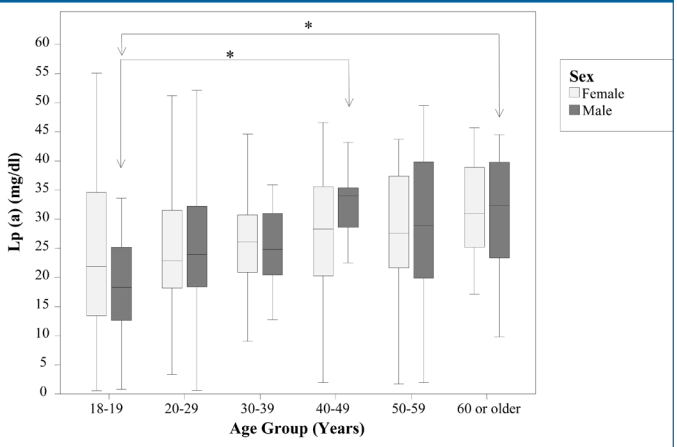
| Reference Intervals | |
|---|---|
| **HDL-C** | **Female:** 42.00 - 56.00 mg/dL.<br>**Male:** 37.00 - 50.00 mg/dL |
| **TAG** | **Female:** 50.35 - 102.53 mg/dL.<br>**Male:** 57.00 - 126.63 mg/dL |
| **VLDL-C** | **Female:** 10.07 - 20.48 mg/dL.<br>**Male:** 11.40 - 25.33 mg/dL. |
| **LDL-C** | 86.25 - 132.80 mg/dL. |
| **Total Cholesterol** | 149.50 - 201.50 mg/dL. |
| **Lp(a)** | 18.40 - 33.85 mg/dL. |

**Table 9: Comparison of lipid profile reference intervals with others populations and commercial lab kits**

| Geographic Location | References | Age (Years) | LIPID PROFILE | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | *Total Cholesterol* | | *HDL-C* | | *LDL-C* | | *Triglycerides* | |
| | | | *(mg/dL)* | *(mmol/L)* | *(mg/dL)* | *(mmol/L)* | *(mg/dL)* | *(mmol/L)* | *(mg/dL)* | *(mmol/L)* |
| **Mexico** | *García-Jiménez et al.*[12] | Adultos | 90.8 – 208.3 | 2.4 – 5.4 | 26 – 74.9 | 0.68 – 1.9 | 31.4 – 126.7 | 0.82 – 3.3 | 40.7 – 215.8 | 0.46 – 2.5 |
| | *NOM-037-SSA2-2002* [22] | Adultos | <200 | < 5.2 | > 35 | > 0.91 | < 130 | < 3.3 | < 150 | < 1.71 |
| | *ENSANUT 2006* [23] | Adultos | 162.4 | 4.2 | 40.6 | 1.05 | 121 | 3.1 | 118.1 | 1.5 |
| **Peru** | *Gómez et al.*[30] | 20 – 50 | 171 – 242 | 4.4 – 6.3 | 30 – 75 | 0.78 – 1.95 | 81.4 – 186.4 | 2.1- 4.8 | 48.– 274 | 0.54 – 3.1 |
| **Camerun** | *Taga et al.*[31] | 20 – 30 | 92 – 216.8 | 2.38 – 5.6 | 30.1 – 92 | 0.78 – 2.38 | 73.1 – 175.1 | 1.89 – 4.53 | 43.7 – 185.5 | 0.5 -2.12 |
| **USA** | *Heil et al.*[32] | Adultos | 100.5 – 232 | 2.6 – 6 | 38.7 – 61.8 | 1 – 1.6 | 100.5 – 129.5 | 2.6 – 3.3 | < 200 | <2.3 |
| | *Roche USA* * | Adultos | < 200 | < 5.2 | > 35 | > 0.91 | < 155 | < 4 | < 200 | < 2.3 |
| **Argentina** | *Wiener Lab* * | Adultos | 175 – 240 | 4.5 – 6.2 | 30 – 85 | 0.78 – 2.2 | < 140 | < 3.6 | 35 – 165 | 0.39 – 1.8 |
| **Spain** | *Spinreact* * | Adultos | < 200 | <5.2 | 30 – 85 | 0.78 – 2.2 | < 100 | < 2.6 | 35 – 165 | 0.39 – 1.8 |
| **Maracaibo** | | Adultos | 114.95-270 | 2.95-6.98 | 30-75.43 | 0.78- 1.94 | 53.64 - 185.41 | 1.37 - 4.78 | 31.88-199 | 0.35-2.25 |

** Reference values according to commercial kit*

**Figure 7: Comparison of Lp (a) medians of concentration in a reference sample by age group. Maracaibo Municipality, Zulia State, 2011.**




** Statistically significant difference (p < 0.05)*

## Discusión

Among the various cardiovascular risk factors, dyslipidemia is one of the most important alterations involved in atherosclerosis, which is the main event behind the pathophysiology of cardiovascular diseases[4,20,21]. In addition, the mortality rate due to cardiovascular events in the Zulia population is among the highest in the country. For these reasons, the main objective of this study was to establish lipid profile reference intervals in adult individuals of the Maracaibo Municipality, Zulia State. The information obtained can be established as reference intervals by gender for HDL-C, TAG and VLDL-C, while for Total Cholesterol, LDL-C and Lp (a) we proposed general reference intervals since their behavior was not influenced by gender (Table 8).These findings will allow development of better diagnosis strategies that will enhance primary and secondary prevention, which will ultimately improve the quality of primary care in our locality.

Our reference population was established taking into account the recommendations of PetirClerc and Solberg[26], as well as the proposals of the NCEP, however, given the important influence of hyperglycemia and insulin resistance in the lipid profile[31-35] we decided to consider them as exclusion criteria for the selection of individuals. Based on a preliminary study from our research center we determined from a reference population that a HOMA-IR higher than 2.00 represented insulin resistance[35].Comparing our intervals (p2.5-p97.5) with those of other populations (Table 9), we agree with the values of HDL-C and TAG proposed by García-Jiménez et al. (Mexico) (12). Our intervals of Total Cholesterol showed a wider range than Wiener Lab (Argentina) (36) and Gómez et al. (Perú)[37]. Also in relation to levels of LDL-C the p97.5 was one of the highest, surpassed only by that of the Peruvian population[38]. Importantly, our p97.5 for Total Cholesterol and LDL-C significantly exceeded the cutoff points established by Roche USA, Wiener Lab andSpinreact except in HDL-C where our intervalswere within the limits of the latter two laboratories.

The authors cited above agree on establishing reference intervals using the 2.5 and 97.5 percentiles as lower and upper limits respectively, however, given the alarm-

ing prevalence of metabolic endocrine disorders worldwide[40,41] and in Venezuela, we recommend a close monitoring of patients in the percentiles 25 and 75, for which we observed interesting findings regarding the ATP III [10]. The 75th percentile of both Triglycerides and VLDL-C were below the cutoff points established by the ATP III to be considered normal (150 mg/dL for TAG and 30 mg/dL for VLDL-C)[10]. The intervals defined by such entity as borderline high level (150 - 199 mg/dL) are similar to the 90 and 97.5 percentiles of TAG observed in our reference population[10].According to the epidemiological behavior of these variables (TAG and VLDL-C)by age group we observed that its concentrations remained higher in males compared to females[42], with an accentuated statistical significant differencein individuals aged 30 to 39.

As for Total Cholesterol the p75 for reference population was 201.50 mg/dL, which is very close to the appeal of ATP III`s<200 mg/dL[10]. Also a similar pattern of Total Cholesterol and LDL-C was found in the age groups, where both male and female individuals showed that their serum concentrations increased with age, resulting in significant differences between the extreme ages groups studied[43,44]. In the analysis of the behavior of LDL-C levels in relation to the classification proposed by the ATP III[10] it was observed that p25 is in the Optimum category (<100 mg/dL), while the p75 matches the lower value of the Borderline High category (130-159 mg/dL). Likewise, the percentiles 90 and 97.5 belong to the high category (160-189 mg/dL) without exceeding the upper limit.

Moreover, it is widely known that HDL-C is a lipid parameter that differs between genders, with higher levels for females (45). Concordant with this, our values in female individuals remained higher and the pattern held in different age groups[46-48]. In the independent study of each gender there were no significant differences in HDL-C concentrations going forward in age groups.By comparing the p25 of HDL-C for women and men (42.00 mg/dL and 37.00 mg/dL respectively) with the cutoff point proposed by ATP III to consider low HDL-C in an individual (50 mg/dL for women and <40mg/dL for men) (10), we found large differences between the values of our population and the cutoff points raised by this organization, behavior that is maintained in all age groups, suggesting that age does not influence this parameter, justifying the high prevalence of hypoalphalipoproteinemia not only in our country but in our continent[49-51].

Although most of the literature describes that Lp(a) concentration is genetically determined and it is not significantly affected by age, gender, diet[52] or exercise[53,54], our study shows that this lipoprotein concentration increases progressively with age. These findings are consistent with those obtained by Naoki Nago et al[55] whostudied 1,235 men and 1,762 women over 30 years old as part of the Jichi Medical School Cohort Study conducted in Japan. In this study we observed an increase in the concentration of Lp(a) as the subjects grew older, concluding that Lp(a) concentrationis closely related to age and influenced by other factors such alcohol consumption and gender.Similarly, in a study conducted by Jenner et al.[56] carried in 1,284 men and 1,394 women participants of the Framingham Offspring Study, a continuous and sustained rise in Lp(a) level from the age group 20 to 29 years to the group of 50 to 59 years was observed, a trend detected in both men and women thatchanged and decreased in the age group 60 to 69 years and in 70 or more years, very much alike to results in our study.

Despite the reported values, the rigorous process of selection of healthy patients hinders proper comparison with other populations. In the present study some characteristics of the region were not considered as eating habits or physical activity, which could influence the alteration of plasma lipid concentrations.

## Conclusions

Lipid levels in our area are different from those reported by other organizations. Due to the large variability of the lipid profile, as it is characteristic of biological entities, we recommend further research both regionally and nationally, for the determination of lipid profile cutoff points and comparison thereof with the upper limit of the reference intervals, obtained in this work in the case of our population. It is necessary to establisha relationship betweencardiovascular risks of each population, and,observethe reality of our situation in respect to the reported values. Likewise, the diversity of commercial test kits (even using the same analysis technique) in addition to the various sample selection methods, generates large numbers of reference intervals that prevent proper comparison of results. Therefore the standardization and consensus in the evaluation is an important premise to follow.

It should be noted that several manufacturers of laboratory reagents use as reference the arithmetic mean to determine "normal" lipid values. Due to the "abnormal" nature of biological variables and as reported in the literature we suggest that it is more convenient to use reference intervals expressed by percentiles.Likewise, we urge that clinical laboratories determine their own reference values, taking into account that eating habits, genetics and lifestyle are characteristics inherent to each population.

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